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Medical technology consultation: Prontosan for acute and chronic wounds

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance
GID-MT551 Prontosan for acute and chronic wounds
External Assessment Centre report

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Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
CI	Confidence interval
DHSC	Department of Health and Social Care
EAC	External Assessment Centre
FLACC	Face, Legs, Activity, Cry, Consolability
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomized controlled trial
SD	Standard deviation
VAS	Visual analogue scale
Vs	Versus

Executive summary

Prontosan is indicated use is for the cleansing and moistening of acute and chronic wounds and for biofilm prevention. The company has proposed a number of clinical scenarios where Prontosan would be used as part of chronic and acute wound management which the EAC has assessed.

The main body of evidence available relates to the use of Prontosan in chronic wound management but there is a lack of evidence relating to acute wound management.

There is a lack of high-quality comparative evidence comparing Prontosan use with saline or water in a consistent wound management approach. The available evidence suggests that Prontosan products may have result in shorter times to wound healing, lower wound infection rates and improved pain management and quality of life.

Economic modelling suggests that the shorter wound healing times and lower infection rates lead to reduced numbers of visits and costs for health care resource associated with wound care in chronic wound care. Both the submitted models and EAC base case find Prontosan to be cost saving compared to saline or water when used with chronic wounds. No economic modelling was submitted for other wound types due to a lack of clinical evidence. Clinical expert input suggests that use of Prontosan may already be widely in use in the NHS in different settings including community wound clinics, post-operative wound management, primary care settings, and maternity settings.

Despite weaknesses in the evidence (clinical and economic), the EAC considers that based on the current available evidence the use of Prontosan products as an option for chronic wound management is supported. The evidence for whether Prontosan products are more effective than water or saline however is limited.

1 Decision problem

The company has not specifically proposed any changes to the decision problem as outlined in the scope (table 1).

The EAC note that the scope does not specify how Prontosan products should be used. Clinical expert input suggests that

- Prontosan wound irrigation solution alone
- Prontosan wound gel or gel X alone
- Prontosan irrigation solution plus wound gel or gel X

are appropriate uses of Prontosan products depending on wound condition and clinical need. Clinical expert input suggests that in the NHS, Prontosan wound irrigation solution is the most commonly used of the Prontosan products.

Table 1: Decision Problem

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	Adults and children with acute or chronic wounds	No change	• Evidence for children and adults • Limited evidence for acute wounds (burns only)
Intervention	• Prontosan wound irrigation solution • Prontosan wound gel • Prontosan wound gel X	No change	• Evidence for all 3 products • Some studies using solution or gel alone. Some studies using combination of solution and gel
Comparator(s)	• Saline • Water • Ringer's Solution	No change	• Limited direct comparator evidence • Ringers solution not widely used in the NHS • Silver sulfadiazine appropriate comparator for burns
Outcomes	• Proportion of wounds with complete closure • Time to complete wound closure • Other outcomes related to wound characteristics including wound size, volume and area	No change	• Limited direct comparator evidence • No evidence for length of hospital stay, number of follow-on treatments including GP, nurse and

	• Number of dressing changes and use of antimicrobial dressings and other consumables • Incidence of wound infection evidenced by adverse events and/or use of antibiotics (related to wound infection)/reduction in clinical signs of infection • Changes to wound bed condition including slough, exudate, granulation and oedema • Staff time • Antibiotic use • Analgesic use • Length of hospital stay • Number of follow-on treatments including GP, nurse and hospital visits • Number of surgical debridement procedures • Number of amputations or skin grafts • Colonisation with antimicrobial-resistant pathogens • Health related quality of life • Patient related outcomes such as pain scores, discomfort and wound odour or level of satisfaction • Carer's level of satisfaction • Mortality rates • Device related adverse events		hospital visits, number of surgical debridement procedures, number of amputations or skin grafts or mortality
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers of combinations of devices are needed.	No change	• Economic analysis based on chronic wounds only (1 model is venous leg ulcer data, 1 model is mixed aetiology) • The model structure may be appropriate for other chronic wound populations • Modelling did not include any acute wound pathways
Subgroups	• Burns • Diabetic foot ulcers • Leg ulcers • Pressure ulcers • Post-operative wounds (with and without surgical site infection) • Trauma wounds • Infected wounds of any aetiology • Recurrent infections • Wound duration • Wound size • Children or adolescents	No change	• All clinical evidence limited in quantity and quality • Clinical evidence for subgroups including burns, venous leg ulcers, diabetic foot ulcers, trauma wounds, pressure ulcers, post-operative wounds • Surgical site wounds are defined as wounds resulting from a surgical procedure but it should be noted that these may differ from

			wounds which require surgery. • Clinical evidence for burn wounds in children • Clinical evidence for wound duration and size. • Economic evidence in venous leg ulcers only

2 Overview of the technology

Prontosan is a class III, CE marked medical device manufactured by B.Braun Medical AG. Documentation relating to the CE mark, declaration of conformity and instructions for use for each of the preparations of Prontosan have been provided to Cedar and checked. The CE mark covers both Prontosan wound irrigation solution and wound gels (see below) and is valid until May 2024.

The indicated use is for the cleansing and moistening of acute and chronic wounds and for biofilm prevention. Prontosan contains 0.1% betaine (undecylenamidopropyl betaine), a surfactant, and 0.1% polyhexanide (polyhexamethylene biguanide, PHMB, polihexanide), a broad-spectrum antimicrobial. The company claims that Prontosan is the only wound cleansing product that contains these active ingredients. The EAC has not identified anything to suggest there are other products which contain the same active ingredients.

The product is available in a range of topical solutions and gels (table 2).

Table 2: Prontosan Products

Product	Composition	Size	Uses
Prontosan Irrigation Solution	• Purified Water • 0.1% Betaine surfactant • 0.1% PolyaminopropylBiguanide (Polihexanide)	• 350ml bottle • 40ml single-use pods • 1,000ml bottle for instillation	Wound irrigation or applied to gauze as a soak
Prontosan Wound Gel	• Purified Water • Glycerol • Hydroxyethylcellulose • 0.1 % Betaine surfactant • 0.1 % Polyaminopropyl Biguanide (Polihexanide)	• 30ml bottle	Applied to wound bed during dressing changes, after wound cleansing and before application of secondary dressing. Suitable for use in deep and tunneling wounds, wound cavities and difficult to access wounds

Prontosan Wound Gel X	• Purified Water • Glycerol • Hydroxyethylcellulose, • 0.1% Betaine surfactant • 0.1 % Polyaminopropyl Biguanide (Polihexanide).	• 50g tube • 250g tube	An extra thick gel applied to the wound bed during dressing changes, after wound cleansing and before application of secondary dressing. Suitable for use in flat or larger surface area wounds such as leg ulcers.

The company claims that the 2 active ingredients work in combination to disrupt and prevent biofilms (aggregations of multispecies micro-organisms including bacteria, fungi, yeasts and other cellular debris) forming on the wound bed as well as cleansing and removing slough, devitalised tissue and other wound debris.

The company highlighted that although Prontosan contains an anti-microbial agent, it is an adjunct to the betaine surfactant. Prontosan alone should not be used where anti-microbial treatment is needed, such as in infected wounds. The company states that Prontosan may have help prevent infection from developing due to its anti-biofilm effect and Prontosan should therefore be used as part of wound bed preparation or maintenance and not in place of secondary dressings for treating infections.

Although the company has submitted each of the listed products as a version, the EAC considers that Prontosan wound irrigation solution and Prontosan wound gels are different products rather than updated versions of the same product.

3 Clinical context

The company proposes to use Prontosan for both chronic and acute wounds. The company has outlined 3 clinical scenarios where Prontosan would be used as part of chronic wound management:

- Granulating, non-sloughy wounds – irrigate to a 5 min soak with Prontosan solution and use of Prontosan gel or gel X should be considered

- Wounds with light to moderate slough – 5 to 10 min soak with Prontosan solution and Prontosan gel or gel X applied before dressing

- Wounds with local-spreading infection – 10 to15 min soak with Prontosan solution and Prontosan gel or gel X applied before dressing

For acute wound treatment the company has also outlined 3 clinical scenarios:

- Suture, post-operative trauma wounds - irrigation with Prontosan solution until visibly clear of debris

- Patient at high-risk of wound infection – 1 to 5 min soak with Prontosan solution and use of Prontosan gel should be considered

- Burns (first/second/third degree) and/or infected wounds – 1 to 15 min soak with Prontosan solution depending on wound severity and Prontosan gel applied before dressing

The EAC note that individual trust policies and approaches to wound management are likely to differ but consider the proposed place for Prontosan likely to be broadly appropriate with possible adjustments to accommodate specific trust protocols. Clinical expert input suggested that wound care approach will depend on wound conditions and all experts were broadly in agreement that best practice would involve cleansing the wound only when needed and not at every dressing change. The experts did note however that the extent to which best practice is followed is variable.

Special considerations, including issues related to equality

The scope notes that certain groups are more likely to have chronic or non-healing wounds including older people, people with diabetes, people with restricted mobility and people with darker skin tones. The EAC did not identify any additional groups for consideration. The EAC notes that type 2 diabetes is strongly correlated with increasing age and a report from Diabetes UK reports that people of South Asian origin are 6 times more likely and people of African and African-Caribbean origin are up to 3 times more likely to have type 2

diabetes compared with people of white European origin. Consideration should be given to any possible increased risk of poorly healing or unhealing chronic wounds resulting from multiple risk factors.

The EAC has identified the following guidelines as potentially relevant:

- NICE NG19 Diabetic Foot Problems: Prevention and Management
- NICE CG179 Pressure Ulcers: Prevention and Management
- NICE NG125 Surgical Site Infections: Prevention and Treatment
- NICE MTG54 The VAC Veraflo Therapy system for acute infected or chronic wounds that are failing to heal

The EAC has identified some potential for confusion to arise based on existing guidance. The recommendations with potential to cause confusion are summarized in table 3. In particular, NICE CG179 on the prevention and management of pressure ulcers states that routine use of topical antiseptics or antimicrobials to treat a pressure ulcer is not recommended in adults or children. The EAC notes that there is the potential for some confusion to arise around the use of Prontosan for pressure ulcers as both Prontosan solution and gels are considered topical agents (table 3, rec 1.4.22).

NICE NG125 on the prevention and treatment of surgical site infections recommends the use of saline for wound cleansing up to 48 hours after surgery and tap water after 48 hours if the wound has separated or surgically opened to drain pus. This may impact clinician choice to use Prontosan solution in this setting, however these recommendations were published in 2008 when Prontosan may not have been available as an option for wound cleansing.

Table 3: Relevant Recommendations from Existing NICE Guidance

NICE Guidance	Recommendation	Comment
NICE CG179	1.4.13: Do not routinely offer adults negative pressure wound therapy to treat a pressure ulcer, unless it is necessary to reduce the number of dressing changes (for example, in a wound with a large amount of exudate) [2014]. 1.4.22: Do not routinely use topical antiseptics or antimicrobials to treat a pressure ulcer in adults [2014].	• This guidance was checked in 2018 and it was determined that no new evidence existed to warrant update. • As negative pressure wound therapy (NPWT) is not recommended routinely, the EAC has excluded evidence relating to NPWT from this Assessment Report. • The recommendation to not routinely use topical antiseptics or antimicrobials may result in clinical staff not using Prontosan.
NICE NG125	1.4.2: Use sterile saline for wound cleansing up to 48 hours after surgery. [2008] 1.4.4: Use tap water for wound cleansing after 48 hours if the surgical wound has separated or has been surgically opened to drain pus. [2008]	• May impact clinician choice to use Prontosan solution in this setting. • Recommendations are from 2008 so may predate the availability of Prontosan which was not CE marked until 2008.
MTG54	1.1: The VAC Veraflo Therapy system shows promise for treating acute infected or chronic wounds that are not healing. However there is not enough good-quality evidence to support the case for routine adoption. [2021]	• The VAC Veraflo system is involves NPWT with instillation. • The EAC has excluded evidence relating to NPWT with instillation from this Assessment Report as it is not currently recommended for routine use in the NHS.

The EAC cannot provide an exhaustive list of local guidelines but notes that every hospital or NHS trust is likely to have their own wound care guidelines for staff. One clinical expert noted that there were Scottish guidelines which specifically recommended the use of Prontosan products in a range of settings including wound care in children, maternity settings and general wound care.

4 Clinical evidence selection

4.1 *Evidence search strategy and study selection*

The company's search strategy was comprehensive using a combination of free text terms and Medical Subject Headings across a range of databases, identifying 1,891 studies for title and abstract review. It is therefore likely that the company have identified all relevant literature. However, to be completely

confident the EAC conducted their own systematic search. Details of the company and EAC searches are provided in appendix A. The EAC literature searches identified 117 references, these were screened by title and abstract in accordance with the scope by one researcher and checked by a second researcher. In total, 42 were selected for further screening and full texts were retrieved and reviewed by one researcher. Queries were checked by another researcher to make a final eligibility decision, and all studies included by the company were also checked by another researcher to make a final decision on inclusion.

The large discrepancy between the number of studies identified by the company and the EAC is due to the way the searches were designed. The company searches, although comprehensive, were very broad and lacked specificity and precision to identify studies specifically including Prontosan. The EAC searches used the key components of Prontosan as well as using index term from key papers to develop a more focused search strategy which produced fewer results. The EAC notes that both the company and EAC approach are appropriate and highlight the fact that both searches identified the same relevant studies.

The inclusion and exclusion criteria applied by the company are summarised in table 4.

Table 4: Company inclusion and exclusion criteria

Inclusion criteria	
Population	Wounds of any aetiology
Comparator	Tap water or saline or Ringer's solution
Interventions	Use of Prontosan irrigation solution and/or gel Polyhexanide 0.1% with betaine
Outcomes	Measurements of wound improvement: • Wound size reduction • Pain reduction (self-reported/reduced analgesics) • Biofilm reduction • Exudate reduction • Slough reduction • Reduced malodour • Patient quality of life • Reduction in bioburden
Study design	Systematic reviews, randomized, non-randomized, cohort, case studies, observational and qualitative studies. Studies with a total sample size of 10 or more patients.
Exclusion criteria	
Population	Surgical procedures, non-wounds (oral, ocular)
Interventions	Any intervention that did not incorporate PHMB solution or gel. Dressings with PHMB incorporated within the dressing. Negative pressure wound therapy. Polyhexanide alone without betaine
Outcomes	Outcomes related to surgical site infections
Study design	Testimonials, non-systematic reviews containing no primary data, editorials, reports describing product news, in vitro studies and animal biofilm studies. Studies with a total sample size of fewer than 10 patients.

4.2 *Included and excluded studies*

The company submission included 15 published studies, 13 of which were identified and included by the EAC.

The EAC included 16 published studies and 2 unpublished studies as key evidence. An additional 4 posters/conference abstracts are included for information and supporting evidence. A summary of studies included by the company and excluded by the EAC is presented in table 5 and a table of the EAC decisions for individual studies is provided in Appendix A.

The EAC identified but excluded one study which the company had included (Collier et al, 2017) as this was a non-peer reviewed meeting report which

discussed the use of Prontosan as part of the wound management pathway for a hospital but did not report methods or results in detail, reporting only that Prontosan was the cleansing agent and that rates of healthcare associated infection (HCAIs) and surgical site infection (SSIs) rates dropped between two periods (Aug 2012 to Nov 2013 and June 2015 to Sept 2016).

An additional study which had been included by the company (Wilkins et al, 2013) has been excluded by the EAC as it was a narrative review which included a summary of 3 studies which have been reviewed individually (Andriessen 2008; Horrocks 2006 and Romanelli 2010) while the remainder of the included studies included in the review were not relevant as they were animal and in-vitro studies.

The EAC identified an additional 3 published studies relevant to the decision problem (Assadian et al. 2018, Borges et al. 2018, Saleh 2020). Two of these (Assadian et al. 2018 and Borges et al. 2018) were identified by the company but excluded as Prontosan was not used according to the company's instructions for use. The EAC notes that there is a possibility that Prontosan will be used in ways that are not strictly defined in the instructions, for example soak times may vary between 10 to 15 minutes despite the IFU's stating soaking with a saturated compress for 'at least 15 minutes' is recommended. The EAC considers that studies which use Prontosan in a way that is not in line with the recommended instructions for use are likely to represent a real world variation in clinical practice and add useful information on how Prontosan might be best used or not. The EAC has therefore included both of these studies as relevant.

One study (Saleh et al, 2020) was identified by the company as part of their search for ongoing studies but excluded it as it was a surgical study. The EAC included this study as it relates to skin grafts following surgery for malignancies and therefore might be considered to be part of the 'post-operative wounds' subgroup as specified in the scope. The EAC note that this study includes patients who have had surgery and the wound being treated/managed is the result of the surgery (e.g. skin graft site or suture site)

and not wounds that have deteriorated to the point of requiring surgical intervention.

The company included data from 3 unpublished studies (Harding 2012, Oropallo 2020 and Salisbury 2020) two of which are Academic in Confidence (Oropallo 2020 and Salisbury 2020). The EAC has excluded data from Salisbury 2020 as it is not relevant the decision problem because it is an in-vitro study. Data from two trials (Harding 2012 and Oropallo 2020) have been included and the EAC identified both as part of searches for ongoing studies. The EAC noted that while both trials are registered on clinicaltrials.gov, one is recorded as 'terminated' while the second is recorded as 'complete'. No peer-reviewed publication for either study has been identified however results from both studies have been reported on clinicaltrials.gov and provided by the company so are discussed as part of the evidence assessment.

The company submission included 3 abstracts/posters, all of which have been included by the EAC. The EAC included one additional poster abstract (Lindsten 2017).

Studies included in the evidence review are summarized in table 6 to table 10 and excluded studies are summarized in table 11.

Table 5: Comparison of Company and EAC evidence selection

		Company submission	EAC search
Number of studies identified in a systematic search (after removal of duplicate records)		1,891	117
Number of studies identified as being relevant to the decision problem.		21	22
Of the relevant studies identified:	Number of published studies	15	16
	Number of abstracts	3	4[1]
	Number of ongoing or unpublished studies	3	2[2]

[1]The EAC identified one additional abstract relating to Prontosan (Roldan 2009) however the abstract was unavailable through any library services and has not been included.
[2]Two studies were identified by the EAC as part of the 'ongoing studies' searches. Cross-checking with the company submission indicated that the company has included unpublished, academic in confidence data from one of these studies, however there are results reported in the public domain on clinicaltrials.gov.

Table 6: Venous Leg Ulcer Studies

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Andriessen (2008) Germany	Retrospective, comparative case series	112 patients with venous leg ulcers **Setting:** Community wound healing clinic	**Intervention**: Prontosan Irrigation Solution (n=59) **Comparator**: Saline or Ringer's Solution (n=53) In both groups wounds were cleansed for 15 minutes with a wet phase and short resting (dry) phase to restore periwound skin integrity (15 mins). **Outcomes:** • Ulcer closure (wound healing) • Wound evolution (time to healing and wound infections) **Follow-up** To ulcer closure or 6 months	**Limitations** • Retrospective comparisons • Control group had mixed interventions (saline or Ringer's) combined • Primarily narrative/descriptive results with limited statistical analysis • Aims, although not clearly stated, do suggest cost-effectiveness is a consideration however this is not included in the results. **Applicability** • Population group is relevant however full inclusion/exclusion criteria are not defined but leg ulcer must be present for at least 3 months; patients with persistent, severe, arterial circulatory disorders (stage II and higher according to Fontaine) were excluded. • Prontosan compared with saline/Ringer's solution is a relevant comparison however the data for the comparison group is combined – no comment can be made on the efficacy of Prontosan compared with saline or Ringer's solution specifically as data are not reported separately. • The number of patients in the comparator group who were treated with saline and with Ringer's solution is not reported. **Funding**: Not reported

Study name and location	Design	Population	Intervention and Outcomes	EAC comments

Borges (2018)
 	
Brazil
	Randomized controlled trial
	
	●
		44 patients with venous leg ulcers
		
		Setting: Dermatology Outpatient Clinic
		●
			Intervention: Prontosan solution (n=22)
			Comparator: Saline (n=22)
			
			In both groups wounds treated with 1 minute irrigation under continuous pressure
			
			Outcomes:
			• Examine characteristics of venous leg ulcers including
			  • Wound duration
			  • Wound area
			  • Necrosis
			• Examine the effect of cleansing solutions on bacterial load
			• Compare the bacterial load reduction of cleansing solutions
			• Detect presence of biofilm
			
			Follow-up
			No follow-up – biopsy taken before and after cleansing
			●
				Limitations
				• Small sample sizes – study likely underpowered but no sample size calculations provided.
				
				Applicability
				• Likely limited applicability to NHS setting as wounds irrigated for 1 minute with no soak applied.
				• Unclear whether wounds had multiple cleansings/dressing changes or whether only a single cleanse. Results suggest a single wound cleanse with Prontosan or saline with bacterial swabs taken immediately before and immediately after.
				• Company excluded this study as Prontosan is not used according to IFU.
				
				Funding/CoI
				Financial support from FAPEMIG

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Romanelli (2010) Italy	Randomized trial ●	40 patients with chronic venous leg ulcers **Setting:** outpatient wound clinic of a dermatology department ●	**Intervention:** Prontosan (n=20) **Comparator:** Saline (n=20) Patients treated every other day with Prontosan or saline plus standard wound care (polyurethane foam and elastic compression) **Outcomes** • Wound size • Wound surface pH • Pain (VAS score) **Follow-up** 4 weeks (treatment duration) ●	**Limitations** • Small sample size • Sample size calculation not reported • Use of Prontosan not clearly reported (no time, soak information) **Applicability** • Not a UK-based study however wound treatment approach appear consistent with UK practice • Population, comparator and interventions are relevant **Funding** Partially funded by B. Braun AG, author received financial support for clinical consulting from B. Braun Medical AG.

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Harding (2012) NCT01153633 UK	Pilot randomized double blind study Prontosan Wound Irrigation Solution and Prontosan Wound Gel Normal saline and placebo	34 patients with venous leg ulcers **Setting:** Outpatient clinic	**Intervention:** Prontosan Irrigation solution plus Prontosan wound gel (n=17) **Comparator:** Saline plus placebo gel (n=17) **Outcomes** • Percent change of wound size from baseline to last visit • Healing of target ulcer at V6/EOS • Absolute change of target ulcer from baseline to last visit • Percent change of wound size from baseline to last visit • Healing of target ulcer at V6/EOS • Absolute change of target ulcer from baseline to last visit **Follow-up** 12 weeks	**Limitations** • Unpublished data provided by the company (not peer reviewed, accessible for wider review) • Trial terminated due to recruitment issues • Small sample size **Applicability** • UK population • Uses both Prontosan irrigation solution and Prontosan wound gel which is reflective of UK practice

Table 7: Burns

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Ciprandi (2018) Germany, Italy, Belgium, UK, Russia	Retrospective, non-comparative data review	198 children including: • newborns 0 to4 weeks • infants 5 weeks to 1 year • children older than 1 year) with burns **Setting:** Hospital	**Intervention:** Prontosan wound irrigation solutions and Prontosan wound gels **Outcomes** Safety based on adverse events including: • Allergies • Infection signs and symptoms • Adverse reactions related to the product or any other signs and symptoms associated with allergic reaction • Healing time (based on last day of dressing change and when wound was healed or re-epithelialised) **Follow-up** Not reported	**Limitations** • No comparator • Retrospective data review from patient medical records using questionnaires to clinical teams • Possible variation in wound management/treatment protocols. • Variation the use of Prontosan, children were treated with any combination of solution and/or gels plus additional wound healing interventions such as debridement. Results not reported according to Prontosan use. • Not all children treated with Prontosan for entire wound healing period **Applicability** • UK data included although only 20 (10.1%) of the questionnaires were from the UK. • Evidence specifically in children is directly applicable to the scope. **Funding:** Authors received grant from B. Braun.

Kiefer (2018) Germany	Prospective, non-comparative, multicentre study	56 patients with burn wounds requiring surgical debridement followed by split thickness skin grafts. **Setting:** 3 Burn Centres	**Intervention:** Prontosan wound gel X *Preoperative:* single shot of antibiotic *Postoperative*: 3-4mm Prontosan wound gel X applied to entire graft immediately, repeated on day 5, continued every other day until day 29 or complete graft take **Primary Outcome** • Healing of split thickness skin graft • Time to complete re-epithelialisation • Wound infection • Reoperation of the grafted site during the 30-day study period **Secondary Outcome** • Tolerability and safety of Prontosan wound gel • Pain at the grafted site **Follow-up** 30 days or until complete graft take occurred	**Limitations** • Non-comparative study • Small sample size • Descriptive/Narrative results (no statistical analysis) **Applicability** • Population is applicable to the scope (burns patients) as is the intervention. **Funding** Sponsored by B. Braun Medical AG

Wattanaploy (2017) Thailand	Prospective randomized controlled trial 🟡	46 adult patients with partial thickness burn wounds **Setting:** Burn Unit 🟢	**Intervention:** Prontosan wound gel X (n=23) **Comparator:** Silver sulphadiazine (n=23) Both groups received daily dressing changes and same standard care, 3-5mm of Prontosan wound gel X or silver sulfadiazine. **Primary Outcome** Healing time (time to complete gross ephithelialisation) **Secondary Outcomes** • Burn wound infection • Bacterial colonisation • Pain during dressing change • Treatment cost • Staff satisfaction • Patient satisfaction **Follow-up** 3 weeks 🟢	**Limitations** • Comparator out of scope • Saline used in both arms for wound cleansing before application of either Prontosan or Silversulfadiazine • Small sample size • Detailed treatment costs not reported • Overall difference in pain scores across the treatment are not reported. Pain scores on individual days of treatment may not be of relevance. **Applicability** • Not a UK-based study however wound treatment approach appear consistent with UK practice. • Population relevant • Intervention somewhat relevant (Prontosan wound gel X) but saline which is the scope comparator is used to cleanse in both arms. This may be one possible treatment pathway in the UK but more likely that Prontosan solution would be used for cleansing.

Table 8: Surgical Site Wounds

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Saleh (2016) Sweden and Singapore	Prospective, double blind, randomized, placebo controlled trial 🟡	40 patients with skin malignancies excised **Setting** Hospital 🟡	**Intervention:** Prontosan irrigation solution (n=20) **Comparator:** Sterile water (n=20) Skin graft sutured, tie-over dressing soaked with Prontosan or sterile water applied. **Outcomes** • Bacterial load • Development of surgical site infection (SSI) • Presence of intranasal *S aureus* and examining its relevance for the bacterial dynamics of surgical wounds **Follow-up** 7 days post-surgery 🟢	**Limitations** • Small sample size • Limited outcome comparisons reported • Time Prontosan soak was applied for is not reported • SSI performed by 1 investigator **Applicability** • Study excluded by company on grounds it was outside of scope. EAC included as surgical site wounds considered relevant. • Only SSI reporting likely to be of relevance • Method of Prontosan and sterile water use may have limited applicability to UK practice **Funding** Funding provided by Swedish government and research council. One author received consulting support from Molnlycke Health Care.

Table 9: Studies with chronic wound patients of mixed aetiologies

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Assadian (2018) Switzerland	Comparative prospective cohort study ●	260 patients with a total of 299 chronic wounds treated with a range of different approaches. **Setting** Wound Centre ●	**Intervention:** Prontosan irrigation solution (n=33 patients/36 wounds) **Comparator:** Saline (n=12 patients/14 wounds) Wounds treated with a 20 minute wet-to-moist cleansing **Outcomes** Difference in the quantitative number of microorganisms per 1cm^2 of wound surface harvested before and after a 20 minute wet-to-moist cleansing. **Follow-Up** No post treatment follow-up ●	**Limitations** • Small sample size • Only a total of 45 patients (50 wounds) relevant to scope **Applicability** • Not a UK-based study • No conclusions can be made on wound healing or prevention/development of wound infection • Company excluded this study on the basis that it was used outside of the Instructions for Use as only a single application of Prontosan was used. EAC agree that a single application of Prontosan irrigation solution is unlikely to be representative of UK practice therefore concludes this study has limited applicability. **Funding** Not Reported

Atkin (2020) UK	Retrospective, multi-centre case series study to evaluate the effectiveness of Prontosan PHMB and betaine wound irrigation solution and gels in hard to heal wounds. 	50 patients with 52 hard to heal wounds. **Setting** Not reported 	**Intervention:** • Prontosan irrigation solution alone (n=16) • Prontosan irrigation solution plus gel (n=36) Soak times with cleansing solution varied according to wound condition, with the majority stating 5–10 minutes. Outcomes • Proportion of wounds achieving partial healing • Impact on complete wound healing for wounds treated to >1 month Wound and patient characteristics were reported where available: • Number of patients and wounds • Type of wound • Previous treatment history • Age of wound • Wound details (malodour, exudate, slough and size) • Pain level (analgesia use) • Dressing change details	**Limitations** • Retrospective pooled analysis of 24 case studies with no specific detail of setting or demographics. • Noted that authors observed large wound areas up to 300cm^2 which had been unhealed for up to 20 years • Non-comparative although does try to make some comparisons between solution plus gel and solution alone • Small sample size • Narrative/Descriptive results – no statistical analysis • Treatment plans not reported (soaks, irrigation etc) • Duration of study not reported • Mixed aetiology wounds **Applicability** • UK based study with very limited patient reported outcomes. • Mix of solution plus gel and solution alone likely to be indicative of wider UK practice. • Population is applicable to scope although some patients with applicable wounds (burns) were excluded. **Funding** One author employee at B. Braun, 2 authors received consulting fees from B. Braun

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
			• Duration of new treatment • Patient quality of life. **Follow-up** Not Reported	

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Bellingeri (2016) Italy	Comparative multi-centre, single blinded, randomized controlled trial 	320 patients with pressure ulcer or vascular leg ulcer of which 289 randomized **Setting** 6 centres in either hospital wards(geriatrics and medicine) or outpatient clinics (phlebotomy, surgery and dermatology) 	**Intervention:** Prontosan Irrigation solution (n=143) **Comparator:** Saline (n=146) Both groups irrigation 20-30ml followed by 10 minute soak **Primary Outcomes:** • Wound improvement as measured by wound size and signs of infection/inflammation **Secondary Outcomes:** • Pain • Adverse Events **Follow-up** Assessment in all patients at T0 (recruitment) T1 (day 7) T2 (day 14) T3 (day 21) T4 (day 28) 	**Limitations** • Study is underpowered based on the sample size calculation reported which calculated 165 patients per group were required. • Comparison may not be reflective of NHS practice for the use of saline. • Risk of selective reporting bias • Bates-Jensen Wound Assessment Tool results for each item, at each time point are not reported • P values are not reported for all significant outcomes. • The narrative results are unclear in relation to what they are reporting. The aim of the study was to report a comparison between saline and Prontosan at different time points. The results however report a combination of between groups (saline versus Prontosan) and within groups (Prontosan only) results. **Applicability** • Applicable to NHS setting **Funding/CoI** No CoI to declare. B.Braun supplied materials and paid ethics committee fees

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Durante (2014) Italy	Retrospective, multicenter study ●	124 patients with chronic wounds **Setting** 6 wound centres ●	**Intervention:** Prontosan Wound Gel **Outcomes** • Reduction in wound size • Evolution of the wound bed and edges and appearance of surrounding skin • Pain during dressing changes • Microbiological examination of the wound **Follow-up** 60 days or complete healing Treatment visits were day 7, 15, 30, 45 and 60 days but no later than eventual complete wound healing. ●	**Limitations** • Not a comparative study • Unclear what the treatment timings were throughout the study (determined by investigator according to clinical need) • Follow-up times not reported • Mixed aetiology wounds **Applicability** • Prontosan gel used which may have limited applicability in the UK NHS setting. • Prontosan used in combination with debridement and secondary dressings which is likely reflective of wound management protocols. **Funding/CoI** Not reported

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Horrocks (2006) UK	Retrospective, non-comparative study ●	10 patients with chronic wounds **Setting** Community ●	**Intervention:** Prontosan irrigation solution (soak applied for at least 10 minutes) plus Prontosan Gel (3mm thick film) if required. **Outcomes** • Removal of biofilm: normal wound bed becoming visible within 3 weeks • Reduction in wound size • Compare use of antibiotic/silver prior to and during use of Prontosan • Patient comfort • Ease of application • Note any adverse reactions **Follow-up** Not Reported ●	**Limitations** • No comparator • Retrospective review • Small sample size • Mixed aetiology wounds • Number of patients using solution + gel not reported – cannot report on results for Prontosan solution alone • Outcome reporting is limited (no statistical analysis) • Conclusions state that Prontosan is safe and cost effective but no cost effectiveness outcomes are reported. **Applicability** • UK setting in a relevant population and setting (community setting) **Funding/CoI** Not Reported

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Möller (2018) Germany	Retrospective data review ●	953 patients with chronic or poorly healing wounds **Setting** Outpatient wound clinic ●	**Intervention:** Prontosan Irrigation Solution and Prontosan wound gel. Wounds irrigated with Prontosan Solution at every dressing change. Wounds with no or moderate exudation were treated with Prontosan Gel or a tamponade moistened with Prontosan Solution. **Outcomes** • Wound Evaluation (healing, improvement, no improvement) • Wound Infection **Follow-up** Not reported ●	**Limitations** • Retrospective review of patient records • No comparator • No formal statistical analysis despite large sample size • Detailed methods reporting is lacking • Unclear if peer reviewed publication • Translation from German language provided by the company, the EAC cannot verify the accuracy of the translation **Applicability** • Although not UK based, the treatment protocol for the included patients appears relevant. • Both Prontosan irrigation solution and gel are used which is relevant to the decision problem • All wounds irrigated with Prontosan solution at every dressing change and wounds with no/moderate exudate treated with Prontosan gel or tamponade moistened with Prontosan solution however the results are not reported separately • Population is relevant to the decision problem **Funding/CoI** Not Reported

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Moore (2016) USA	Retrospective case series (patients chart analysis)	49 patients, presenting 70 chronic non-healing wounds **Setting** Wound Clinic	**Intervention:** Prontosan **Outcomes:** • Time to wound closure • Absolute change in wound size • Initiation of antimicrobial therapy • Adverse events **Follow-up** Not Reported	**Limitations** • Retrospective (data extracted from medical records) • Small sample size • Non-comparative • Mixed aetiology wounds although results are separated by wound type • Full inclusion/exclusion not reported • Details of Prontosan solution or gel use including soak times not reported beyond its use as part of standard care **Applicability** • Not a UK based study • Not clear how Prontosan was used (soaks, cleansing, single applications) **Funding/CoI:** One author is a consultant for BBraun Three authors receive grant/research funding from BBraun

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Oropallo et al NCT03369756 USA	Open label, non-comparative study	N=43 patients with chronic leg wounds	**Intervention:** Prontosan Wound Irrigation Solution and Prontosan Wound Gel **Outcomes** • Wound Quality of Life global score	**Limitations** • Non-comparative study • Study reported as 'terminated' on clinicaltrials.gov • Results from the study have been provided by the company as Academic in Confidence (not peer reviewed or accessible for review in public domain). • Publication anticipated 2021 • Some results available in the public domain via clinicaltrials.gov **Applicability** • Quality of life outcomes reported

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Ricci (2018) Italy	Prospective evaluation ●	70 patients with chronic wounds with varying aetiologies. **Setting** Not Reported ●	**Intervention:** Prontosan Irrigation Solutiuon **Group A** (single application; n=40): Cleansing with PP (10ml) for 2, 5, 10 and 15 minutes – 10 patients for each time point **Group B** (n=30): daily soak with PP (10 mins) removed without cleansing – once a day for 14 days **Outcomes** • Wound bed preparation score • Wound photographic relief • Infection score • Pain **Follow-up** Group A: 2, 5, 10 or 15 mins Group B: 14 days ●	**Limitations** • Study appears to be prospective however it is not clearly stated. • Non-comparative study • Small sample size in each of the groups, with smaller sample sizes for each of the time points in group A • Descriptive results (no statistical analysis) **Applicability** • Not a UK based study however wound treatment approach consistent with UK practice • Population and interventions are relevant • Use of Prontosan in Group A (single applications) may not be relevant however do suggest that the longer application times (10 and 15 minutes) are required for effect. **Funding/CoI** Author is consultant for B. Braun

Study name and location	Design	Population	Intervention and Outcomes	EAC comments
Valenzuela (2008) Spain	Randomized, multi-centre, non-masked clinical trial ●	142 patients with chronic wounds (no more than 2 lesions per patient) **Setting** Not Reported ●	**Intervention:** Prontosan Wound Gel (n=78) **Comparator:** Saline (n=64) **Outcomes** Evolution of bacterial build-up in the wound bed and the size of wounds Polyhexanide gel as a debridement option **Follow-up** 2 weeks ●	**Limitations** • Not clear from the study what the specific outcomes were • No blinding in the study • Short follow-up (2 weeks), unclear if wounds were followed to complete healing but unlikely • This is a translation of a Spanish language paper provided by the company. The EAC cannot verify the accuracy of the translation. **Applicability** • Population, intervention and comparator relevant to the scope • Not a UK-based study however wound treatment approach appears consistent with UK practice • Prontosan gel is the intervention in this study, while relevant to the scope, it is possible that Prontosan wound gel is not widely used in the UK **Funding/CoI** Not reported

Table 10: Posters/Abstracts

Study name and location	Design and intervention(s)	Participants	Interventions and Outcomes	EAC comments
Atkins (2018) Poster	Case Series/Review	N=12 patients with leg ulcers	**Intervention:** Prontosan solution used at each dressing change **Outcomes**: • Wound size • Presence of slough	• Unclear if retrospective or prospective • Small number of patients • Limited reporting of methodology and results
Cairns (2012) Poster	Case series/review.	N=15 patients (mixed aetiology wounds)	• Wound healing including wound area, depth, exudate and odour, pain severity, time to complete healing	• Unclear if retrospective or prospective • Small number of patients • Limited reporting of methodology and results
Collier (2016) Poster	Retrospective Evaluation of wound healing pathway	N=279 wounds	• Bacterial Counts	• Retrospective before and after review • Limited methodology information reported • Limited outcomes, may inform biofilm formation
Lindsten (2017) Abstract	Case series	N=6 patients with persistent chronic wounds after surgery for pilonidal sinus disease	• Complete healing • Change in wound size/depth	• Poster abstract with very limited information reported

Table 11: Studies included by company and excluded by the EAC

Study name and location	Design and intervention(s)	Participants	Outcomes	EAC comments
Collier (2017)	Meeting report	Hospital patients (all wounds in the acute trust)	Percentage change in frequency of Health Care Associated Infection (HCAI) for wounds and Surgical Site Infections (SSI)	The EAC has excluded this study for the following reasons: • Meeting Report, not a peer reviewed publication • Details of methods are not reported • Patient population details are not reported
Wilkins (2013)	Narrative literature review	Not reported	Classification of supporting evidence using AACP grading system	The EAC has excluded this study for the following reasons: • Purpose of the study was to evaluate the safety and efficacy of available wound cleaning agents and their ability to enhance wound healing in terms of quality of available evidence rather than specific data • Systematic searches were conducted but no data were reported • 3 studies which have been reviewed individually (Andriessen 2008; Horrocks 2006 and Romanelli 2010) • Remainder of the included studies were animal and in-vitro studies.

5 Clinical evidence review

5.1 *Overview of methodologies of all included studies*

Considering the evidence by wound type, the available studies can be grouped according to

- venous leg ulcers (3 RCTs; 1 comparative non RCT)
- burns (1 RCT; 1 comparative before and after study; 1 non-comparative retrospective case series)
- surgical site wounds (1 RCT)
- patients with wounds of mixed aetiologies (3 RCTs; 1 comparative before and after study; 6 non-comparative studies)

Venous leg ulcers

Four studies reported on venous leg ulcers, comprising 3 randomized trials (Borges 2018; Harding 2012; Romanelli 2010) and one non-randomized comparative study (Andriessen 2008). Three studies used Prontosan irrigation solution alone (Andriessen 2008, Borges 2018; Romanelli 2010) and one used Prontosan irrigation solution and Prontosan wound gel (Harding 2012). Use of Prontosan irrigation solution for wound cleansing is reflective of NHS practice however soak and application times varied across the studies including one study (Borges 2018) where patients were treated with 1 min irrigation under continuous pressure which the EAC considers may not be reflective of how wounds are cleansed in the NHS. Comparators in all four studies included saline however one study (Andriessen 2008) also included Ringer's solution which is not widely used in the NHS. Outcomes reported were all relevant to the decision problem and included wound closure/healing, assessment of bacterial load, presence of biofilm and wound infections.

Burns

Three studies reported on use of Prontosan in burn wounds, comprising 1 RCT (Wattanaploy 2017) and 2 non-comparative studies (Ciprandi 2018, Keifer 2018). A range of Pronotsan products were used in all studies. One study (Ciprandi 2018) used Prontosan irrigation solution, Prontosan wound gel and Prontosan wound gel x but did not report specific details of Prontosan use (e.g. soak times, dressing change frequency, combinations of Protnosan products). One study (Kiefer 2018) used Prontosan wound gel X. Neither study included a comparator group therefore they can only provide an overview of the effectiveness of Prontosan products in isolation. One randomized trial (Wattanaploy 2017) compared Prontosan wound gel X with silver sulphadiazine which although not included in the scope is used in the NHS for burn wounds and therefore a relevant comparator. Outcomes reported were all relevant to the decision problem however the extent to which outcomes from non-comparative studies are informative may be limited. Outcomes such as allergies, adverse reactions to Prontosan products, tolerability and safety provide and patient/clinician satisfaction give an oversight of the acceptability and safety of Prontosan. Outcomes such as healing time or wound infection will provide useful information on how well Prontosan works however will not facilitate any conclusions on whether use of Prontosan is more effective than saline or water.

Surgical Site Infections

One randomized controlled trial (Saleh 2016) reported on the use of Prontosan irrigation solution used as a soak. This study was excluded by the company but the EAC consider is to be relevant to the decision problem. The EAC note that although the study compares the use of Prontosan and saline soaked dressings, this treatment approach may have limited applicability to the NHS.

Wounds of mixed aetiologies

A total of 10 studies included patients with chronic wounds of mixed aetiologies. Two RCTs compared Prontosan with saline with one (Bellingeri 2016) comparing Prontosan irrigation solution and saline and one (Valenzuela

2008) comparing Prontosan gel with saline. One comparative cohort study (Assadian 2018) was excluded by the company as the use of Prontosan was outside the instructions for use with a single 20 minute wet-to-moist cleansing of wounds using either Prontosan irrigation solution or saline whereas the IFU's advise frequent use of Prontosan. The EAC agrees that the approach to wound cleansing in this study is likely to have limited applicability to the NHS however has included it as a reflection of the potential variation in practice of wound management.

The remaining studies were all non-comparative studies (Atkin 2020; Durante 2014; Horrocks 2016; Moller 2008; Moore 2016; Oropallo 2020; Ricci 2018). Prontosan irrigation solution alone was used in one study (Ricci 2018), Prontosan wound gel alone was used in one study (Durante 2014), a combination of Prontosan irrigation solution and Prontosan wound gel was used in three studies (Horrocks 2006, Oropallo 2020, Ricci 2018) and in the remaining studies the Prontosan products used were not specified (Moller 2008, Moore 2016).

Application of Prontosan varied across all studies in terms of length of soaks, cleansing approaches and dressing change frequencies. The EAC considers that the use of Prontosan irrigation solution or saline for irrigation followed by 10 minute soak as in Bellingeri (2016), Prontosan soak times of 5-10 minutes (Atkin 2020) and Prontosan soak times of 10 mins followed by gel if necessary (Horrocks 2006) to be most applicable to NHS practice.

Posters and Abstracts

An additional 4 posters (Atkin 2020; Cairns 2012; Collier 2016; Lindsten 2017) reported briefly on wound healing and infection outcomes however as the reporting of methodology and results is limited in detail, these posters have not been critically appraised and results are reported for information only.

5.2 *Critical appraisal of studies and review of company's critical appraisal*

The company submission included a critical appraisal of the included studies using recognised checklists (Cochrane Risk of Bias tool for randomized trials and CASP checklist for non-randomized studies). The EAC has reviewed the

company critical appraisals for each study and agree with the company overall assessment of the evidence quality.

Table 12 summarises the results of the company and EAC critical appraisal of study quality with full details reported in Appendix C. The EAC considers all studies to be relevant to the current decision problem however acknowledge that in each of the studies, there are elements which will limit the extent to which they are applicable to UK clinical practice.

Table 12: Summary of quality assessment of included studies

Study	Study Design	Wound type	EAC Comments	Conclusion
Andriessen (2008)	Comparative non-concurrent cohort study	Venous Leg Ulcers	Agree with company that low quality study. Note that comparator was either saline or Ringer's	**High risk of bias**
Assadian (2018)	Comparative prospective cohort	Mixed wound aetiology	Not included in company submission See Appendix C for detailed appraisal results	**High risk of bias**
Atkin (2020)	Non-comparative Secondary analysis	Mixed wound aetiology	Agree with company that low quality study	**High risk of bias**
Bellingeri (2016)	Comparative randomized controlled trial	Mixed wound aetiology	Agree with company that low RoB, tool does not assess power and this study still underpowered	**Low risk of bias**
Borges (2018)	Randomized trial	Venous Leg Ulcers	Not included in company submission See Appendix C for detailed appraisal results	**High risk of bias**
Ciprandi et al (2018)	Non-comparative retrospective data review (case series)	Burns	Agree with company that low quality study	**High risk of bias**
Durante (2014)	Non-comparative observational Study	Mixed wound aetiology	Agree with company that low quality study	**High risk of bias**
Harding et al (2012) NCT01153633	Pilot randomized trial	Venous leg ulcers	Assessed by company as Low Risk of Bias	**Some Concerns**
Horrocks (2006)	Non-comparative case series	Mixed wound aetiology	Agree with company that low quality study	**High risk of bias**
Kiefer et al (2018)	Prospective non comparative study	Burns	Agree with company that low quality study	**High risk of bias**
Möller, Nolte & Kaehn (2008)	Non-comparative case series	Mixed wound aetiology	Agree with company that low quality study	**High risk of bias**
Moore (2016)	Non-comparative case series	Mixed wound aetiology	Agree with company that low quality study	**High risk of bias**

Study	Study Design	Wound type	EAC Comments	Conclusion
Oropallo et al (unpublished, NCT03369756)	Non-comparative case series	Mixed wound aetiology	Agree with company that low quality study	**High risk of bias**
Ricci (2018)	Non-comparative case series	Mixed wound aetiology	Agree with company that low quality study	**High risk of bias**
Romanelli (2010)	Comparative Randomized controlled trial	Venous Leg Ulcers	Disagreed on some domains but the overall conclusion is same The EAC assumed in data extraction that analysis was per protocol and not ITT but no definitive information so change to 'unknown'	**Some concerns**
Saleh (2018)	Randomized trial	Surgical Site Wounds	Not included in company submission See Appendix C for detailed appraisal results	**Some Concerns**
Valenzuela (2008)	Comparative Randomized controlled trial	Mixed wound aetiology	Disagreed on some domains but the overall conclusion is same Note: add ITT analysis to data extraction table	**Some concerns**
Wattanaploy (2017)	Comparative Randomized controlled trial	Burns	Disagreed on some domains but the overall conclusion is same	**Some concerns**

Randomized Trials

The company submission noted that while randomized studies were generally low risk of bias, all included studies presented some concerns because of incomplete reporting, lack of blinding, lack of sample size calculations, and data collection methods. The EAC, while having some differences in judgements made about individual components within each study, concurred with the overall quality assessments made by the company (table 12 and Appendix C)

Two additional randomized trials (Assadian 2018; Borges 2018) included by the EAC were assessed using Cochrane Risk of Bias tool (Sterne 2019) and judged to be high risk of bias due to concerns relating to randomization process, changes from intended interventions, selection of reported results and missing outcome data. One randomized trial, not included in the company submission (Saleh 2016) was judged by the EAC overall as having some concerns arising from the randomization and blinding processes.

One unpublished study (Harding 2012) was critically appraised based on the unpublished clinical trial report provided by the company and was judged to have some concerns based on differences in baseline characteristics included the proportion of male and female participants and a variation in the length of leg ulceration history.

Non-randomized studies

The results of the company submission indicate that the studies assessed using CASP were all at high risk of bias and the EAC agrees with this assessment.

Overall Assessment of Quality

The EAC highlight some key points for consideration in relation to the quality of the included studies:

- Mixed study methodologies: the body of evidence comprises a range of study types including randomized trials and both prospective and retrospective non-randomized studies. Randomized trials would generally be considered to be higher quality studies however the randomized trials may be at risk of bias as a result of methodological, selection or reporting issues which will lower the overall robustness and quality of the study.

- Study sample sizes: Most of the included studies have small sample sizes and some of the larger randomized trials are underpowered which result in increased risk of bias. Consideration should be given to whether the sample sizes in the studies are reflective of the population as it is possible larger sample sizes would not be achievable.

- Interventions: Prontosan is not used consistently across the studies and not all use is reflective of NHS practice or in line with company instructions for use. Consideration should be given to how Prontosan is likely to be used in an NHS setting and whether any of the included studies provide relevant evidence.

- Outcomes: Outcomes are not always clearly reported and similar outcomes are reported differently across different studies making it difficult to make direct comparisons/draw conclusions across the evidence base though some limited grouping of results by wound type is possible.

5.3 *Results from the evidence base*

Overall, the results from the studies suggest that the use of Prontosan as a cleansing solution may have some positive impact on wound healing and management, particularly in chronic wounds although the extent of the benefit of using Prontosan versus saline cannot be determined with any certainty based on current evidence.

Considering the data by wound type indicates that results can be categorised according to wound type including venous leg ulcers, burns, pressure ulcers, surgical site wounds and mixed aetiology wounds. A summary of the results from each study is presented by wound type in table

Venous Leg Ulcers

Evidence for effectiveness of Prontosan in venous leg ulcers is taken from 2 randomized controlled trials (Borges 2018; Romanelli 2010) and 1 comparative study (Andriessen 2008) including a total of 196 adult patients. One unpublished pilot randomized trial (Harding 2012) randomized 34 patients (17 patients to each arm). One additional non-comparative study (Moore 2016) reported results for a subset of 16 venous leg ulcers. Results are summarized in table 13.

Wound Healing

One comparative, non-concurrent cohort study (Andriessen 2008) reported a *wound healing rate* of 97% (57/59 patients) for wounds cleansed with Prontosan solution for 15 minutes and 89% (47/53 patients) in the saline/Ringer's solution at 6 months ($p<0.0001$). *Mean time to healing* was significantly shorter in the Prontosan group compared with saline/Ringer's solution group (3.31 months versus 4.42 months respectively; $p<0.0001$) in 1 study (Andriessen 2008). Another study (Moore 2016) reported mean days to

closure of venous leg ulcers of 38±24 days in patients treated with Prontosan solution and/or gel, followed up to complete epithelialisation. One study (Romanelli 2010) reported no significant difference in *wound size* from baseline to study end (4 week treatment duration) between Prontosan solution and saline.

Results from one unpublished pilot RCT (Harding 2012) reported that (47.1%) 8/17 of wounds healed in the Prontosan group compared with 29.4% (5/17) with saline (P=0.4813), a treatment difference of -17.6% (95% CI -14.5-49.8). Percentage change in wound size was -60.30% (SE±12.18) with Prontosan compared to -45.48% (SE±12.18) with saline. Treatment difference is calculated at -14.82% (95% CI -49.82-20.35), (p=0.3968).

Wound Infection and factors associated with wound infection
One comparative, non-randomized study (Andriessen 2008) reported a *wound infection rate* of 3% (2/59) patients in the Prontosan group compared with 13% (7/53) in the saline/Ringer's solution group. One study (Romanelli 2010) reported significantly better control of *bacterial burden* in the Prontosan group compared with the saline group (p values not reported) whereas one study (Borges 2018) reported that both Prontosan and saline solutions reduced *bacterial load* but no significant difference was observed between the 2 groups.

One unpublished study (Harding 2012) indicated that the *infection rate* was 23.5% (4/17) in the Prontosan group compared with 17.6% (3/17) in the saline group. Mean *number of micro-organisms* post-treatment was 0.8 (SD 0.9) in the Prontosan group compared with 1.0 (SD 0.8) in the saline group.

Pain
One randomized trial (Romanelli 2010) reported significantly better pain control at 4 weeks in patients treated with Prontosan solution compared with saline solution ($p<0.05$).

One unpublished study (Harding 2012) reported a reduction in pain score of -9.5 (SD 19.5) in the Prontosan group and -9.0 (SD 23.6) in the saline group.

Table 13: Summary of Results for Venous Leg ulcers

	Wound Healing	Wound infection and outcomes associated with infection	Pain
Andriessen (2008)	At 6 months 97% (57/59) of wounds in Prontosan group were healed compared to 89% (47/53) in saline/Ringer's group (p<0.0001) Mean time to healing was 3.31 months (SE 0.17) with Prontosan versus 4.42 months (SE 0.19) with saline/Ringer's solution (p<0.0001)	*Wound infection* 3% (2/59) in the Prontosan group and 13% (7/53) in the saline/Ringer's group experienced infection	Not Reported
Borges (2018)	Not Reported	*Bacterial Load (CFUs/g)* After a single irrigation both Prontosan and saline reduced the bacterial load compared with baseline but there was no significant difference in reduction of bacterial load between solutions.	Not Reported
Romanelli (2010)	Wound size did not differ significantly between the 2 groups (Prontosan and Saline) from baseline to study end	*Bacterial Burden* Prontosan group showed significantly better control of bacterial burden at the end of the study (p values not reported)	Significantly better pain control at 4 weeks in patients treated with Prontosan solution compared with saline solution (p<0.05)
Moore (2016) Subset reporting based on 16 venous leg ulcers	Mean days to wound closure: • 38±24 days for venous leg ulcers Mean change in absolute wound area: • 198±256 $mm^2$for venous leg ulcers	Not Reported	Not Reported
Harding (2012) UNPUBLISHED	ITT: Prontosan group;n=8/17 (47.1%) wounds healed. Saline group n=5/17 (29.4%) (P=0.4813),a treatment difference of -17.6 (95% CI -14.5-49.8).	IIT Prontosan n=4/17 (23.5%), Saline n= 3/17 (17.6%) control group Number of different microorganisms post-treatment (mean)	Change in pain (VAS score) (mean) PPS PPS: Prontosan: -8.9 (SD=20.4) Saline: -12.8 (SD=26.0) ITT: Prontosan: -9.5 (SD=19.5) Saline: -9.0 (SD=23.6)

	Wound Healing	Wound infection and outcomes associated with infection	Pain
		PPS Prontosan: 0.8 (SD=0.9) Saline: 1.0 (SD=0.8)	

Burns

Evidence for effectiveness of Prontosan in burn wounds is taken from 1 randomized controlled trial (Wattanaploy 2017) and 2 non-comparative case series studies (Ciprandi 2018; Kiefer 2018). One additional study (Moore 2016) reported results for a subset of 7 burn wounds (10%). None of the studies were based in the UK although one multi-centre study (Ciprandi 2018) included 20 patients (10.1%) from the UK. Results relating to burns are summarized in table 14.

The evidence for effectiveness of Prontosan wound gel X compared to silver sulfadiazine in healing burn wounds and wound infections suggests no significant difference. The evidence suggests that Prontosan wound gel X leads to improved pain control compared to silver sulfadiazine. This evidence cannot be considered to have a high degree of certainty because it is based on 1 randomized trial with only 46 patients.

The effectiveness of Prontosan in burns is likely to be dependent on several factors including choice of comparator, approach to Prontosan use, severity of burn wounds and impact of any additional treatments.

Wound Healing

One randomized trial including 46 patients with partial thickness burn wounds (Wattanaploy 2017) treated with Prontosan wound gel X or silver sulfadiazine reported that *time to healing* was 17.8±2.2 days with Prontosan wound gel X compared with 18.8 days±2.1 days with silver sulfadiazine (p=0.13).

One non-comparative study (Kiefer 2018) in which 56 patients with burn wounds requiring surgical debridement followed by split thickness skin graft reported that 27.5% of patients showed *complete graft take* on post-operative day 5 and a median time to *complete re-epithelialization* of 7±0.2 days (95%

CI, 5-9 days). *Time to complete re-epithelialization* did not depend on wound size at baseline (p=0.92).

One non-comparative study (Ciprandi 2018) in which 198 children were treated with any combination of Prontosan solution and gels reported that *healing time* for burn wounds differed depending on total burn surface area however it was not clear whether the values presented were means or medians.

One non-comparative study (Moore 2016) reported a *mean time to healing* of 44±17 days for a subset of burns (n=7).

Wound Infection and factors associated with wound infection
One randomized trial (Wattanaploy 2017) reported 6 patients (26.1%) in each group (Prontosan wound gel X and silver sulfadiazine) had positive surface swab culture without signs/symptoms of *wound infection* but routine swab cultures a week later were negative.

One non-comparative study (Ciprandi 2018) reported that 16 patients had clinical signs of *wound infection* with 11/16 developing clinical signs of infection during treatment and antibiotics given to 8/11. It should be noted that 5 patients had clinical signs of infection before treatment. No changes were made to the treatment plan because of clinical signs of infection and Prontosan use continued.

One non-comparative study (Kiefer 2018) reported no *wound infections* in 56 patients.

Treatment Satisfaction
Results from one randomized trial (Wattanaploy 2017) stated that staff consistently reported Prontosan was easier to use when changing dressings and wound dressing was easier to evaluate with Prontosan. One non-comparative study (Ciprandi 2018) reported that 73.2% of physicians were satisfied with Prontosan, 16.2% considered it ‘good’ and 10.6% considered it ‘very good’.

Patients also reported being satisfied with Prontosan but the study did not report on how this compared with saline (Wattanaploy 2017).

Table 14:Summary of Results for Burns

Study	Wound Healing	Wound infection and associated factors	Pain	Treatment Satisfaction
Ciprandi (2018)	Healing time (not clear if mean, median or other) was • 11.5 days for TBSA < 5% • 15 days for TBSA 5-19% • 8.5 days for superficial burns • 10.9 days for superficial, partial thickness burns • 13.5 days for deep partial thickness burns • 17.2 days for full thickness burns	16 patients had clinical signs of infection during treatment with 11/16 developing clinical signs of infection during treatment and antibiotics given to 8/11. No treatment changes resulted due to clinical signs of infection and Prontosan use continued.	Not Reported	73.2% of physicians were satisfied with Prontosan, 16.2% considered it good and 10.6% considered it very good
Kiefer (2018)	14 patients (27.5%) showed complete graft take on post-operative day 5. Median time to complete re-epithelialisation was 7 days (mean 7.1±0.2; 95% CI, 5-9 days) Time to complete re-epithelialisation did not depend on wound size at baseline (p=0.92)	No wound infections were reported	Changes in pain over time showed a monotonic trend (p<0.01) Changes from baseline was not significant in 2 centres but significant in one centre (p=0.01)	Not Reported
Wattanaploy (2017)	All patients showed complete epithelialisation of wounds within 3 weeks. Time to healing did not differ significantly between the groups: 17.8±2.2 days (Prontosan) compared with 18.8 days±2.1 days (silver sulphadiazine); p=0.13.	No infections reported 6 patients (26.1%) in each group had positive surface swab culture without signs/symptoms of infection. Routine swab cultures a week later were negative	Pain score was significantly less in the Prontosan group at 4 to 9 days and 12 days after treatment (p<0.05) but not on any other treatment day.	Staff consistently reported • Prontosan was easier to use when changing dressings • Wound dressing was easier to evaluate with Prontosan Patients reported being

Study	Wound Healing	Wound infection and associated factors	Pain	Treatment Satisfaction
				satisfied with Prontosan
Moore (2016) Subset reporting based on 7 burn wounds	Mean days to wound closure: • 44±17 days for burns Mean change in absolute wound area: • 449±507 $mm^2$for burns	Not Reported	Not Reported	Not Reported

Surgical Site Wounds

Evidence for effectiveness of Prontosan solution compared to sterile water for surgical site wounds is taken from one randomized trial including only 40 patients with skin malignancies excised (Saleh 2020). One additional non-comparative study (Moore 2016) reported outcomes for a subset of surgical wounds (19 wounds). Results for surgical site wounds are summarized in table 15.

Wound Healing

One study non-comparative study (Moore 2016) reported a *mean time to wound closure* of 67±38 days for surgical wounds (based on 19 surgical wounds).

Wound Infection and factors associated with wound infection

One randomized trial (Saleh 2020) reported a statistically significantly higher rate of infection in the Prontosan group, with 8 wounds in the Prontosan group *assessed as infected* compared with 2 in the sterile water group (p=0.028). One non-comparative study (Moore 2016) reported that *antimicrobial therapy* was initiated in 10.9% of patients all in the surgical and trauma categories but does not report the results separately.

Table 15: Summary of Results for Surgical Site Wounds

Study	Wound Healing	Wound infection and associated factors
Saleh (2020)	Not Reported	No significant difference in bacterial load levels measured • before surgery

Study	Wound Healing	Wound infection and associated factors
		• end of surgery • at 1 week after surgery 10 wounds were assessed as infected of which 8 were in the intervention (Prontosan) group giving a statistically significantly higher rate of infection (p=0.028)
Moore (2016) Subset reporting based on 19 surgical wounds	Mean days to wound closure: • 67±38 days for surgical wounds Mean change in absolute wound area: • 2170±5501 mm^2 for surgical wounds	Not Reported

Patients with Chronic Wounds of Mixed Aetiology

Evidence for effectiveness of Prontosan compared with saline or water for mixed aetiology wounds is taken from 2 randomized trials (Bellingeri 2016, Valenzuela 2008), one comparative, non-randomized study (Assadian 2018) and 6 non-comparative studies (Atkin 2020, Durante 2014; Horrocks 2006, Möller 2018, Moore 2016; Ricci 2018).

Wound types encompassed in the studies included vascular ulcers, pressure ulcers, diabetic foot ulcers, burns, trauma wounds and surgical wounds. A summary of results is reported in table 16.

Wound Healing

One randomized trial (Bellingeri 2016) comparing 10-minute soak with Prontosan to 10-minute soak with saline reported significant reductions in total Bates-Jensen Wound Assessment Tool (BWAT) scores between baseline (T0) and day 28 (T4) indicating *better progression of wounds* in the Prontosan group compared with the saline group (p=0.0248).

One study (Ricci 2018) reported that cleansing with a single application of Prontosan solution for 2 mins or 5 mins had no impact on *wound bed score* (reduction in score indicates improvement) compared with baseline. Cleansing for 10 minutes resulted in reductions in score in 4/10 cases and cleansing for 15 minutes resulted in reductions in 5/10 cases. In patients

treated with 10-minute soak, 23/30 patients showed reduction in wound bed score, with 6 unchanged and 1 worsening. In patients treated over 14 days with daily 10 min applications, 26 patients showed improvement in wound bed scores and 3 remained unchanged.

One non-comparative case series (Moore 2018) reported *mean days to wound closure* and *mean change in absolute wound area* by wound type: 34±22 days and 545±697 mm^2 for trauma wounds, 91±26 days and 850±1207 mm^2 for diabetic ulcers and 44±17 days and 552±726 mm^2 for pressure ulcers.

One non-comparative case series (Atkin 2020) reported *complete healing* in 12 wounds (10 treated with solution and gel, 2 treated with solution alone) with 26.1% of wounds healed within 2 months. In 5 wounds a >90% reduction in *wound area* was reported within 3-6 months with a *mean wound size reduction* of 75.6%.

One non-comparative case series (Horrocks 2006) reported that 7/10 patients showed *dramatic improvements* in wounds within 3 weeks with 6/7 patients no longer requiring use of silver products or antibiotics.

One randomized trial comparing use of Prontosan wound gel with saline for wound cleansing (Valenzuela 2008) reported *mean absolute reduction in lesion size* of 19.71cm^2 (95% CI: 3.79-24.31) with Prontosan gel compared 5.65cm^2 (95% CI -0.17 to 11.47) with saline (p=0.013). *Mean percentage reduction* in the Prontosan group was 43.64% ± 35.07% compared with 17.3%±35.07% in the saline group (p=0.000).

One non-comparative study (Durante 2014) reported significant *reduction in wound size* following introduction of Prontosan wound gel including significant reductions in maximum wound length, minimum wound length and wound area (all p<0.0001).

Wound Infections and factors associated with wound infection

One randomized trial (Assadian 2018) reported no significant reduction in *bacterial bioburden* when using either saline (p=0.761) or Prontosan solution (p=0.051) during a 20-minute wet to moist irrigation.

One non-comparative study (Durante 2014) reported that patients with presence of *biofilm* reduced from 23.4% at baseline to 1.6% at final visit and that 74% of wounds were *non-exuding* at final visit compared with 14.5% at baseline. One study (Ricci 2018) reported that no patient had an *infection score* higher than 2 positive signs on enrolment with 4 patients scoring 2, 16 patients scoring 1 and 12 patients scoring 0 upon enrolment. At the end of 14 days observation, the number of patients scoring 1 or 2 had decreased (1 patient scored 2 and 5 patients scored 1), with infection signs overall decreased by day 14 and most patients scoring 0.

One non-comparative case series (Möller 2018) reported that 41% of patients had *wound infections* at outset of treatment with Prontosan solution and wound gel but did not report outcomes for these infected wounds. The study reported that during treatment with Prontosan, 3% of wounds developed infections compared with 40% before Prontosan was used. One non-comparative case series (Atkin 2020) reported outcomes related to infection including odour, exudate and slough. Results reported that *odour* improved in 5/6 wounds evaluated with 3 reporting complete resolution. Improvement in *exudate* in 20/20 wounds with 10 fully resolved and *slough* was removed in 16/16 wounds.

Pain

One randomized trial reported an *average pain score* of 3.0 (measured using Visual Analgue Scale (VAS)) with minimal change during 28 day follow up for both groups (Bellingeri 2016).

One non-comparative study (Durante 2014) reported significant reductions in *average pain scores* from baseline to final visit on both VAS (4.67±2.7; 95% CI -5.36 to – 3.98 (p<0.0001)) and Face, Legs, Activity, Cry, Consolability (FLACC) scale (-12±4; 95% CI -10.22 to -7.75 (p<0.00005)) indicating improvement in pain. One comparative before and after study (Ricci 2018)

reported an average reduction in pain scores of 47% after introduction of Prontosan. In one non-comparative case series (Horrocks 2006) all patients reported elimination or reduction of wound pain.

Dressing Changes

From 1 non-comparative study (Atkin 2020) based on data from 27% of wounds (n=14), of which 13 were treated with Prontosan solution plus gel, *dressings changes* occurred an average of 4.68 times per week (SD 2.14) before treatment and 2.25 times per week (SD 0.88) after treatment. The *mean reduction* in dressing change frequency was 55% and reduction was observed an average of 16.5 days after treatment began.

Quality of Life

From 1 non-comparative study (Atkin 2020) 10 patients indicated improvements in quality of life, 7 patients reported improvements in mobility during course of treatment and psychological improvements were noted including improved morale, resumption of social activities, ability to engage in family life, going abroad, attending social activities.

One unpublished non-comparative study (Oropallo 2020) assessed quality of life using the Wound QoL Subscore: Body Dimension administered weekly to cover 4 weeks of treatment. Details reported on clinicaltrials.gov suggest that mean global scores decreased from 2.41 (SD 0.99) to 1.30 (SD 0.87), mean body dimension subscore decreased from -0.76 (SD 1.15) to -1.17 (SD 1.21), mean Psyche Dimension subscore decreased from -0.77 (SD 1.12) to -1.26 (SD 1.14) and mean everyday life subscore decreased from -0.58 (SD 1.05) to -1.00 (SD 0.99) indicating an improvement in QoL from baseline to week 5. As yet unpublished results suggest [redacted] in all QoL measures from baseline to the final measurement 4 weeks later: Global Wound-QoL score [redacted] Body Wound-QoL sub-score [redacted] Psyche Wound-QoL sub-score [redacted] and in Everyday Life Wound-QoL [redacted].

Table 16: Summary of results for chronic wounds of mixed aetiology

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
Assadian (2018)	Not Reported	*Reduction of bacterial bioburden after a single application* • Using 0.9% NaCL (saline) did not significantly reduce the planktonic bacterial burden on wounds (p=0.761). • Using Prontosan did not significantly reduce the bacterial burden (p=0.051)	Not Reported	Not Reported	Not Reported

Atkin (2020)	N=23 wounds included in analysis (n=77 wounds not followed up)
	• Complete healing in 12 wounds (10 treated with solution and gel; 2 with solution alone
	• 26.1% of healed wounds were healed within 2 months
	• Of the remaining 11 wounds, 8 demonstrated improvements and
		Malodour, exudate, slough
		• 5/6 wounds (1 not followed up) reported improvements in odour with 3 reporting resolution
		• 20/20 wounds reported improvement in exudate with 10/20 fully resolved
		• 16/16 wounds reported slough removed
			Pain was reported for 21 wounds prior to PHMB/Betaine.
			• 18 (86%) reported reduction in pain of which 2 were pain free
			• 2 patients previously unable to tolerate compression for leg ulcers were able to initiate compression
			• 3 wounds were not followed up
				Data for 14 (27%) wounds (13 solution + gel).
				• Before treatment, dressings were changed an average of 4.68 times per week (SD 2.14)
				• Follow-up data for 6 wounds indicated a
					• N=10 patients indicated improvements in QoL
					• 7 patients reported improvements in mobility during course of treatment
					• Psychological improvements were noted including
					  ○ Improved morale
					  ○ Resumption of social activities
					  ○ Able to engage in family life
					  ○ Go abroad

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
	wound size reduction and 3 had no details Wound area outcomes reported for 8 wounds • >90% reduction observed in 5 wounds within 3-6 months • Mean wound size reduction of 75.6% *Initial Improvements* N=33 (63%) wounds, for others only endpoint data available. • Earliest initial improvement was observed within 2 days in the solution + gel group and within 4 weeks in the solution alone group Considering both groups together, initial wound improvements were observed • Within 1 week for 19% (10/52) of wounds • By week 4 for 63% (33/52) of wounds		• 1 wound reported increased pain and stopped treatment. • 8 patients used pain medication at outset with 4 reducing their use and 2 stopping medication	mean reduction in dressing change frequency of 55% • After treatment dressing change frequency was 2.25 times per week (SD 0.88) • Reduction was observed an average of 16.5 days (SD 8.8) after treatment started	Attend social activities

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
Bellingeri (2016)	*Wound Improvement* Significant changes between T0 (baseline) and T4 (day 28) observed for: • Reduction in total BWAT score of overall wound evolution indicating better progression of wounds in the Prontosan group compared with the saline group (p=0.0248) • Reduction in average total BWAT score was significantly better at T4 versus T0 in the Prontosan group • BWAT average inflammatory score indicates a significantly better progression of wounds in the Prontosan group (p=0.03) • Reduction in the average BWAT scores for inflammatory signs that was significantly better at T4 than at T0 in the Prontosan group (n p-value)	Not Reported	Pain scores were similar for both groups Average score was 3.0 Minimal to no change during follow-up No significant difference in pain associated with study wounds or dressing changes or in pain suffered between dressing changes	Not Reported	Not Reported

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
Durante (2014)	*Wound size* Significant reduction in mean • Maximum length: -17.5±21.4cm (p<0.0001) • Minimum length: -15.5±21.1cm (p<0.0001) • Wound area: -8.3±16.7cm^2 (p=0.0001) *Wound bed improvement* • Patients with increase in re-epithislializing wounds from 0.8% at baseline to 26.6% at final visit • Patients with intact periwound skin increased from 17.7% to 75.8% and intact wound edges from 28.2% to 75.8%	• Patients with presence of biofilm reduced from 23.4% at baseline to 1.6% at final visit • 74% of wounds were non-exuding at final visit compared with 14.5% at baseline	Average VAS/FLACC score decreased from baseline to final visit: • VAS: -4.67±2.7; 95% CI -5.36 to – 3.98 (p<0.0001) • FLACC: -12±4; 95% CI -10.22 to -7.75 (p<0.00005)	Not Reported	Not Reported
Horrocks (2006)	7/10 patients showed dramatic improvements within 3 weeks with 6/7 no longer requiring use of silver products or antibiotics	Elimination of biofilm and reduction of exudate levels were reported by staff Previously malodourous wounds had no odour	All patients reported elimination or reduction in wound pain	Visits by community nurses reduced from daily to alternate days or twice weekly visits	All patients reported that the use of Prontosan irrigation and Prontosan gel in the care and management of their chronic wounds resulted in significant improvements to the quality of their lives.

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
Möller (2018)	3% of the wounds did not improve or deteriorated with the treatment. The other 97% had a good cleansing result with improved findings. 80% of these wounds had wound closure.	At treatment outset, • 41% of patients had wound infection • 11% had heavily contaminated wounds These patients were given systemic antibiotics as well as combination treatment. • 8% of patients were given infection treatment prophylactically • Two thirds of patients with diabetic foot had wound infections at treatment outset but these persisted for maximum 5 days after treatment • 3% developed infection during treatment compared with 40% before the use of Prontosan • 620/953 patients reported a great or complete improvement in wound odour	Not Reported	Not Reported	Not Reported
Moore (2016)	*Wound Closure* Days to wound closure varied according to aetiology:	• Antimicrobial therapy was initiated in 5/49 (10.2%) patients, all in surgical and trauma categories.	Not Reported	Not Reported	Not Reported

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
	Mean days to wound closure: • 67±38 days for surgical wounds • 34±22 days for trauma wounds • 38±24 days for venous leg ulcers • 44±17 days for burns • 91±26 days for diabetic ulcers • 44±17 days for pressure ulcers *Wound Area* Change in absolute wound area varied on aetiology: Mean change in absolute wound area: • 2170±5501 mm^2 for surgical wounds • 545±697 mm^2 for trauma wounds • 198±256 mm^2 for venous leg ulcers • 449±507 mm^2 for burns • 850±1207 mm^2 for diabetic foot ulcer • 552±726 mm^2 pressure ulcer				

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
Ricci (2018)	*Wound Bed Score* *Group A- single application of Prontosan* 2 patients had wound related injuries: 1 periwound inflammation 29 days after initial Prontosan administration and 1 periwound itchiness 71 days after Prontosan administration *Group B – daily application for 14 days* • 16 cases were classified as B at enrolment. 12 cases had evolved from B to A, 3 remained unchanged, 1 worsened from B to C • 14 cases were classified as C at enrolment. 2 evolved to A, 9 to B and 3 remained unchanged. • Exudate scores were unchanged	*Group B – daily application for 14 days* No patient had a score higher than 2 on enrolment At the end of observation, 1 patient recorded 2 positive signs and 5 cases reported 1 positive sign of infection	Pain score was evaluated in 26 patients and showed an average reduction of 47%	Not Reported	Not Reported

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
	Improvement in the parameter of periwound skin was observed in 29/30 cases and worsened in one case				
Valenzuela (2008)	*Lesion Size* Mean absolute reduction was 19.71cm^2 (95% CI: 3.79-24.31) with Prontosan and 5.65cm^2 (95% CI -0.17 to 11.47) in the control group (p=0.013) Mean percentage reduction in the Prontosan group was 43.64% ± 35.07% compared with 17.3%±35.07% in the control group (p=0.000). Surface of lesion decreased significantly from baseline in the Prontosan group compared with control group (p=0.013) % granulation tissue increased significantly from baseline in the Prontosan	*Mincrobiological Cultures* No significant difference between the groups at the beginning of the study (p value not reported). There were significant variations in the cultures between the groups (p=0.004). Note, the EAC is unclear what result this is reporting due to the translation. % slough reduced significantly from baseline compared with the control group (p=0.002) % purulent exudate reduced significantly from baseline in the Prontosan group compared with control group (p=0.005)	Prontosan group Baseline: 50 (65.8%) 2 weeks: 15 (20.3%) Control group Baseline: 36 (57.1%) 2 weeks: 20 (35.7%) No significant difference between the intervention and control group (p=0.049).	Not Reported	Not Reported

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
	group compared with the control group (p=0.001)				
Oropallo (2020)	Pre debridement change in wound size from week 1 to week 5 = -6.6cm^2 ±18.3 (35 participants analysed) Post debridement change in wound size from week 1 to week 5 = -8.2cm^2 ±19.2 (31 participants analysed)				• Mean global scores decreased from 2.41 (SD 0.99) to 1.30 (SD 0.87) • Mean body dimension subscore decreased from -0.76 (SD 1.15) to -1.17 (SD 1.21), • Mean Psyche Dimension subscore decreased from -0.77 (SD 1.12) to -1.26 (SD 1.14) • Mean everyday life subscore decreased from -0.58 (SD 1.05) to -1.00 (SD 0.99) indicating an improvement in QoL from baseline to week 5. As yet unpublished results suggest [redacted] in all QoL measures from baseline to the final measurement 4 weeks later: • Global Wound-QoL score [redacted], • Body Wound-QoL sub-score [redacted],

Study	Wound Healing	Wound infection and associated factors	Pain	Dressing Changes	Quality of Life
					• Psyche Wound-QoL sub-score [redacted]. In Everyday Life Wound-QoL [redacted].

6 Adverse events

The EAC searched the MHRA's field safety notices and medical device alerts and no adverse events were identified. The MAUDE (FDA) database was searched and 61 adverse events were identified of which 20 were duplicate entries, giving a total of 41 unique reports. The company reported no adverse events in the MHRA safety notices and 40 unique incident reports in the MAUDE database. The discrepancy is likely due to a difference in search dates. Results for adverse events searches are summarized in table17.

Two studies reported no adverse events with Prontosan products (Bellingeri 2016; Durante 2014). One study reported adverse events in 5 children including itching, rashes and hypergranulating tissue with Prontosan use (Ciprandi 2018), one study reported a mild burning sensation in 1% of patients (Moller 2018) and one study reported that 2 patients had wound related injuries: 1 periwound inflammation 29 days after initial Prontosan administration and 1 periwound itchiness 71 days after Prontosan administration (Moore 2016). One unpublished study (Harding 2012) reported that the rate of adverse events was comparable between Prontosan and Saline and the most common adverse events were skin and subcutaneous tissue disorders.

Table 17: Summary of Adverse Events

Device Problem	N	EAC Comment
Patient – Device incompatibility	23	Symptoms experienced by patients included: • skin reactions such as itching or tingling, skin rash/flushing, swelling or blisters • reduced blood pressure, palpitations, cardiac/cardiorespiratory arrest, hyper tension
Adverse event without identified device or use problem	15	• Prontosan used for all patients but not identified as the cause of the reaction. • Symptoms experienced by patients included rash, itching, burning sensations and anaphylaxis
Use of Device Problem; Improper or Incorrect Procedure or Method	3	• Mix-up concerning diluting agent • Accidental injection of the product • White/yellow slough formation

7 Evidence synthesis and meta-analysis

The EAC considered the data to be heterogeneous and therefore do not consider it appropriate to conduct a meta-analysis.

8 Interpretation of the clinical evidence

A considerable volume of evidence including evidence from several randomized trials was available to address the decision problem and the EAC and company submissions were broadly in agreement as to which studies provided the most relevant evidence.

Although there are weaknesses in the evidence, the EAC considers that based on the current available evidence the use of Prontosan products for chronic wound management is supported. The evidence for whether Prontosan products are more effective than water or saline however is limited.

Adverse events are rare and easily managed and the EAC does not consider there to be safety concerns provided clinical staff are aware of the contraindications as outlined in the instructions for use.

The evidence for acute wounds is very limited and therefore less certain though there is some evidence that using Prontosan for burn wounds is beneficial.

The evidence for improved wound healing, although uncertain, suggests that using Prontosan may result in better wound healing rates, shorter time to healing and reduced infection, however this may depend on how the outcome wound healing is measured and over what follow-up duration as well as how Prontosan solution is used. It is important to note that Prontosan itself does not treat infections and any impact on infection rates is likely the result of the cleansing effect of Prontosan and shorter times to healing. Use of Prontosan does appear to improve pain management and control compared with saline and it is important to consider the impact of this on patient well-being.

The EAC considered the strength of the evidence to be limited with only 1 RCT (Bellingeri 2018) at low risk of bias. The remaining RCTs were judged to

have a high risk of bias or to have some concerns indicating a possible high risk of bias.

Three studies were conducted in the UK and one study (Ciprandi 2017) included patients from the UK. Although the remaining studies are not UK based, the EAC considered that the results would be generalisable to the UK setting as in all cases the population, settings and wound types and the approach to wound management are in line with how clinical experts have described UK practice. Clinical expert input suggests that chronic wound management approaches are likely to be similar regardless of wound aetiology therefore the EAC considers that results from studies including patients with wounds from mixed aetiologies are broadly generalisable while acknowledging some limitations. The main area of concern around generalisability of the evidence is likely to relate to how Prontosan products are used (e.g. soak times, until complete wound healing) and in what combination (i.e. Prontosan solution, Prontosan gel or both). The EAC considers that the variability in approaches noted in the evidence is likely to reflect the natural variability in management approaches in the NHS that arise from necessary clinical judgements made when managing and treating chronic wounds.

Table 18 summarises the company claimed benefits and EAC interpretation of whether these have been met.

Table 18: Evidence for Claimed Benefits of Prontosan

Claimed benefit/ benefit observed in literature	Rationale	EAC Comment
Improved wound bed condition: reduced wound odour, exudate and slough etc.	Chronic wounds are often stuck the inflammatory phase of healing, with poor wound bed condition e.g. low amounts of granulation tissue and increased exudate levels, slough and signs of inflammation. Studies report rapid improved wound bed condition (reduced slough, odour, exudate and improved granulation etc.) following Prontosan treatment compared with saline/Ringer's treatment. Demonstrated in 2 RCT's, with other non-comparative studies	This claim is partially supported by the evidence. The quality of the evidence informing these outcomes in variable. Mix of RCTs and observational studies

	also demonstrating rapid improvement in wound bed condition once wounds move onto using Prontosan for wound cleansing as part of wound bed preparation.	Overall, Prontosan appears to improve wound condition however the evidence for whether it is better than saline/water is less certain
More rapid wound healing and high healing rate, wound size reduction	Chronic wounds can persist for many months, even years, becoming stalled often in the inflammatory phase. Wounds progressing to healing show increased granulation tissue and show reduced wound size over a period of time. Prontosan has been demonstrated in studies to have higher, and faster, rates of wound healing compared with saline/Ringer's solution. In other studies with wounds of long duration a high and rapid healing rate, reduced wound size and increased epithelisation is observed after treatment with Prontosan.	This claim is partially supported by the evidence. The quality of the evidence informing these outcomes in variable. Mix of RCTs and observational studies Overall, Prontosan appears to improve wound condition however the evidence for whether it is better than saline/water is less certain
Reduced infection rate/ markers of infection	Chronic wounds are at higher risk of infection, due to the duration of being unhealed, poor wound condition and biofilm formation and maturation among other factors. Compared with saline, wounds treated with Prontosan have been shown to have fewer infections in comparative studies. Implementation of Prontosan as standard practice in a UK hospital was linked with a 92% reduction in hospital acquired wound infections in the Trust. In burns low infection rates following treatment with Prontosan are reported.	This claim is partially supported by the evidence. The quality of the evidence informing these outcomes in variable. Mix of RCTs and observational studies Overall, Prontosan appears to improve wound condition however the evidence for whether it is better than saline/water is less certain
Pain reduction	Pain is frequently reported in patients with chronic wounds. In comparative studies with saline, pain was reported to be reduced following Prontosan treatment. In other studies with wounds of long duration initial wound pain was reported to be reduced or resolved after commencing treatment with Prontosan.	This claim is partially supported by the evidence. Limited evidence suggests that pain management is improved with use of Prontosan
General improvement to quality of life e.g. improved mobility and socialising.	Chronic wounds have a negative impact on patient quality of life. Pain, high levels of exudate and malodour can result in patients limiting social activities, being anxious and having their days revolve around dressing changes. In the elderly, a chronic wound can be debilitating and significantly interfere with how they self-care (Benbow 2008). Prontosan, by improving wound bed	This claim is partially supported by the evidence. Limited evidence suggests that patients report improved quality of life when wounds are treated with Prontosan.

	preparation, reduces: pain, excessive exudate, slough and malodour - positively impacting patients' quality of life. [redacted] in numerous case studies patients and healthcare workers report positive changes to patients' ability to socialise and recommence recreational activities after treatment with Prontosan.	This appears to be due to improvements in wound condition.
More effective than saline	Standard habitual practice is to irrigate wounds with saline at dressing change. Multiple comparison studies demonstrate improved wound bed condition, wound healing rate and more rapid wound healing when wounds are treated with Prontosan compared with saline. As standard practice is to irrigate with saline at dressing change non-comparative studies reporting on the introduction of Prontosan therefore demonstrate the impact of moving from saline irrigation to Prontosan; reporting improved wound bed condition, wound healing rate and more rapid wound healing, reduced pain and markers of infection.	This claim is partially supported by the evidence. The evidence for Prontosan versus saline is limited and at high risk of bias.
Freeing up nursing time to care and Reduce resource use: Nursing visits, dressing change frequency and medications and consumables Due to: • Faster wound healing time • High healing rate • Reduced exudate • Reduced pain	The action of Prontosan on slough, wound debris and biofilm improves the wound bed condition; reducing pain, excessive exudate and resulting in more rapid wound healing and a higher rate of healing. Reduced exudate and improved wound condition reduces the number and frequency of dressing changes required (Vowden et al. 2015; Tickle 2015). Improved wound healing and reduced time to healing directly reduces resource use such as nursing time and consumables such as dressings. Analgesic use reduction as a result of reduced pain, as measure by patients; and reduced need for systematic antibiotics due to reduced infection risk and rate.	This claim is partially supported This claim is not directly supported by the clinical evidence. None of the studies reported on the impact of Prontosan use on nurse time. The economic modelling is based on a shorter time to healing in the Prontosan arm resulting in fewer visits and reduced staff costs.

Reducing resource use and nursing visits by: • Faster wound healing time • High healing rate • Reduced dressing changes • Reduced excessive exudate resulting in reduced use of consumable items per nurse visit, dressings etc.	More rapid wound healing reduces nursing visits required to manage chronic wounds. In the UK 37.5 million primary care appointments are attributable to wounds (Guest et al. 2015) – this figure has recently been updated to in excess of 82 million in an updated paper (Guest et al. 2020). Improved wound bed condition, such as reduction in excessive exudate and malodour, reduces the need for additional dressing changes to manage poor wound condition. The resource impact of managing chronic wounds in the UK has been documented widely documented (Guest et al. 2017; Guest et al. 2018a; Guest et al. 2018c; Guest et al. 2015; Guest et al. 2020) Prontosan improves wound bed condition, reduces exudate and odour and promotes wound healing which allow for reduced dressing change frequencies, overall nursing visits and associated consumables and costs.	This claim is partially supported This claim is not directly supported by the clinical evidence. None of the studies report on nurse time or resource use. The economic modelling is based on a shorter time to healing in the Prontosan arm resulting in fewer visits and reduced staff costs and a reduction in total consumables. The economic models do not include any reduction in the consumables used per visit.
Reduced cost of additional medication reduced: analgesia, antibiotics and antimicrobial dressings	Reduced pain and reduced markers of infection can reduce the need for prescription analgesics, antibiotics and advanced antimicrobial wound dressings e.g. silver-containing dressings.	This claim is not supported by the evidence.
Improved sustainability through reduced treatment duration, fewer clinical appointment and the associated consumables (e.g. aprons, gloves, gauze and dressing etc), reduced medication wrappings.	The annual prevalence of chronic wounds is growing at the rate of 12% (Guest and Vowden 2017), increasing the burden of wound care on NHS resources; recent data has shown an increase in the prevalence of wounds by 71% over 5 years with the annual costs to the NHS of managing wounds increasing at a rate of 8-9% per annum, representing a 48% increase over 5 years (Guest et al. 2020). Faster and higher healing rates will help offset this increasing burden by overall reducing the number of clinical visits and the associated consumables cost.	This claim is not directly supported by the clinical evidence. Issues relating to sustainability and use of consumables is not reported in the evidence The economic modelling is based on a shorter time to healing in the Prontosan arm resulting in fewer visits and an associated reduction in the use of consumables.
Reduction in transportation related pollution due to decreased patient visits required.	By reducing patient visits for additional dressing changes (at home, clinic, GP or hospital)	This claim is not directly supported by the evidence. Clinical expert input suggests that many patients with chronic wounds are already being treated in the home or community setting The economic modelling is based on a shorter time to

		healing in the Prontosan arm resulting in fewer visits. Transportation costs are not explicitly included in the model.
Minimises waste due to shelf life once opened	Bottles and tubes have an 8 week shelf life once opened, preventing waste at dressing change as the same container can be used over multiple dressing changes. Ampoules are single use for when a smaller amount of product is required, further preventing wastage.	This claim is not directly supported by the evidence. Clinical expert input suggests that single use saline sachets are used therefore it is unclear whether the extent to which Prontosan use would generate less waste. Clinical experts note that some patients will be given Prontosan gels to take home with them for use until wound healing . This may reduce waste if patients use all of the product however conversely, there is a risk of increased waste if patients do not use open tubes/bottles to completion.

8.1 *Integration into the NHS*

Clinical expert input suggests that use of Prontosan may already be widely in use in the NHS in different settings including community wound clinics, post-operative wound management, primary care settings, and maternity settings. Discussions with clinical experts suggest that they broadly support the use of Prontosan in their clinical practice however do acknowledge some potential issues.

A change to using Prontosan is not likely to require a significant change to the current care pathway. Patients with chronic or acute wounds would remain in their normal treatment pathways with no change to setting or clinical team. Prontosan soaks require 10 to 15 minutes of a standard appointment time therefore there may be changes to how an appointment is approached, with the clinical staff having to apply a Prontosan soak before doing anything else to ensure efficiency in what is already a very time limited setting.

Clinical experts suggest that the use of Prontosan may result in changes to secondary dressings/other wound care products used by the clinical teams, with less use of more expensive secondary dressings. There EAC did not identify any specific evidence to support this, however 1 UK study (Atkin 2020) did report a reduction in the number of dressing changes with Prontosan.

Currently there is inconsistency in how cleansing and irrigation are defined and applied by clinical teams. This may need to be resolved to ensure most appropriate use of Prontosan i.e. that it is used for cleansing where needed so that additional cleansing such as may be done (for example wound debridement) when using saline or water will not be required. There are potential resource implications if Prontosan is used inappropriately. For example, 1 clinical expert noted that there is a risk that the more expensive Prontosan gel may be used in place of standard hydrogels to hydrate wounds.

Clinical experts have suggested that clear guidelines on how and when Prontosan products are to be used would be very beneficial both from a clinical effectiveness and resource impact perspective.

8.2 *Ongoing studies*

The EAC searched ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP) and identified 13 studies where Prontosan was used or mentioned. In total, 3 ongoing studies were considered potentially relevant to the decision problem; 1 of which is based in the UK. The company submission also included details of one ongoing case series study not identified by EAC searches. Table 19 summarises these 4 studies.

The EAC notes that while all of these ongoing studies are relevant, the potential impact on the current evidence base is uncertain at this time. Two of the ongoing studies are large randomized trials and the NEWfeet trial is of particular interest as it is a UK-based trial. Results from this trial will inform on the effectiveness of Prontosan solution compared with electrolysed water for a specific patient group of interest (patients with diabetic foot ulcers) which will

be an addition to the evidence base as currently there is no evidence for diabetic foot ulcers specifically.

Table 19: Summary of relevant ongoing trials

Trial ID	Title	Recruitment Status	Target size	Intervention	Condition	Primary outcome
NCT01048307 Sponsor: Calvary Hospital, Bronx, NY Country: United States Study Type: Open label, prospective randomized trial Expected Completion: July 2010, no results posted	Randomized, Controlled, Clinical Trial on the Safety and Efficacy of Prontosan Wound Irrigation Solution Compared to Standard Therapy in the Treatment of Hard-to-Heal Venous Leg Ulcers	Not recruiting (Completed)	20	Prontosan wound irrigation solution	Wound Care Venous Ulcer Care Wound Cleansing Chronic Wound Care	Reduction of bacterial burden (quantitative bacteriology) Reduction in slough and necrotic tissue (clinical score) Amount and quality of granulation tissue (clinical score) Exudate type and amount (clinical score)
NCT01333670 Sponsor: Associazione Infermieristica per lo studio delle Lesioni Cutanee Country: Italy Study Type: Single blind randomized trial Expected Completion: Dec 2012, no results posted	Efficacy of Prontosan Solution on Chronic Ulcers	Not recruiting (Completed)	289	Prontosan wound irrigation solution *versus* Isotonic solution (saline or lactated ringer)	Pressure Ulcer Chronic Wound Care Wound Cleansing	Reduction of necrotic tissue (Pressure Sore Status Tool-PSST);Reduction of inflammatory tissue(Pressure Sore Status Tool-PSST)
NCT02841969	NEWfeet	Recruitment Status Unknown	200	Electrolysed water Prontosan	Diabetic foot	Rate of complete wound healing

Trial ID	Title	Recruitment Status	Target size	Intervention	Condition	Primary outcome
Sponsor: NHS Lanarkshire Aqualution Systems Ltd Country: United Kingdom Study Type: Double blind, randomized trial Expected Completion: March 2020, no results posted						
B.Braun literature (Company Submission)	No Details	No details	27	Prontosan irrigation/soak plus Prontosan gel	Burns	Patient reporting on dressing removal: easy and painless. Wound condition: exudation and wound maceration. Wound odour. Skin graft take. Microbial count reduction

9 Economic evidence

9.1 *Published economic evidence*

Search strategy and selection

The company conducted a separate search for economic evidence, identifying 9 records, however none of these met the inclusion criteria. It is assumed that the records retrieved from the searches for clinical evidence were also screened for relevant economic evidence. The searches for clinical evidence were broader but lacked specificity whereas the searches for economic evidence were very specific and therefore had the potential to miss records. However, the EAC searches, a combined search for clinical and economic evidence, did not retrieve any economic evidence relating to the use of Prontosan.

Published economic evidence review

No published economic evidence relating to the use of Prontosan in the NHS was identified.

Results from the economic evidence

None reported.

9.2 *Company de novo cost analysis*

Economic model structure

The company submitted 2 separate models, with different structures. Some, but not all of the cost and resource values are shared between the models, and clinical inputs are taken from different sources. Both models are for chronic wounds (e.g. pressure ulcers or venous leg ulcers), there was no cost modelling submitted for acute wound care (e.g. burns, wounds due to surgery).

The EAC will describe each model, with its inputs, separately, and then describe each set of results. For reference, the scopes of the 2 models are summarised in table 20.

Table 20: Model Scope

Model title (in company submission)	PICO and key clinical sources of information
Wound Closure Markov model, 1 year time horizon.	P: Patients with venous leg ulcers I: Prontosan irrigation and Prontosan gel X for duration of model C: Saline irrigation O: Complete wound healing Clinical inputs are taken from two alternative papers giving two scenarios. Both are comparative and include venous leg ulcers only: Andriessen 2008 (Retrospective comparative study): 112 patients; total ulcer closure or 6 months; Prontosan solution only; 15-minute soak followed by 15 minute drying phase before dressing. Harding 2012 (Pilot RCT): 34 patients; 12 week treatment; Prontosan solution plus Prontosan gel (15-minute soak).
Wound Bed Preparation, Cost comparison, time to endpoint (BWAT of 14)	P: Patients with chronic wounds, mixed aetiology I: Prontosan irrigation and Prontosan gel X for duration of model C: Saline irrigation O: Time to reach BWAT wound healing score of 14, with 75% epithelialisation. Clinical inputs are taken from Bellingeri 2016 (RCT): 289 patients with pressure ulcer or vascular leg ulcer; follow-up day 7, 14, 21 and 28; Prontosan solution (irrigation using 20-30mls, followed by 10-minute soak).

Although both models are fully described, the wound closure Markov model, with clinical inputs from Andriessen 2008 is used as the EAC base case. The Markov structure allows for improvement, deterioration and recurrence of wounds which reflects clinical realities for chronic wounds. The choice of inputs and the advantages and limitations of each model are described in the subsequent sections.

9.3 *Wound closure model*

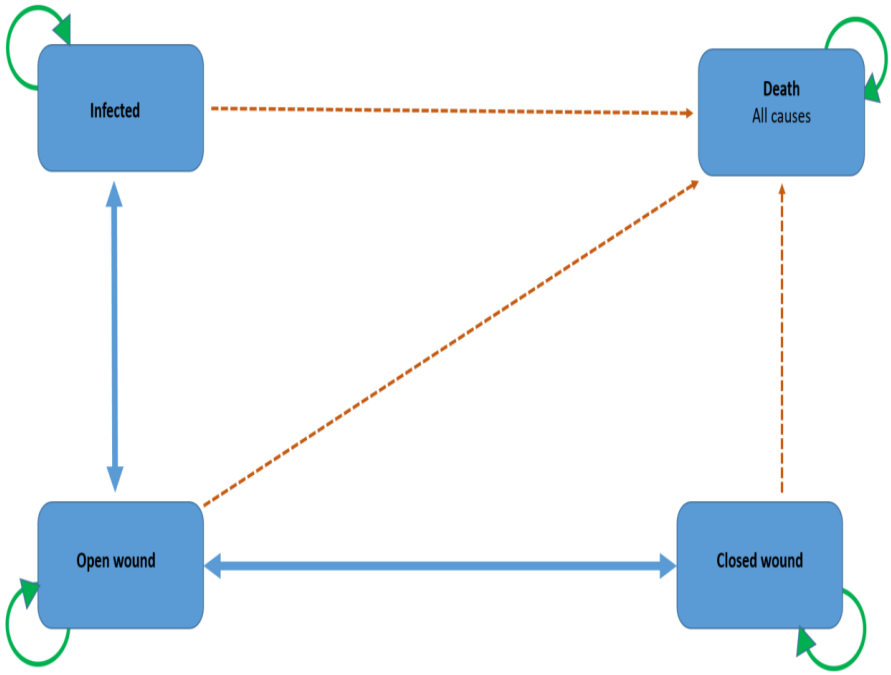
Economic model structure

The company submitted a Markov model with a one-year time horizon, and an NHS and personal social services perspective. No discounting was included,

due to the short time horizon. The EAC consider the model structure, perspective and time horizon to be appropriate

The company submitted a diagram of the model (figure 1), which is a good reflection of the actual modelling examined by the EAC.

Figure 1: Wound Healing Model Structure (from company submission)



The model states are open wound, infected wound, closed wound or death from any cause. The model allows infection of open wounds and recurrence of closed wounds, which are both important aspects of chronic wound healing. It does not allow for different treatment methods and costs for a deteriorating, static wound, or healing wound.

The model is specific to patients with venous leg ulcers, as the available comparative evidence was in this population. The EAC consider that the clinical pathways are likely to be similar for patients with other types of chronic wound, although time to healing may be different. The model structure is not intended for patients with acute wounds and is unlikely to capture the appropriate pathways for these groups. The EAC notes that amputation is not included in the model as it is more commonly associated with diabetic foot ulcers. This potential impact of amputation should be considered when

assessing how generalisable the results from the wound closure model are.

Key assumptions are summarized in table 21.

Table 21: Key assumptions

Assumption	Justification	EAC comment
All patients start in one of the two open wound states (open or infected)	In line with how VLU wounds first present to health care professional (Guest, Fuller, and Vowden 2018).	This is in line with stated population
30% of wounds start as infected	At initial presentation, 18% of VLUs reported as infected and a further 12% of VLUs prescribed an anti-infective. (Guest, Fuller, and Vowden 2018)	This is a reasonable assumption
Death is not cost incurring		This is reasonable for this model and population
Mean VLU is 52.3 cm^2	Based on average wound sizes for VLU as reported from UK data. (Guest, Fuller, and Vowden 2018)	Average wound size from a total of 505 patients (Guest, Fuller, and Vowden 2018) The mean wound area was not stated in Andriessen 2008, and was 11.3cm2 in Harding 2012, with a range from 2 to 36cm2. The impact in the model is limited to the amount of gel used. It does not influence the transitions in the model. A smaller wound size would result in less gel use and is therefore a conservative assumption in the model. When considering the applicability of the model to other patient groups, it will be important to reflect the study data in Andriessen 2008 or Harding 2012, rather than focusing on the wound area.
One sachet of saline (25ml or 20ml) used as standard per dressing change for a 52.3cm^2 VLU	Clinicians provided opinion that 1 sachet would be used for an average sized wound. Clinical expert opinion Dec 2020	This is reasonable for this model and population, and has been confirmed by clinical experts, although large wounds may require more.

Assumption	Justification	EAC comment
Intervention group utilised Prontosan Solution and Gel X	Addition of both for every wound is more cost incurring and stresses robustness of model. Clinical expert opinion Dec 2020	Clinical experts advised that this is not normally the case, and Prontosan gel X was not used in Andriessen 2018. Its use would be more costly and therefore a conservative assumption.
40ml Prontosan Solution per dressing change for a 52.3cm^2 VLU	Smallest volume able to be purchased and volume suitable to soak gauze for the average VLU size. Drug Tariff December 2020, Clinical experts	This is reasonable for this model and population.
2mm thick Prontosan Gel X used per application for a 52.3cm^2 VLU	2mm taken as an average for flat wounds such as VLUs. Clinical expert opinion Dec 2020, and company advice	2mm thick Prontosan Gel X per application equates to 10g of gel per wound. Several papers state thicker applications (3-4mm), which would increase the cost of Prontosan, with a small reduction in cost saving. This is considered in the sensitivity analysis.
Practice nurse appointment 15 minutes	Nationally reported standard appointment time. (Phillips et al. 2015)	Clinical expert advice suggests that dressing change appointments are scheduled for 15 mins.
Community nurse appointment 20 minutes	Clinical experts reported 20-30 average appointment time. The shorter time makes the model more conservative. Clinical expert opinion Dec 2020, PSSRU 2008	Clinical experts noted that chronic wound appointments would typically need 30-45 minutes in the non-specialist setting.
Additional assumptions identified by the EAC		
There are no amputations	If amputation were included, it would be likely to occur where wounds were deteriorating or infected, and would incur an additional cost over the one year time horizon. In the submitted model fewer wounds heal in the saline arm, and therefore the comparator would be expected to experience more amputations and additional costs, increasing the cost saving. This does not consider the general appropriateness of the clinical input data to diabetic patients.	
Price of Prontosan wound gel X is based on the average cost per dressing change of the 50g and 250g tube.	The submission states that this is based on data from [redacted]. There is a minimal impact on the overall modelled results from using either of the sizes.	

Assumption	Justification	EAC comment
Prontosan products are used at each dressing until healing	Clinical experts agreed that once the wound began to epithelise it would not be cleansed, and that the use of a cleansing solution or soak should be dictated by clinical need following wound assessment.	
Practice nurse and community nurse appointments are the same for both Prontosan and Saline.	This was confirmed by clinical experts, with the proviso that nurses start the soaking procedure straightaway, and then move onto other tasks while the soak is taking effect. It is possible that simpler wound dressing appointments may require slightly more time to achieve a 15 min soak with Prontosan.	
Treatment costs and outcomes are the same for all states of open wound.	Wounds may often be described as deteriorating, static and progressing, with variations in expected treatments in each stage. The model combines these together in an “open” state, and uses Prontosan and associated transition probabilities throughout that state. In later stages of healing, wounds may not need Prontosan or saline and the probabilities of moving to other states will have changed. The EAC have attempted to explore this question further in the sensitivity analysis.	

There is a possibility that the structure of the model exaggerates the benefit of Prontosan products by using a single open wound state. If a progressing wound state were included, with the same costs and transition probabilities in both arms of the model, the impact of Prontosan (very slightly higher cost, less infections, shorter time to wound progression) would be seen over fewer months and the cost saving would be reduced. Insufficient data has been identified to populate a model of this type.

Economic model parameters

The following sections outline the key clinical parameters and resources used in company Markov model.

Clinical parameters and variables

The clinical parameters are used to populate the transition matrix, determining how patients move between wound healing states in the model (table 22)

Table 22: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value			EAC value	EAC comment
	Monthly transition probability	**Value as stated in source**	**Source**		
Death from any cause (applied to all states, in both arms)	0.00254	3% per year	Guest (2017)	No change	Chronic wound study, death from any cause, UK
Prontosan					
Healing (Open to Healed)	0.25346	(Mean KM estimated time to healing 3.31 months)	Andriessen (2008)	No change	VLU population, using Prontosan solution but not gel. Derived from survival analysis using exponential model.
Alternative Healing	*0.16799*	*47% (8/17) in 12 weeks*	*Harding 2012*	No change	*VLU population, using Prontosan solution and gel.*
Infection (Open to Infection)	0.00573	3% (2/59) in 6 months	Andriessen (2008)	No change	VLU population, using Prontosan solution but not gel
Alternative Infection	*0.09233*	*24% (4/17) in 12 weeks*	*Harding 2012*	No change	*VLU population, using Prontosan solution and gel.*
Recurrence (Healed to open)	0.01553	17% in 1 year	Gohel (2005)	No change	VLU, UK study
Infection resolution (Infected to open)	*0.79542*	*51.92% resolved at 2 weeks*	*Valenzuela (2008)*	*No change*	*Mixed aetiology chronic wound population*
Saline					
Healing (Open to Healed)	0.18197	(Mean KM estimated time to healing 4.42 months)	Andriessen (2008)	No change	VLU population, using Prontosan solution but not gel. Survival analysis methods discussed in text

Variable	Company value			EAC value	EAC comment
Alternative Healing	*0.06771*	*33% (5/15) in 12 weeks*	*Harding 2012*	*No change*	*VLU population, using Prontosan solution and gel.*
Infection (Open to Infection)	0.02333	13% (7/53) in 6 months	Andriessen (2008)	No change	VLU population, using Prontosan solution but not gel
Alternative Infection	*0.06771*	*7% (1/15) in 12 weeks*	*Harding 2012*	*No change*	
Recurrence (Healed to open)	0.01553	17% in 1 year	Gohel (2005)	No change	VLU, UK study
Infection resolution (Infected to open)	0.58460	33.33% resolved at 2 weeks	Valenzuela (2008)	No change	Mixed aetiology chronic wound population

Wound healing (movement from open to healed states)

The company presented two alternative data sets for wound healing (Andriessen 2008 and Harding 2012). Both studies include patients that did not reach wound healing in the study duration and the company have used survival analysis to predict healing over a 12 month duration and derive a transition probability. The company used an exponential parametric model which allows a constant transition probability to be used in the Markov model. The EAC have recreated this for Andriesssen (2008) and graphs showing the time to healing from the exponential model and Kaplan-Meier analysis are in Appendix D. The EAC have also explored the use of a Weibull model for extrapolation, and presented these graphs. This model cannot be represented by a single transition probability and therefore does not readily fit into the submitted Markov model. Mean time to healing from each of the model approach are presented in table 23.

Table 23: Mean time to healing

	Mean Time to healing (months)		
	Prontosan	Saline	Difference
Kaplan-Meier	3.31	4.42	1.11
Exponential	3.42	4.98	1.56
Weibull	3.38	4.44	1.06

Andriessen (2008) was a retrospective comparative study of 112 patients with venous leg ulcers and a follow up time of 6 months. The EAC consider that Andriessen 2008 is a more suitable data source due to the larger number of participants and longer follow up (table 13)

Harding (2012) was a small UK pilot RCT study with 34 patients, also based on a population with VLU and used Prontosan solution and wound gel. The shorter follow-up period of 12 weeks means that there was greater reliance on extrapolation for the calculation of transition probabilities for wound healing. Although separate model files were submitted for wound bed closure using Andriessen (2008) and Harding (2012), the model structures are the same, and no variables other than those associated with wound healing and infection rates were altered.

The EAC explored possible alternative data sources for wound healing transition probabilities. Many of the reported clinical outcomes in the available evidence from other studies are reductions in wound size or change in wound bed condition. These are not generally reported in a format that can readily be associated with model states or costs without a large number of additional assumptions

The EAC considers there are no suitable alternative data sources for wound healing transition probabilities (in either venous leg ulcer or mixed aetiology populations) as other studies either do not report wound healing, or do not report it in a format that would allow survival analysis.

Infection (movement from open to Infected states)

The same two studies (Andriessen 2008 and Harding 2012) were used for infection rate, with the monthly transition probabilities being derived from the number of infections reported during the study period. For Harding 2012 the comparator experienced slightly fewer infections that the Prontosan group, however the study numbers are low.

Recurrence (movement from healed to open states)

The company used data from a UK study in patients with venous leg ulcers between 1998 and 2003. The 12 month recurrence rate of 17% was derived from data on 1195 legs. The EAC agree that this is a reasonable data source.

Infection resolution (movement from infected to open state)

The source data (Valenzuela et al. 2008) is a study of 142 patients with mixed aetiology chronic wounds and a two week follow-up. Both groups had irrigation by saline, but wounds in the Prontosan arm were treated with Prontosan gel at each dressing. Samples for bacterial culture were collected at the start of the study and at completion after 2 weeks. The authors report a change from 36 to 24 positive culture for the control group (n=64, lost cultures are 7 and 11 at weeks 0 and 2) and a change from 52 to 25 positive cultures for the intervention group (n-64, lost cultures are 6 and 5 at weeks 0 and 2). There is some difference in the number of lost cultures between the groups, and the authors report the results as a bacterial culture, not as a clinical infection. This means that the use of the data to inform the probability of infection resolution should be treated with caution, however the EAC have not identified any alternative data source.

Resource identification, measurement and valuation

Costs and resources are calculated per dressing change visit, and used to give a monthly cost for each model state (table 24 and table 25). The largest costs are for general healthcare in each state, composed of staff time for visits and consumables. The costs for Prontosan and saline products are added to the cost of each visit, but constitute a small portion of the overall cost.

Wound Irrigation and gel

Costs for Prontosan Wound Gel X are not stated in the company report, but are included in the model as shown in table 16. The EAC found that there is slight variation in prices from British National Formulary and NHS Supply Chain.. For both saline and Prontosan, a number of product sizes were considered, a cost per dressing calculated for each, and the average cost used.

Costs of healthcare per state

Harding et al 2013 reported costs for wound care based on 827 observations of wounds across 3 leg ulcer specialist clinics in 2000 (reported costs were inflated to 2008/9). The costs were grouped into categories of healed; progressing; static; deteriorating or severe. The company have used the reported data to split the costs further into three types: staff and outpatient costs; hospital admissions; other costs.

Hospital admissions

The company have removed hospital admission costs from the monthly healthcare cost, due to the low number of hospitalisations experienced by people with VLU. Guest 2020 reported that in a study with 7% had a hospital admission without surgery and 0% had a hospital admission with surgery. Hospital admission costs make up a variable proportion of the cost in each state: healed (0%), progressing (4.4%) or static (2.0%), deteriorating (25%) and severe (46%). The EAC considers this to be a reasonable and approach and that inclusion of hospital admissions would increase the cost saving due to Prontosan.

Staff costs and number of visits

The total weekly cost for each of community nursing, practice nurses and outpatient visits (Harding et al. 2013) has been used to calculate the number of visits using staff costs from PSSRU 2008 and an assumption of 20 minutes for community nurses and 15 minutes for practice nurses per visit.

This number of visits is used to recalculate total staff costs (updated to 2019 using PSSRU 2019) and to calculate a monthly cost for Prontosan and Saline consumables.

Due to this methodology, any exploration of different visit lengths has minimal impact on the model results. A longer visit length results in fewer calculated visits, and no overall cost impact other than costs of Prontosan and Saline. If there were a change in visit length between the data collection in 2000 and the current date, or if there were a change in visit length due to the use of Prontosan products this would have a much more significant impact. Clinical experts advised that it was necessary to train staff to start the Prontosan soak at the beginning of the visit, but that if this was achieved they would not expect it to result in additional time.

The EAC made some adjustments to the staff costs in the model. Community nurses had been taken as an average of bands 5 to 8. The EAC altered this to include only bands 5 and 6, as higher bands are unlikely to be doing community visits. Additional minor changes to calculations for staff costs are listed in appendix F. This also results in small changes to the number of visits per month.

Other costs

These costs include dressings, antibiotics, analgesics and investigations. They were inflated using pay and prices index (PSSRU 2019), the EAC made some very minor corrections in the values used for inflation.

Table 24: Cost parameters used in the company's model and changes made by the EAC

Parameter	Unit	Company value	EAC value	Source
Prontosan				
Prontosan irrigation solution ampule	40ml unit	£0.62	Unchanged	Drug Tariff, Jan 2021
Prontosan irrigation solution bottle	350ml	£5.03	Unchanged	Drug Tariff, Jan 2021 (£0.57 per dressing)
Mean cost per Prontosan irrigation (40 ml)		£0.60	Unchanged	[redacted], company submission.
Prontosan Wound Gel	30ml	£6.71	Unchanged	Drug Tariff, Jan 2021

Parameter	Unit	Company value	EAC value	Source
				This is unused in model
Prontosan Wound Gel X	50g	£12.29	Unchanged (	Drug Tariff, Jan 2021. (£2.51 per dressing)
Prontosan Wound Gel X	250g	£32.89	Unchanged	Drug Tariff, Jan 2021. (£1.34 per dressing)
Mean cost per Gel X dressing	10g	£1.97	£1.93	
Saline				
Irripod solution sachet	20ml	£0.24	Unchanged	Drug Tariff, Jan 2021
Steripod solution sachet	20ml	£0.20	Unchanged	Drug Tariff, Jan 2021
Normasol solution sachet	25ml	£0.26	Unchanged	Drug Tariff, Jan 2021
Mean cost per Saline irrigation	20-25ml	£0.23	Unchanged	
Monthly health care cost per state				
Parameter	**Company value**	**EAC value**		**Source**
Health care cost, open	£635.76	£512.73		Harding (2013), cost for static, progressing and deteriorating wounds, inflated to 2018/19 prices, excluding hospital admissions. EAC corrections: see text
Health care cost, infected	£2,034.15	£1,847.05		Harding (2013), cost for severe wounds, inflated to 2018/19 prices, excluding hospital admissions. EAC corrections: see text
Health care cost, healed	£42.87	£34.36		Harding (2013), cost for healed wounds, inflated to 2018/19 prices, excluding hospital admissions EAC corrections: see text

Table 25: Resource use in the Company Model and changes made by the EAC

Parameter	Company value	EAC value	Source
Resources per Dressing			
Mean wound size	54.1cm2	unchanged	No change following discussion with experts
Gel thickness	2mm	unchanged	No change following discussion with experts, but thicker gel is considered in sensitivity analysis
Gel used per dressing change	10g	unchanged	The gel required for area and thickness is 10.8 cm^3. This is assumed to be 10g of gel.
Prontosan Solution	40ml	unchanged	Either a 40ml sachet or 40ml from a bottle of 350ml
Saline solution	20-25ml	unchanged	A single sachet may be 20 or 25ml
Dressings per month:			
Open	11.48	10.42	Harding (2013), based on cost of nursing visits and hourly cost of nursing staff. EAC corrections for staff costs and weightings.
Infected	14.18	13.75	
Healed	0.34	0.30	

Sensitivity analysis

In addition to submitting model variations with alternative data sources for key clinical inputs, the submission included: threshold analysis for healing rate, one-way sensitivity analysis for clinical, resource and cost variables, bivariate analysis varying costs of saline and Prontosan. The model does not contain functionality to re-run these analyses, however the EAC have explored the impact of key variables using the updated EAC base case.

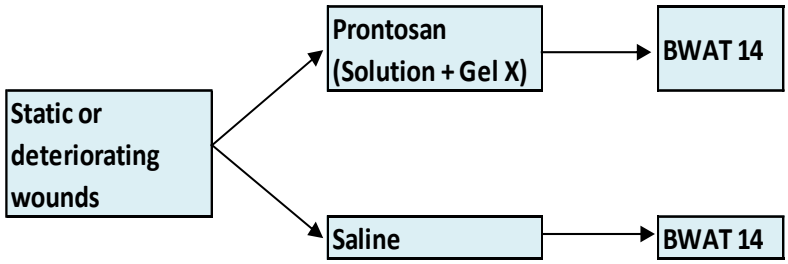
9.4 *Wound Bed Preparation Model*

Economic Model Structure

The company submitted a simple cost comparison between Prontosan wound irrigation solution and saline of the cost of achieving a healthy wound condition defined by a BWAT score of 14 (75% epithelialisation) (Figure 2). There is an assumption that these wounds are on a pathway to healing and

will not deteriorate. No additional cost or modelling is included for deteriorating or recurring wounds, or for additional treatment until healing. The time horizon is until a BWAT score of 14 is reached, which is 4.1 or 11.3 weeks in Prontosan and Saline respectively. There is no discounting included or required for this time period.

Figure 2: Wound Bed Preparation Model Structure



EAC assessment of the model noted a small number of discrepancies in prices and inflation rates which were adjusted for the EAC base case with minimal impact. The EAC stress tested the model to ensure functionality and while the model largely functions as expected the EAC identified some minor issues (appendix E).

The EAC considers the Markov model structure to be more appropriate for the wound care setting, however this model allows consideration of an alternative clinical input and use of Prontosan for a shorter period. Clinical experts advised that wound cleansing should only be carried out where clinically indicated, and some experts would not typically use Prontosan products for the duration of healing. Key assumptions in the wound bed preparation model are summarised in table 26.

Table 26: Assumptions in the wound bed preparation model

Assumption	Justification	EAC comment
40ml Prontosan Solution per dressing change	Smallest volume able to be purchased and volume suitable to soak gauze for leg ulcers up to 52.3 cm^2	Average wound size from a total of 505 patients (Guest, Fuller, and Vowden 2018) This is reasonable for this model and population
One sachet of saline (25ml) used as standard per dressing change	Clinicians provided opinion that 1 sachet would be used for an average sized wound	This is reasonable for this model and population, and has been confirmed by clinical experts, although large wounds may require more.
10g Prontosan Gel X used per dressing change	Gel X use will depend on size of wound. 10g is estimating for quite a large wound – circa 52.3cm^2 and 2mm thick gel per wound.	2mm thick Prontosan Gel X per application equates to 10g of gel per wound. Several papers state thicker applications (3-4mm), which would increase the cost of Prontosan, with a small reduction in cost saving. This is considered in the sensitivity analysis.
Once wound is progressing cost of care is reduced	Weekly cost UK wound care cost in 2008 is reported as less for a progressing wound (£87.59) compared with a static wound (£100.27) or deteriorating wound (£159.45)	This is not used in the model. There is a standard wound care cost of £162.60 per week modelled, which is a weighted mean of static and deteriorating wound costs. This is applied to the duration of the model. A lower weekly cost of wound care for part of the healing process would reduce the cost savings due to Prontosan.
Once wound is progressing care and cost is the same for both arms and not included in model	Model represents impact on cost to achieve a healthy progressing wound only, cost will continue until wound healing but will be at a lesser extent	This assumes costs Prontosan is only used to BWAT14 and subsequent costs are the same in both arms. This is reasonable as this is a cost comparison, rather than a calculation of total cost burden. Note that this includes an assumption that wounds will continue to closure and not breakdown (discussed below), and that this pathway will be the same in both arms
Additional assumptions		
Practice nurse appointment 15 minutes	This is reasonable for this this model and population. Clinical expert advice suggests that dressing change appointments are scheduled for 15 mins. although longer may be needed for some patients.	
Community nurse appointment 20 minutes	Clinical experts noted that chronic wound appointments may need 30-45 minutes in the non-specialist setting.	
Time to reach mean BWAT score of 14 is appropriate	The model is based on the mean time taken to reach BWAT 14. The data used is the time taken to reach a mean score of BWAT 14, which does not have the same value. We do not know how many patients did not reach BWAT 14, or how long they took to reach it after the 28 day follow up.	
The benefit of reaching BWAT 14 in a shorter time is carried through to subsequent healing	There is an assumption that reaching BWAT 14 is of clinical benefit, and that a shorter time to reach BWAT 14 will result in needing fewer visits from health care professionals subsequently	
Wounds that reach BWAT 14 do not deteriorate or reoccur.	If wounds deteriorate after reaching BWAT 14, they would be considered a new incident of open or infected wounds, but there are no costs included for this.	

Clinical parameters and variables

Clinical inputs are taken from Bellingeri (2016), an RCT comparing the use of Prontosan solution with saline in 289 patients with pressure ulcers or vascular

leg ulcers. The follow up was 28 days, and wounds were assessed for BWAT wound healing score. The mean BWAT score was reported at follow up points of 7, 14, 21 and 28 days. The mean BWAT score at 28 days was 14 for Prontosan and 22 for Saline. The company used an excel trendline to extend the graphs to reach a mean score of BWAT for both arms. Although there are concerns about the data, no improved data source has been identified, and therefore the clinical inputs remain unchanged by the EAC (table 27).

Table 27: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value	Source data	EAC value	EAC comment
Time to reach BWAT 14 (weeks				
Prontosan	4.13 weeks	Bellingeri (2016),	No change	This is derived from within the model from the clinical data
Saline	*11.28 weeks*	Bellingeri (2016),	No change	

Resource identification, measurement and valuation

Costs and resources are calculated per dressing change visit, and used to give a weekly cost for each model state (table 27 and 28). Similarly, to the Markov model, the largest costs are for general healthcare in each state, composed of staff time for visits and consumables. The costs for Prontosan and saline products are added to the cost of each visit, but constitute a small portion of the overall cost.

The details of the health care, saline and Prontosan costs are the same as for the Markov model with the following exceptions:

Wound Irrigation and gel

For both saline and Prontosan, a number of product sizes were considered, and separate scenarios used for different combinations. The EAC have accepted this approach. It is different from the mean value used in the wound

closure model, however has very minor impact. The costs were updated to current drug tariff costs, as described in the Markov model.

Costs of healthcare per state

Harding (2012) reported costs for wound care based on 827 observations of wounds across 3 leg ulcer specialist clinics in 2000 (reported costs were inflated to 2008/9). The costs were grouped into categories of healed; progressing; static; deteriorating or severe. The company used an average of static and deteriorating costs to calculate the weekly cost of health care. The EAC considered that an improvement to BWAT 14 would include a progressing state, and therefore used a weighted average of static, deteriorating and progressing costs.

The company have used the reported data to split the costs further into three types: staff and outpatient costs; hospital admissions; other costs.

Staff costs and number of visits

The total weekly cost for each of community nursing, practice nurses and outpatient visits (Harding 2012) has been used to calculate the number of visits using staff costs from PSSRU 2008 and an assumption of 20 minutes for community nurses and 15 minutes for practice nurses per visit.

This number of visits is used to recalculate total staff costs (updated to 2019 using PSSRU 2019) and to calculate a monthly cost for Prontosan and Saline consumables.

Due to this methodology, any exploration of different visit lengths has minimal impact on the model results. A longer visit length results in fewer calculated visits, and no overall cost impact other than costs of Prontosan and Saline. If there were a change in visit length between the data collection in 2000 and the current date, or if there were a change in visit length due to the use of Prontosan products this would have a much more significant impact. Clinical experts advised that it was necessary to train staff to start the Prontosan soak at the beginning of the visit, but that if this was achieved they would not expect it to result in additional time.

The EAC made some adjustments to the staff costs in the model. Community nurses had been taken as an average of bands 5 to 8. The EAC altered this to include only bands 5 and 6, as higher bands are unlikely to be doing community visits. Additional minor changes to calculations for staff costs are listed in appendix F This also results in small changes to the number of visits per month.

Hospital admissions

The company have also removed hospital admission costs from the monthly healthcare cost in this model, however the stated reason was due to the low number of hospitalisations experienced by people with VLU. As this model is mixed aetiology, the EAC has included hospital admission costs (inflated to 2019 costs), resulting in a small increase in cost saving.

Other costs

The EAC made the same minor corrections for inflation as reported in the Markov model.

Table 28 and table 29 summarise the cost and resource parameters in the company model and changes made by the EAC.

Table 28: Cost parameters used in the company's model and changes made by the EAC

Parameter	Unit	Company value	EAC value	Source
Prontosan				
Prontosan irrigation solution sachet	40ml unit	£0.62	Unchanged	Drug Tariff, Jan 2021
Prontosan irrigation solution bottle	350ml	£5.03	Unchanged	Drug Tariff, Jan 2021 (£0.57 per dressing)
Prontosan Wound Gel X	50g	£32.89	Unchanged	Drug Tariff, Jan 2021. (£2.51 per dressing)
Prontosan Wound Gel X	250g	£12.29	Unchanged	Drug Tariff, Jan 2021. (£1.34 per dressing)
Saline				

Parameter	Unit	Company value	EAC value	Source
Irripod solution sachet	20ml	£0.24	Unchanged	Drug Tariff, Jan 2021
Steripod solution sachet	20ml	£0.20	Unchanged	Drug Tariff, Jan 2021
Normasol solution sachet	25ml	£0.26	Unchanged	Drug Tariff, Jan 2021
Mean cost per Saline irrigation	20-25ml	£0.23	Unchanged	
Weekly cost of healthcare				
Health care cost, weekly (monthly)	£162.60 (£704.61)	£118.32 (£512.73)		Harding (2013), cost for static, progressing and deteriorating wounds, inflated to 2018/19 prices, excluding hospital admissions. EAC corrections: see text

Table 29: Resource use in the Company Model and changes made by the EAC

Dressings per month:			
Dressings per week (monthly)	2.74 (11.89)	2.40 (10.42	Harding (2013), based on cost of nursing visits and hourly cost of nursing staff. EAC corrections for staff costs and weightings.

Sensitivity analysis

The company presented one-way sensitivity analysis on time to BWAT14, costs of Prontosan and saline products, and weekly health care costs. The EAC have not recreated all of the analysis with the EAC base model, but have explored the impact of key variables.

9.5 *Results from the economic modelling*

Base case results

The EAC have presented the company results for the wound closure Markov model (with half cycle correction), at 1 year, in table 30.

Table 30: Summary of base case results for Markov wound closure model

	Company submission			EAC base case		
	Prontosan	Saline	Cost saving per patient	Prontosan	Saline	Cost saving per patient
	Andriessen and Eberlein (2008) data					
Healthcare cost	£3,223.41	£4,446.33	£1,222.92	£2,647.10	£3,693.37	£1,046.27
Technology	£119.39	£14.73	-£104.65	£108.72	£13.46	-£95.26
Total	**£3,433.04**	**£4,461.06**	**£1,118.26**	**£2,755.82**	**£3,706.83**	**£951.01**
	Harding (2012) data					
Healthcare cost	£5,052.85	£6,396.27	£1,343.42	£4,234.16	£5,368.82	£1,134.66
Technology	£175.61	£20.66	-£154.96	£160.88	£18.93	-£141.95
Total	**£5,228.46**	**£6,416.93**	**£1,188.47**	**£4,392.05**	**£5,387.75**	**£992.71**

The EAC have made a number of corrections and changes (appendix F), in the Markov wound care model that have resulted in a small reduction in the cost saving due to the use of Prontosan solution and gel X. Prontosan remained cost saving compared to saline throughout these changes.

Table 31: Summary of base case results for wound bed preparation model

	Company submission			EAC base case		
	Prontosan (40ml)	Saline	Cost saving per patient	Prontosan (40ml)	Saline	Cost saving per patient
Healthcare cost	£671.33	£1,833.48	£1,162.15	£537.94	£1,469.17	£931.23
Technology	£34.87	£7.12	-£27.75	£30.56	£6.24	-£24.32
Total	**£706.20**	**£1,841.28**	**£1,134.40**	**£568.49**	**£1,475.40**	**£906.91**

Sensitivity analysis results

The company carried out sensitivity analysis that identified the time to healing (or wound bed improvement), reduced time in infected state, and costs of healthcare visits as they key drivers of the model. This remains unchanged in the EAC base case.

The cost saving is due to the reduction in visits for dressing changes, and the healthcare resource associated with these visits. The model is robust to variation, due to the large costs of these visits relative to the costs of saline or Prontosan products.

If the transition probabilities for healing with Prontosan are set to be equivalent to those for saline, the model remains slightly cost saving due to the reduction in infections. Where all transition probabilities are set to the values for saline the EAC base case is slightly cost incurring.

9.6 *The EAC's interpretation of the economic evidence*

The EAC have made a number of small corrections to the models and to the inputs, as described in clinical input and resource tables and Appendix F however both models remain cost saving, and the overall impact of the changes was small.

The EAC consider the **Markov wound healing model** the most appropriate structure from the submitted models, as it captures some of the complexities of chronic wound pathways. The model may be improved by the use of a "progressing" state where the use of Prontosan solution and gel might case prior to healing, and with a reduced healthcare cost. However no data has been identified that would be suitable for this structure.

The structure of the model is likely to be suitable for all chronic wound types, however the inputs have been selected specifically for venous leg ulcers.

Within the Markov model, the EAC consider data from Andriessen (2008) to be the most appropriate healing and infection inputs for venous leg ulcers, due to the longer follow up and larger number of patients. However, the incremental cost savings per person for both models are very similar.

The study data for healing has been extrapolated to 12 months using an exponential survival model, limited by a requirement for a constant transition probability. The exponential model results in a slightly higher difference in mean time to healing (1.56 months) than either the Kaplan Meier data (1.11 months) or the Weibull model (1.06 months). Since one month of open state

wound care is modelled at £512.73 for general health care (EAC base case), use of an alternative modelling approach is likely to lead to a moderate reduction in the overall cost saving due to Prontosan. It would however remain clearly cost saving.

The key drivers of the model are the time to healing and the cost of wound care during this process. The same drivers are also found in the wound bed preparation model.

The wound closure model was robust to variation in inputs during sensitivity analysis and testing, due to the high relative cost of frequent visits to change dressings

The wound closure model is largely (but not entirely) based on clinical data for venous leg ulcers. Clinical evidence available for other types of chronic wounds are not suitable for use with the Markov model. The model structure would be appropriate for other types of chronic wound, however many of the clinical inputs, and some of the cost inputs, have been specifically selected for a population with venous leg ulcers.

The **wound bed preparation model** is based on wound progression towards healing for a population with mixed aetiology chronic wounds, however the findings are limited by the model simplicity. The overall cost saving due to the use of Prontosan modelled is however very similar to that for the Markov wound closure model. The model is essentially the cost of open state healthcare and saline or Prontosan products multiplied by the mean time to an improved wound bed condition. As such it remains cost saving throughout sensitivity analysis and testing unless mean times to BWAT14 are very similar.

Atlhough both models include the use of Prontosan solution and gel X at every dressing, the clinical data used to inform the wound closure model comes from studies that use only Prontosan solution (Andriessen 2008) or Prontosan solution and Prontosan gel (Harding 2012). The time to healing or wound progression is a much larger driver in the models than the cost of the

products. The selection of different Prontosan products is a clinical decision, and should not be influenced by the modelling approach.

No modelling was submitted for burns or acute surgical site wounds. A non-Markov model may be more suitable in these populations where deterioration of wound condition and recurrence of wounds are less common, however there is very little available evidence to populate it.

10 Conclusions

10.1 *Conclusions from the clinical evidence*

The EAC consider there is a lack of high quality comparative evidence comparing Prontosan use with saline or water in a consistent wound management approach.

The majority of the evidence is related to chronic wounds including venous leg ulcers, diabetic ulcers, pressure ulcers and other chronic wound types. The evidence for acute wounds is very limited and focused of burn wounds. There is very limited evidence relating to management of surgical site wounds.

Adverse events are rare and easily managed and the EAC does not consider there to be safety concerns provided clinical staff are aware of the contraindications as outlined in the instructions for use.

The EAC consider the company claimed benefits relating to the clinical effectiveness of Prontosan have been partially met however the claimed benefits relating to resource use, nurse time and sustainability are not currently supported by the clinical evidence.

Clinical expert input suggests that use of Prontosan may already be widely in use in the NHS in different settings including community wound clinics, post-operative wound management, primary care settings, and maternity settings. Discussions with clinical experts indicate that they broadly support the use of Prontosan in their clinical practice however do acknowledge some potential issues, particularly around the time it takes to cleanse wounds using Prontosan and the impact this may have on appointment times.

Although there are weaknesses in the evidence, the EAC considers that based on the current available evidence the use of Prontosan products as an option for chronic wound management is supported. The evidence for whether Prontosan products are more effective than water or saline however is limited. Based on the limited comparative evidence as well as clinical expert input that not all wounds will need cleansing at every dressing change, it is unlikely that Prontosan will replace saline or water.

10.2 *Conclusions from the economic evidence*

The economic models submitted both show that the use of Prontosan solution and gel X compared to saline for chronic wounds is cost saving. The key drivers are the time to healing or wound bed progression, combined with the cost of dressing visits, and a reduction in those costs once either healing or progression have been achieved.

The clinical studies used to populate the models do not all use Prontosan solution and gel X at each visit, and therefore the findings are likely to be applicable to broader uses of Prontosan products.

The key limitations are that the models rely on clinical evidence which is comparative, but not of high quality. The Markov wound closure model uses an exponential survival analysis which results in a slightly larger difference in mean times to wound healing than some alternative methods. The wound bed preparation model does not consider infections, reoccurrences or if the use of Prontosan has a real longer term impact past the arrival at a score of BWAT 14.

Despite these limitations, the models are robust to variation in the clinical inputs, requiring only a small impact on time to healing or reduction in infections to remain cost saving.

The modelling supports the company claims that use of Prontosan leads to a reduced number of visits and a reduction in the associated resources.

The economic modelling is entirely for a chronic wound population and there is no modelling submitted for burns or acute surgical site wounds. The EAC agrees with the company that there is insufficient evidence to populate an economic model in these populations.

11 Summary of the combined clinical and economic sections

The EAC consider that based on the clinical evidence, Prontosan is a safe and effective approach to chronic wound management. High quality comparative evidence is lacking and it is therefore less certain to what extent Prontosan is more effective than saline or water.

The economic modelling finds that the use of Prontosan is cost saving based a reduction of resources associated with a reduced time to healing, or improvement of wound bed condition, and reduced infections. The evidence base for this is limited, but the model remains cost saving with a wide range of inputs.

12 Implications for research

The EAC consider that while comparative evidence does exist comparing Prontosan with saline, the quality and consistency of that evidence makes it difficult to compare results across studies.

Future comparative studies should consider:

- Clearly defined intervention including a clear description of the Prontosan products being used
- Cleary defined comparator such as saline or water or, where appropriate, alternative relevant comparators such as silver sulphadiazine for burns.
- Clearly stated approach to wound management (i.e. soak times, irrigation or cleansing).
- Consistent approach to measurement of outcomes of importance such as wound healing and wound infection.

Randomized trials appear to have difficulty recruiting enough patients to the study which makes the generation of robust evidence difficult. It might

therefore be worth considering a ‘before and after’ approach to evidence generation.

A ‘before and after’ approach should consider:

- A prospective approach
- Clearly defined study periods for the ‘before’ and ‘after’ time frames
- A detailed reporting of the wound management approach in the ‘before’ period including relevant details such as whether saline, water or other relevant approach is being used.
- A clear reporting of how Prontosan in being implemented in the ‘after’ period.
- Consistent measurement and reporting of outcomes in both time periods

Any future research should also consider the setting and wound types with subgroup analysis based on wound type where possible.

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14 Appendices

Appendix A: Clinical and Economic Evidence Identification

Appendix B: Data Extraction Tables

Appendix C: Critical Appraisals

Appendix D: Survival analysis graphs

Appendix E: EAC Model Stress Testing

Appendix F: EAC Model changes

Appendix A: Clinical and economic evidence identification

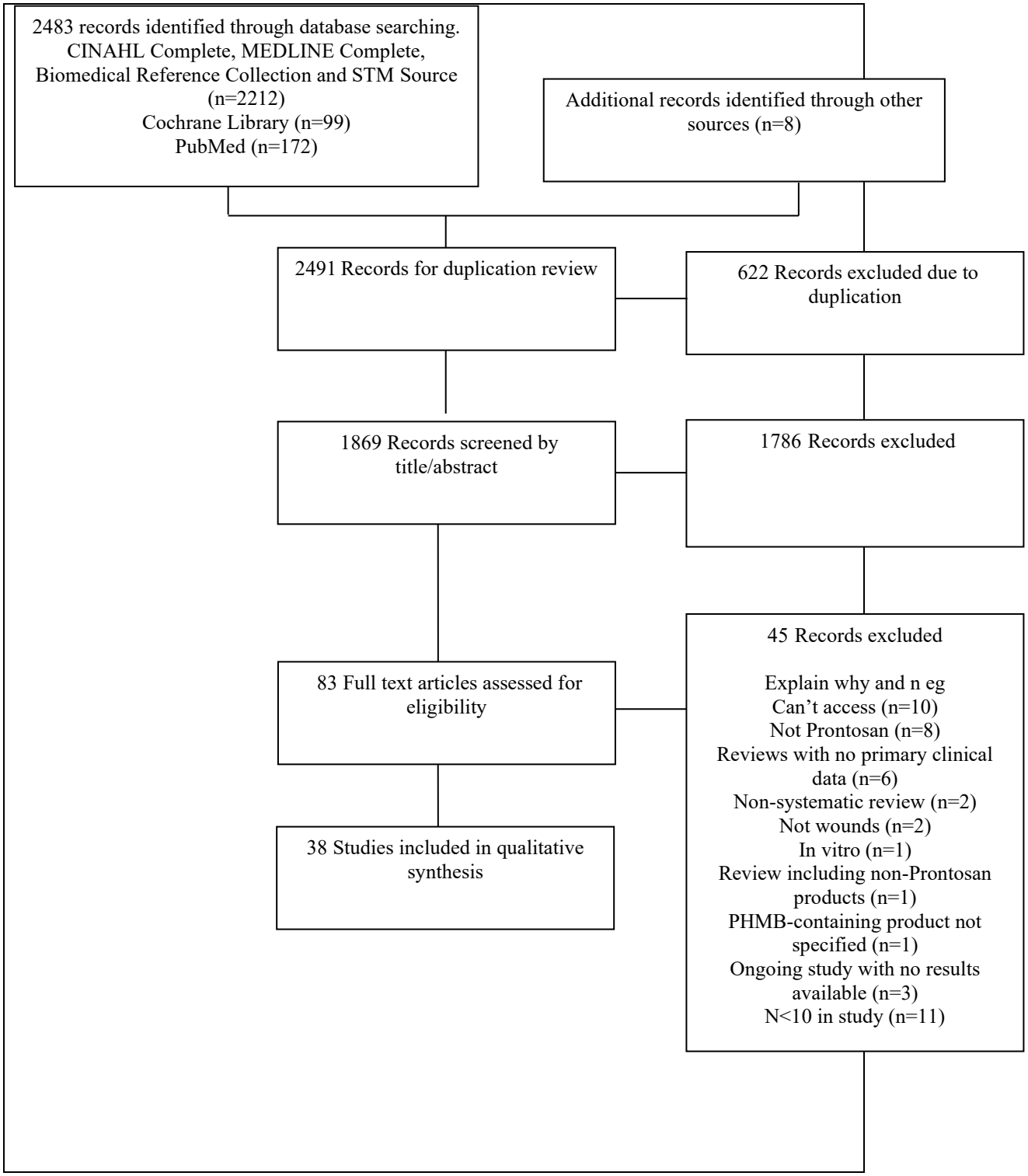
Company search strategy, screening criteria and process for clinical evidence

A literature search was performed in 5 databases (EBSCO – CINAHL Complete, Medline Complete, Biomedical Reference collection and STM, Cochrane & PubMed) to include the period from 1st January 2005 to 1st October 2020). The searches included a range of free text terms and Medical Subject Headings to describe 'wounds', the intervention product and key components of the intervention product. No language restrictions were applied. Additional publications were sought from the company. The company applied the following exclusion criteria:

Population	Surgical procedures, non-wounds (oral, ocular)
Interventions	Any intervention that did not incorporate PHMB solution or gel. Dressings with PHMB incorporated within the dressing. Negative pressure wound therapy. Polyhexanide alone without betaine
Outcomes	Outcomes related to surgical site infections
Study design	Testimonials, non-systematic reviews containing no primary data, editorials, reports describing product news. In vitro studies and animal biofilm studies. Studies with a total sample size of fewer than 10 patients.

Study selection diagram (Company Submission)

The EAC noted that there are some discrepancies in the company PRISMA chart but based on information in the submission is appear that the company has run the same search strategy for adverse events which resulted in 28 (23 published and 5 unpublished) being selected but these overlap with those in appendix A clinical evidence. From looking at adverse event table in appendix B, there are 14 additional studies with adverse events that are separate from 24 that were included for clinical evidence. The EAC therefore assumes that the PRISMA diagram reflects both the clinical evidence and additional adverse events evidence included by the company (24 clinical evidence selection + 14 additional adverse events).



Company search strategy, screening criteria and process for economic evidence

A literature search was performed in 5 databases (EBSCO – CINAHL Complete, Medline Complete, Biomedical Reference collection and STM, Cochrane & PubMed) to include the period from database inception to 13th

October 2020). The searches combined 'Prontosan' with free text terms for wound, ulcer and burn with terms to identify economic literature. Additional publications were sought from the company data bank. The company applied the following exclusion criteria:

Population	Surgical wounds, trauma
Interventions	Other topical agents containing PHMB not prontosan solution, gel or gel X
Outcomes	No economic outcomes reported
Study design	In vitro, review or discussion articles
Language restrictions	Non-English Language

Company search strategy for adverse events

The company searched for publications reporting adverse events from publications identified in their main clinical evidence search. The company also conducted a search of the MAUDE FDA database on 20th October 2020 identifying 59 potential relevant reports.

EAC search strategy and study selection for clinical and economic evidence

The EAC conducted a single search for both clinical and economic evidence as directed by the scope. Ten bibliographic databases were searched, to include periods from date of database inception to 5th January 2021, using a range of free text terms and (where appropriate) subject headings. Two clinical trial registries were also searched for ongoing and unpublished trials; the company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices and the MAUDE database were searched for adverse events.

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
05/01/21	Cochrane Library CDSR CENTRAL	0 0 24	
05/01/21	CRD DARE HTA	0	

	NHS EED		
05/01/21	EMBASE	73	
05/01/21	Medline (ALL – includes Medline In Process & Medline Epub Ahead of Print)	39	
04/01/21	PubMed	28	
05/01/21	Web of Science	37	
05/01/21	Scopus	86	
05/01/21	Records from manufacturer or other sources https://www.bbraun.com/en/products/b/prontosan-wound-irrigationsolution.html	13	
			117
06/01/21	MAUDE adverse events https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm	61	
11/01/2021	MHRA – search MDA & FSN in following: https://www.gov.uk/drug-device-alerts?keywords=&issued_date%5Bfrom%5D=&issued_date%5Bto%5D=	0	
05/01/21	Clinicaltrials.gov	1	13
05/01/21	ICTRP	12	

Search strategies

Cochrane Library

#1 MeSH descriptor: [Wound Healing] this term only

#2 MeSH descriptor: [Wounds and Injuries] this term only

#3 (wound* or burn*):ti,ab,kw

#4 #1 OR #2 OR #3

#5 ((Polyhexanide AND betaine) OR (polihexanide AND betaine)):ti,ab,kw

#6 (Prontosan):ti,ab,kw

#7 #5 OR #6

#8 #4 AND #7

CRD

Searched for:

1	MeSH DESCRIPTOR wound healing	0
2	MeSH DESCRIPTOR wounds and injuries WITH QUALIFIER TH	0
3	(wound*) OR (burn*)	2594
4	#1 OR #2 OR #3	2594
5	(polyhexanide) OR (polihexanide)	2
6	(betaine)	2
7	#5 AND #6	0
8	(prontosan)	0
9	#7 OR #8	0
10	#4 AND #9	0

EMBASE <1947-Present>

1 Wound Healing/ (127736)
2 injury/th [Therapy] (7481)
3 (wound* or burn*).tw. (409159)
4 1 or 2 or 3 (459113)
5 ((Polyhexanide and betaine) or (polihexanide and betaine)).tw. (26)
6 prontosan.tw. (67)
7 5 or 6 (83)
8 4 and 7 (73)

Ovid MEDLINE(R) ALL <1946 to January 04, 2021>

1 Wound Healing/ (95347)
2 "Wounds and Injuries"/th [Therapy] (15100)
3 (wound* or burn*).tw. (297594)
4 1 or 2 or 3 (355476)
5 ((Polyhexanide and betaine) or (polihexanide and betaine)).tw. (19)

6 prontosan.tw. (32)

7 5 or 6 (44)

8 4 and 7 (39)

Pubmed

Searched for: prontosan and wound

Web of Science

5 37 #4 AND #1

4 42 #3 OR #2

3 27 TS=(Prontosan)

2 23 TS=((Polyhexanide AND betaine) OR (Polihexanide and betaine))

1 442,102 TS=(wound* OR burn*)

Scopus

(TITLE-ABS-KEY (wound* OR burn*)) AND ((TITLE-ABS-KEY ((polyhexanide AND betaine) OR (polihexanide AND betaine))) OR (TITLE-ABS-KEY (prontosan)))

MAUDE – adverse events

Searched for: Prontosan

MHRA

Searched for: Prontosan = 0 results

polyhexanide betaine = 0 results

polihexanide betaine = 0 results

Clinicaltrials.gov
Results = 1

prontosan | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies = 1 study
polyhexanide betaine | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies = 0 studies
polihexanide betaine | Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies = 0 studies

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ICTRP
Results =

Prontosan AND wound* = 13 (but 1 withdrawn so 12)
Prontosan AND burn* = 0 additional
Polyhexanide betaine AND wound* = 0
Polyhexanide betaine = 0

EAC study selection

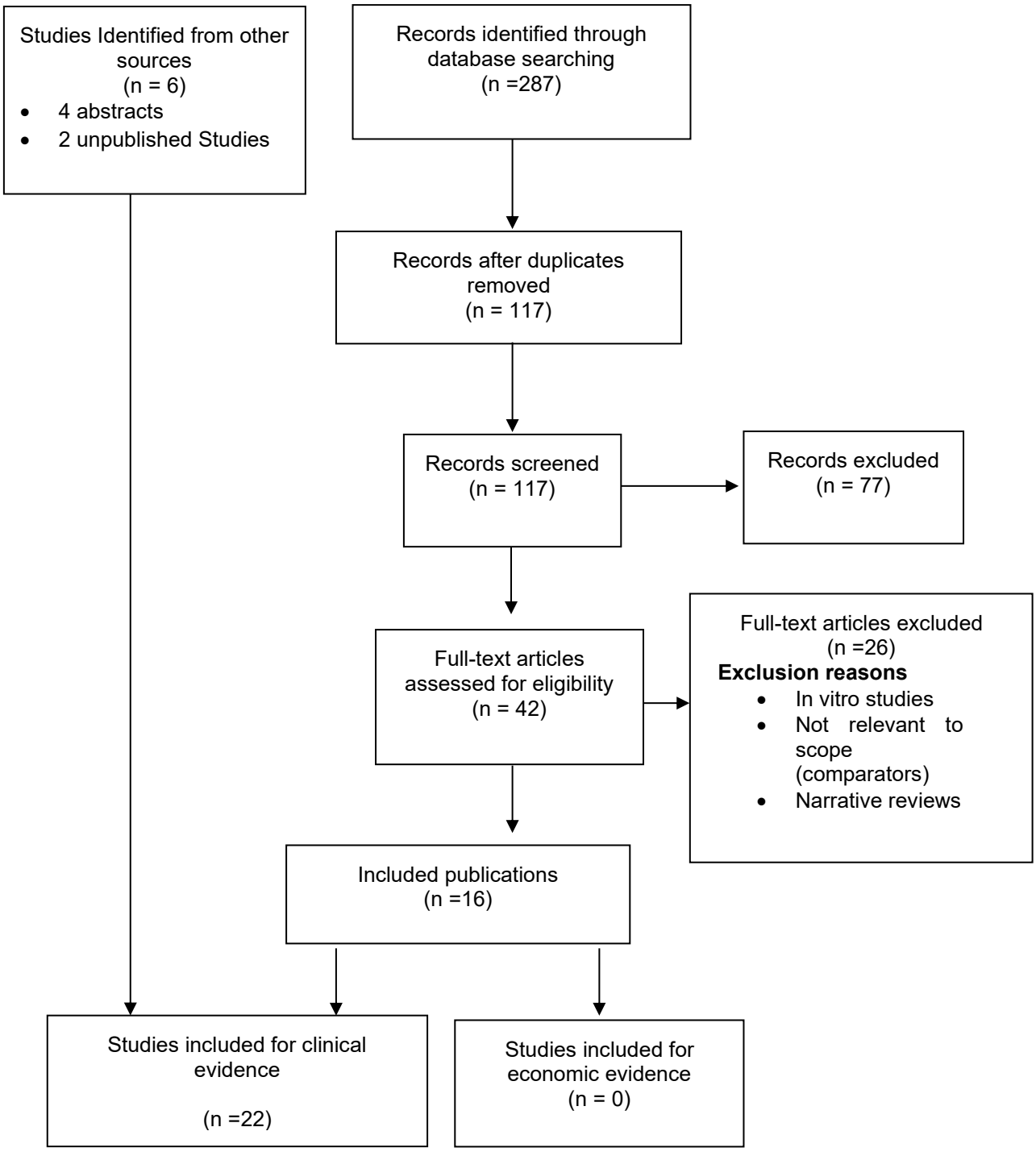


Table XX: Company and EAC included studies comparison

Author	Company Submission	EAC	Comment
Andriessen 2008	Yes	Include	
Assadian 2018	Excluded	Include	Prontosan and Prontosan+Octenilin compared with a number of different approaches including saline - use only the Prontosan data. The company excluded because Prontosan has not been used according to the instructions but I think it should be included for full spectrum of possible uses although applicability will be limited.
Atkin 2020	Yes	Include	
Belingeri 2016	Yes	Include	
Borges 2018	Excluded	Include	Prontosan The company excluded because Prontosan has not been used according to the instructions but I think it should be included for full spectrum of possible uses
Ciprandi 2018	Yes	Include	Prontosan
Collier 2017	Yes	Exclude	Meeting report, not clinical study data.
Davis 2013	No	Exclude	Not human study
de mattos 2019	No	Exclude	Prontosan is included but study not evaluating Prontosan
Durante 2014	Yes	Include	Prontosan gel

Author	Company Submission	EAC	Comment
Findlay 2013		Exclude	Publication related to Trial ID EUCTR2006-006928-18-GB. Not identified in the searches. Not relevant to scope – not wounds
Finnegan 2018	No	Exclude	Ex vivo study
Hirsch 2009	No	Exclude	In vitro study
Hirsch 2010	No	Exclude	In vitro study
Hirsch 2011	No	Exclude	In vitro study
Horrocks 2006	Yes	Include	
Hunt 2016	No	Exclude	N=1
Kaehn 2007	No	Exclude	In vitro study
Kiefer 2018	Yes	Include	
Kim 2015	No	Exclude	Negative Pressure wound therapy is not relevant to the scope
Kim 2020	No	Exclude	Negative Pressure wound therapy is not relevant to the scope
Kramer 2018	No	Exclude	Review Article
Kristiano 2020	No	Exclude	Study in rats

Author	Company Submission	EAC	Comment
Möller 2008	Yes	Include	
Moore 2016	Yes	Include	
Nunes 2019	No	Exclude	Not relevant to scope. All patients treated with Prontosan and saline before being treated with one or other of the study treatments.
Queiros 2013	No	Exclude	Systematic review protocol
Ricci 2018	Yes	Include	
Romanelli 2010	Yes	Include	
Saleh 2016	No	Include	Publication is related to trial ID NCT02253069 Include as skin grafts could be considered sub-group in scope - post-operative wound
Schroder 2014	No	Exclude	Danish language
Stolarick 2010	No	Exclude	In vitro study
Uygar 2008	No	Exclude	Study in rats
Valenzuela 2008	Yes	Include	
Wattanaploy 2017	Yes	Include	Include as relevant but out of scope as the comparator in the scope is not silver sulfadiazine
Wilkins 2013	Yes	Exclude	Not systematic review/meta-analysis
Wiegand 2017	No	Exclude	In vitro study

Author	Company Submission	EAC	Comment
Wu 2016	No	Exclude	Chinese language
Yang 2020	No	Exclude	Study in rats

Appendix B Data Extraction Tables

Data Extraction for Included Studies by wound type

Venous Leg Ulcers

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Andriessen (2008) **Country** Germany **Data collection** Not reported **Study Design** Comparative: non-concurrent cohort study	To investigate the clinical and cost effectiveness of wound antiseptic to treat problem wounds **Outcomes** Ulcer closure Wound evolution	112 patients with venous leg ulcers **Demographics** Females/males: 81/31; age range: 47 to 93 years Detailed inclusion/exclusion criteria not reported but leg ulcer must be present for at least 3 months; patients with persistent, severe, arterial circulatory disorders (stage II and higher according to Fontaine) were excluded **Setting**	**Wound Treatment** Wounds were cleansed for 15 minutes with a wet phase and short resting (dry) phase to restore periwound skin integrity (15 mins) All patients received standardised compression treatment, bandages were changed every 5 days. An absorbent moist wound healing dressing (alginate and/or foam) was used if necessary.	**Study Group:** Prontosan solution (n=59) **Control Group:** Saline or Ringer's solution (n=53) Wet Phase: 15 min cleanse Dry Phase: 15 min resting phase to restore periwound skin integrity	**Wound healing** • 47/53 (89%) in the saline/Ringer's solution group healed completely at 6 months • 57/59 (97%) in the Prontosan group healed completely at 6 months • Wounds in the Prontosan group healed in a shorter time compared with saline/Ringer's (60% versus 28% within the first 3 months) • At 6 months 97% of wounds in Prontosan group were healed compared to 89% in saline/Ringer's group ($p<0.0001$) • Wounds in the Prontosan group	**Limitations** • Retrospective comparisons • Control group had mixed interventions (saline or Ringer's) combined • Primarily narrative/descriptive results with limited statistical analysis • Aims, although not clearly stated, do suggest cost-effectiveness is a consideration however this is not included in the results

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		Community wound healing clinic	**Statistical Analysis** Kaplan-Meir mean estimate for healing time for both treatment groups **Follow-up** To ulcer closure or 6 months.		healed significantly quicker than the saline/Ringer's group (mean time to healing was 3.31 months (SE 0.17) versus 4.42 months (SE 0.19) p<0.0001). **Wound Infection** (defined as clinical signs) • 7/53 (13%) in the saline/Ringer's group experienced infection • 2/59 (3%) in the Prontosan group experienced infection	**Applicability** • Population group is relevant however full inclusion/exclusion criteria are not defined • Prontosan compared with saline/ringers solution is a relevant comparison however the data for the comparison group is combined – no comment can be made on the efficacy of Prontosan compared with saline or Ringer's solution specifically as data are not reported separately

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
						The number of patients in the comparator group who were treated with saline and with Ringer's solution is not reported. **Funding/CoI** Not reported
Borges (2018) **Country:** Brazil **Data collection** Not reported **Study Design: Comparative:** randomized controlled trial	To investigate the effect of a PHMB cleansing solution on bacterial load and bacterial biofilm in venous leg ulcers. *Primary/secondary outcomes not defined* **Outcomes:** Examine characteristics of venous leg ulcers including • Wound duration • Wound area • Necrosis	N=44 patients with venous leg ulcers **Demographics** Not reported for randomized participants only those analysed, age range: 33-90 years; female/ male: 18/9 **Inclusion** • Adult patients • Confirmed venous leg ulcer • Clinical signs of venous	**Sample Size** No sample size calculation **Randomisation & Allocation** Random number table, not reported if 3rd party or allocation concealment method **Wound Treatment** • Wounds were measured and anaesthetized	**Intervention:** Prontosan, 1 minute irrigation under continuous pressure (n=22) **Comparison:** Saline (0.9%), 1 minute irrigation under continuous pressure (n=22)	Patients with an absence of bacteria in the first wound tissue fragment biopsied were eliminated (3 from the saline group and 14 from the Prontosan group) **Analysis included:** N=19 in the saline group N=8 in the Prontosan group No significant difference in baseline characteristics No significant differences between the groups and the effect of the	**Limitations** Patients were not followed until complete wound healing Small sample sizes – study likely underpowered Not intention to treat analysis **Applicability** Likely limited applicability to NHS setting as wounds irrigated for 1

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
	Examine the effect of cleansing solutions on bacterial load Compare the bacterial load reduction of cleansing solutions Detect presence of biofilm	insufficiency (oedema, varicose veins, hyperpigmentation, liopdermatasclerosis, ankle-brachial pressure index between 0.8 and 1.3) • Wound at least 8 weeks duration • Area greater than 6cm^2 • No clinical sign of infection • No systemic/topical antibiotics/antiseptics to the wound in the week prior **Exclusion** • Pregnancy • Cancer • Immunosuppressant drugs • Radiotherapy	• Area with lowest concentrations of necrotic tissue chosen for sampling • Two fragments collected using a 3mm punch both before and after irrigation **Assessment** • Number of CFUs per gram of tissue • Transmission electron microscopy (TEM) to visualise bacteria and biofilm **Statistical Tests** • Cochran and Shapiro-Wilk test for homogeneity of variance and normality		• Wound duration (months) • Wound area (cm^2) • Necrosis (%) **Bacterial Load** Bacterial profile at baseline *Staphylococcus aureus* (10 patients) *Proteus Mirabilis* (10 patients) *Pseudomonas aeruginosa* (10 patients) *Escherichia coli* (7 patients) *Proteus Vulgaris* (3 patients) *Morganella morganii* (3 patients) *Enterobacter cloacae* (3 patients) *Enterobacter aerogenes* (2 patients) *Proteus penneri* (2 patients) *Citrobacter freundii* (2 patients) *Enterobacter spp.* (2 patients) *Escherichia blattae* (2 patients) *Citrobacter spp* (1 patient)	minute with no soak applied. Unclear whether wounds had multiple cleansings/dressing changes or whether only a single cleanse. Results suggest a single wound cleanse with Prontosan or saline with bacterial swabs taken immediately before and immediately after. Company excluded this study as Prontosan not used according to IFU **Funding/CoI** Financial support from FAPEMIG

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		Setting Dermatology outpatient clinic	• Students t-test or F-test • Pearsons correlation coefficient **Follow-up** No follow-up – biopsy taken before and after cleansing.		Both cleansing solutions reduced the bacterial load (CFUs/g) compared with baseline. No significant difference in reduction of bacterial load between solutions. Interaction between group and sampling time variables was not significant. There was a significant correlation between wound area and bacterial count after wound cleansing (p=0.0070; *r*=0.51) TEM revealed the presence of large numbers of bacteria with indications of biofilm in the majority of cells after cleansing in both groups.	
Romanelli (2010) **Country** Italy	To evaluate the efficacy and tolerability of a propylbetaine and polyhexanide solution to control the	N=40 patients **Demographics** Age range: 55-73 years;	**Randomisation & Allocation** Electronic system randomized into two groups of 20 patients, allocation	**Group A** Patients treated every other day with Prontosan solution plus standard wound care (polyurethane foam and elastic compression), (n=20)	**Demographics** No statistically significant differences at baseline with regard to • Age • Mean disease duration	**Limitations** • Small sample size • Use of Prontosan not clearly reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Duration Not reported **Study Type** Comparative: randomized controlled trial	bacterial burden of chronic wounds **Outcomes** • Wound size - Dedicated planimetry software (Silhouette, Arnaz, New Zealand) • Wound surface pH - Flat glass electrode connected to a meter (skin pH meter HI99181, Hanna Instruments, Italy) • Pain - Self-assessment reported by patients using VAS	females/males: 22/18. **Inclusion** • Painful chronic leg ulcer >8weeks old • Clinical and instrumental signs of venous insufficiency • Wound size up to 100cm^2 • Compression therapy for at least 2 weeks before inclusion • Aged over 18 years **Exclusion** • Allergy to one of the materials used • Severe systemic diseases • Acute superficial or deep vein thrombosis	details not reported or if 3rd party. **Statistical Tests** • Analysis of variance and students t-test to evaluate change in wound surface pH and pain • Wilcoxon test and Mann-Whitney test to analysis wound healing time and ulcer planimetry Per-protocol analysis. **Follow-up** 4 weeks (treatment duration)	**Group B** Patients treated every other day with saline plus standard wound care (polyurethane foam and elastic compression), (n=20) 2 patients from group B lost during treatment	• Mean wound size Pain score • Mean disease duration was 24 months (2-191 months) **Wound surface pH** • Median baseline pH was 8.9±0.6 After 4 weeks of treatment • median pH was reduced to 7.0±0.3 in group A. • Wound surface pH was significantly lower in group A compared with group B (p<0.005) • Mean wound surface pH showed statistically significantly higher values compared with normal skin (p<0.03) **Bacterial Burden** Group A showed significantly better control of bacterial burden at the end of the study (p	(no time, soak information) **Applicability** • Not a UK based study however wound treatment approach appear consistent with UK practice • Population, comparator and interventions are relevant **Funding/CoI** Partially funded by B. Braun AG, author received financial support for clinical consulting from B. Braun Medical AG.

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Arterial occlusive disease (stages II, III or IV) • Any arterial disease with an Ankle Brachial Pressure Index <0.8 • Immobile/bedridden patient • Pregnancy/breastfeeding • Severe lymphoedema of the leg • Diabetes with complications • Well-known hypercoagulability • Thrombophilia with deep vein thrombosis **Setting** Outpatient wound clinic of dermatology department			values not reported) **Pain** • By 4 weeks, pain control was significantly better in group A compared with group B ($p<0.05$) **Wound Size** • Wound size did not differ significantly between the two groups from baseline to study end **Adverse Events/Tolerability** • No serious and/or unexpected adverse events reported • Prontosan was well tolerated by patients	

Burns

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Ciprandi (2018) **Country:** Germany, Italy, Belgium, UK, Russia **Data collection** December 2012 and March 2016 **Study Type** Non-comparative: retrospective data review	To obtain information on the safety profile of the Prontosan range of products in children **Outcomes** Safety based on adverse events including: • Allergies • Infection signs and symptoms • Adverse reactions related to the product or any other signs and symptoms associated with allergic reaction Burns were characterised by their diagnosis, total body surface area and depth.	N=198 children treated with Prontosan **Demographics** Newborns 0-4 weeks =1; infants 5 weeks to 1 year=48; children older than 1 year=149; female/male: 83 (41.9%)/115 (58.1%) 74.7% of burns were partial and deep thickness 46% of patients had only one burn site Locations including: • 33.3% thorax • 29.3% hands • 22.2% upper arm • 20.2% face	Prontosan was used as per usual standard treatment practice in each centre Data were collected from medical records via questionnaire and transferred to a case report form (CRF) **Follow-up** Not reported	**Intervention** Prontosan products including gels and irrigation solutions combined with skin substitutes and skin grafts where needed. 58.6% of children were treated with Prontosan throughout the healing period and 25.3% for more than 80% of the time. Dressings were changed on average every 2-4 days 79.3% of children were administered analgesics 30.3% took antibiotics to complement burn treatment with Prontosan. There were 117 surgical interventions for burns including, 46 split skin grafts, 35 debridements, 33 necrectomies and three escharotomies.	**Baseline Characteristics** The majority of children treated for burns (80.1%) were under the age of 4 years and there were more boys than girls Adverse events were reported in 5 children after using Prontosan • Itching (n=3) • Rash (n=1) • Hyper-granulating tissue (n=1) 4 cases were mild and one was moderate with treatment withdrawal, none were severe. N=16 patients had clinical signs of infection during treatment with 11/16 developing clinical signs of infection during treatment and antibiotics given to 8/11. No treatment changes resulted due to clinical	**Additional Information** Dressing used in combination with Prontosan included: • Low adherent/non-adherent/non-adhesive or basic care dressings/bandages/plasters **Limitations** • No comparator • Retrospective data review • Possible variation in wound management/treatment protocols • Not all children treated with Prontosan for the entire healing period.

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		Inclusion Treated burns of any degree including: • Scalds • Flame • Contact • Electric • Explosion Third degree with known treatment outcome. **Exclusion** Not specified. Paper states 'any exclusion criteria was defined before the data collection' **Setting** Not reported			signs of infection and Prontosan use continued. **Healing time** Healing time (not clear if mean, median or other) was • 11.5 days for TBSA < 5% • 15 days for TBSA 5-19% • 8.5 days for superficial burns • 10.9 days for superficial, partial thickness burns • 13.5 days for deep partial thickness burns • 17.2 days for full thickness burns **Physician Reported Satisfaction** 73.2% were satisfied 16.2% considered it good 10.6% considered it very good	**Applicability** UK data included although only 20 (10.1%) of the questionnaires were from the UK. Evidence specifically in children is directly applicable to the scope. **Funding/CoI** Authors received grant from B. Braun. No CoI to declare.
Kiefer (2018) **Country** Germany	To evaluate graft take and healing of skin grafts following moistening and	N=56 patients with burn wounds requiring surgical debridement	**Statistical Tests** • Wilcoxon and Kruskal-Wallis tests for clinical	Prontosan Wound Gel X **Wound management**	N=51 patients included in analysis (n=4 withdrew, n=2 reassessed and did not receive STSG, n=1 had	**Limitations** • Non-comparative study

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Data collection April 2015 to May 2015 **Study Type** Non-comparative: case series	cleansing with Prontosan wound gel X **Primary Outcome** • Healing of split thickness skin graft • Time to complete re-epithelialisation • Wound infection • Reoperation of the grafted site during the 30 day study period **Secondary Outcome** • Tolerability and safety of Prontosan wound gel • Pain at the grafted site	followed by split thickness skin grafts (STSG) **Demographics** • 70.6% male • BMI 26.3±4.3kg/m^2 • 47.1% smokers • Mean total burn surface area: 10.7±11.9% of total body surface • Target wound size: 177.2±191.2cm^2 **Inclusion** • Aged ≥18 years • Clinically assessed deep partial or full thickness wounds requiring STSG • Wound size between 10cm-1000cm^2 **Exclusions**	and photo-planimetric assessment of re-epithelialisation • Survival analysis (Kaplan-Meier, log rank plot) for time to complete re-epithelialisation • Rank test for monotonic trend to assess change in pain **Follow-up** 30 days or until complete graft take occurred	• Prontosan gel X applied immediately after skin grafting as a thin (3-4mm) layer • Cover dressing consisting of Vaseline gauzes followed by sterile compresses and elastic bandages • Prontosan treatment repeated on post-operative day 5 and every other day until day 29 or earlier if skin graft took. • No systemic antimicrobials were administered postoperatively unless required	pre-existing allergy to polihexanide) **Primary Outcome** • 14 patients (27.5%) showed complete graft take on post-operative day 5. • Median time to complete re-epithelialisation was 7 days (mean 7.1±0.2; 95% CI, 5-9 days) • Time to complete re-epithelialisation did not depend on wound size at baseline (p=0.92) **Secondary Outcomes** • No wound infections were reported • 1 graft failure was reported but not considered related to Prontosan use • 12 patients experienced one to four adverse events resulting in 28 individual events.	• Small sample size • No baseline infection data **Applicability** • Population is applicable to the scope (burns patients) as is the intervention. **Funding/CoI** Sponsored by B. Braun Medical AG

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Pregnant women • Exposed hyaline cartilage • Previous skin graft failure • Total burn surface area ≥70% • Infection at target wound site • Insulin dependent type I diabetes • Allergy or sensitivity to any of the ingredients in the gel or to chlorhexidine • Immunosuppression drugs, steroid therapy or chronic haemodialysis **Setting** Not specified			**Pain Assessment** • Changes in pain over time showed a monotonic trend ($p<0.01$) • Changes from baseline was not significant in 2 centres but significant in one centre ($p=0.01$)	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Wattanaploy (2017) **Country** Thailand **Duration** September 2013 to May 2015 **Study Type** Comparative: randomized controlled trial	To compare clinical efficacy of polyhexadine/betaine gel with silver sulphadiazine in partial-thickness burn treatment **Primary Outcome** • Healing time (time to complete gross ephithelialisation) **Secondary Outcomes** • Burn wound infection • Bacterial colonisation • Pain during dressing change • Treatment cost • Staff satisfaction • Patient satisfaction	N=46 patients with partial-thickness burn wounds **Demographics** Age: intervention 36.2 (±7.6), comparator 34.9 (±7.8); female/male: intervention 9/14, comparator 11/12 **Inclusion** • 18 to 60 years of age • Partial thickness burn wounds within 48 hours after injury • Burns more than10% of total body surface area (TBSA) **Exclusion** • Pregnancy or lactating patients • Underlying disease that	**Randomization & Allocation** Randomized by computer and allocated to one of 2 groups, allocation details not provided and unclear if 3rd party. **Wound management** • Cleansed once daily with saline and either intervention or comparator (3-5mm thickness) and covered with gauzes • Wounds evaluated daily • Wound surface swab culture once weekly **Statistical Tests** • Student t-test to analyse	Intervention (N=23) Polyhexadine/betaine gel (Prontosan wound gel X), (n=23) Comparator Silver sulphadiazine, (n=23) Cleansing was performed with saline before 3 to 5 mm thickness of treatment and then the wound was covered with gauzes. Wounds cleansed once daily.	**Demographics** No significant difference observed between the groups for any parameter. **Wound Healing** All patients showed complete epithelialisation of wounds within 3 weeks No infections or surgical treatment was required Time to healing did not differ significantly between the groups: 17.8±2.2 days (Prontosan) compared with 18.8 days±2.1 days (silver sulphadiazine); p=0.13. 6 patients (26.1%) in each group had positive surface swab culture without signs/symptoms of infection. Routine swab cultures a week later were negative **Pain Score** Pain score was significantly less in the Prontosan group	**Limitations** • Comparator out of scope • Saline used in both arms • Small sample size • Detailed treatment costs not reported • Overall difference in pain scores across the treatment are not reported. Pain scores on individual days of treatment may not be of relevance. **Applicability** • Not a UK based study however wound treatment approach appear consistent with UK practice

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		interferes with wound healing (diabetes, end-stage renal disease, postradiation, on immunosuppressant drugs, immunocompromised disease) • Hypersensitivity to polyhexanide/betaine gel or silver sulphadiazine • Impaired consciousness or endotracheal intubation **Study setting** Burn unit of hospital	difference of means • Chi-square test to explore relationships between parameters • Kaplan-Meier analysis for healing time **Follow-up** 3 weeks		at 4 to 9 days and 12 days after treatment ($p<0.05$) but not on any other treatment day. **Treatment Satisfaction** Staff consistently reported • Prontosan was easier to use when changing dressings • wound dressing was easier to evaluate with Prontosan Patients reported being satisfied with Prontosan **Treatment Costs** No significant difference in treatment costs between the groups ($p=0.057$)	• Population relevant • Intervention somewhat relevant (Prontosan wound gel X) but saline which is the scope comparator is used to cleanse in both arms. This may be one possible treatment pathway in the UK but more likely that Prontosan solution would be used. **Funding/CoI** Nothing to declare

Surgical Site Wounds

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Saleh (2016) **Country** Sweden **Duration** September 2014 and September 2015 **Study Type** Comparative: randomized controlled trial	To assess the efficacy of a PHMB based antiseptic solution in lowering bacterial loads of full-thickness skin grafting wounds and the risk of surgical site infection **Outcomes** • Bacterial load • Development of surgical site infection (SSI) • Presence of intranasal *S aureus* and examining its relevance for the bacterial dynamics of surgical wounds	N=40 patients with skin malignancies excised **Demographics** Age range: 45-92; Female/Male: 22/18 **Inclusion** • Aged ≥18 years • Planned facial FTSG • Grafts harvested from the neck **Exclusion** • Diabetes • Antibiotics within 4 weeks before surgery • Planned antibiotic therapy **Setting** Hospital	**Randomization & Allocation** Software used to generate randomisation lists, allocation details not provided or if 3rd party. **Sample size** 16 patients in each arm for 80% power with α value 0.05 **Statistical tests** • Mann-Whitney U test to examine differences between groups. • Chi-square test for differences in categorical variables • Student t-test for continuous variables	Intervention Skin graft sutured, tie-over dressing soaked with Prontosan applied (n=20) Comparator Skin graft sutured, tie over dressing soaked with sterile water applied (n=20)	**Demographics** No significant difference between the groups for • Age • Sex • Wound location • Tumour excised No significant difference in bacterial load levels measured • before surgery • end of surgery • at 1 week after surgery 10 wounds were assessed as infected of which 8 were in the intervention (Prontosan) group giving a statistically significantly higher rate of infection (p=0.028) Presence of intranasal *S aureus* before surgery was associated with a	**Limitations** • Small sample size • Limited outcome comparisons reported • Time Prontosan soak was applied for is not reported • SSI performed by 1 investigator **Applicability** • Only SSI reporting likely to be of use • Method of Prontosan and sterile water use may have limited applicability to UK practice **Funding/Col**

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
			Intention to treat analysis. **Follow-up** 7 days post-surgery		higher post-operative bacterial load.	Funding provided by Swedish government and research council. One author received consulting support from Molnlycke Health Care.

Mixed Aetiology Wounds

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Assadian (2018) **Country**Switzerland **Data collection** June 2011 to April 2016 **Study Design** Multi-arm parallel group randomized trial	To evaluate the antibacterial effect of different irrigation solutions during a 20 minute wet-to-moist cleansing in chronic wounds **Primary Outcome** Difference in the quantitative number of microorganisms per 1cm^2 of wound surface harvested	260 patients (308 randomized) with a total of 299 chronic wounds. **Demographics** Mean age 72 years (± 12). There were significantly more female patients ($p<0.01$) female patients presented more frequently with venous or	**Sample size:** A priori power analysis indicate that 11 participants per intervention and minimal bacterial bioburden of 10^3 CFU per wound be appropriate to test for equivalence ($\alpha = 0.05$, power 95%). **Statistical Tests:**	• Nawalution (n=11) • ActiMaris forte 3% (n=20) • Povidone-iodine 1% (n=22) • Anosteralyt (n=14) • Octenilin (n=22) • Prontosan + Ocetenilin (n=16) • ActiMaris sensitive 1.2% (n=31) • Microdacyn 60 (n=17) • Prontosan (n=33) • Biosept (2013) (n=37)	**NOTE: Only results relating to PRONTOSAN and SALINE are reported** N=33 patients (36 wounds) treated with Prontosan N=12 (14 wounds) patients treated with saline **Microbial Colonisation Spectrum**	No clearly defined control, patients randomized to one of a number of treatment options. Author labelled study as a cohort study Only relevant Prontosan and saline results presented which

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Note: the study methods report that patients were randomized to one of 12 wound irrigation solution using a computerised randomisation programme, dynamic allocation and stratification by wound size. Patients and wound care-givers were aware which irrigation solution was used. Microbiologist and statistician were blinded.	before and after a 20 minute wet-to-moist cleansing. Swabs taken using the Levine technique. **Secondary Outcomes** None	mixed arterial venous leg ulcers ($p<0.01$). Males presented more frequently with pressure ulcers ($p<0.01$) **Inclusion Criteria:** One or more of following had been present for more than 3 months irrespective of previous treatment: • arterial ulcer • pressure ulcer • venous leg ulcer, mixed arterial-venous leg ulcer • diabetic foot ulcer **Exclusion Criteria:** • Pregnancy • Systemic antibiotics within 14 days before dressing change	CFU counts transformed to natural log Two-sample comparisons at per wound level using two-sample t-tests (two-tailed homoscedastic paired t-test or Wilcoxon rank-sum test for continuous and ordinal variables **Follow-Up** No post treatment follow-up	• Biosept (2012) (n=25) • NaCl (saline) (n=12)	*Most common reported for the whole cohort (% of all wounds)* • 8% of cultures – multiple organisms • 25.5% - *Staphyloccus aureus* of which 8% were methicillin resistant strains • 16.3% - *Enterococcus* spp • 17.7% *Proteus mirabillis* • 14.3% *Pseudomonas aeruginosa* • 9.5% - *Escherischia coli* **Reduction of bacterial bioburden** • Using 0.9% NaCL (saline) did not significantly reduce the planktonic bacterial burden on wounds ($p=0.761$). • Using Prontosan did not significantly reduce the bacterial burden ($p=0.051$)	may impact study power All wounds were cleansed with saline and swabbed and then a soak applied for 20 minutes before a second swab taken. **Applicability** Company excluded this study on the basis that it was used outside of the Instructions for Use. The EAC included it as clinical experts suggest a wide variation in practice therefore it is useful for the committee to understand the impact of using Prontosan outside the instructions for use.

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Known allergy to the applied wound irrigation solution • Unable to provide consent **Setting** Wound Competence Centre			All other interventions apart from Biosept resulted in a significant reduction in bacterial burden.	Overall applicability is limited No conclusions can be made on wound healing or prevention/development of wound infection According to the authors, tissue biopsy is considered the gold standard for determining bacterial bioburden. **Funding/CoI** Not reported
Atkin (2020) **Country** UK **Data collection** Not reported **Study Design** retrospective, multi-centre case series	To review and combine results of multiple case studies in the UK into a case series to evaluate outcomes and provide an overview of effectiveness of PHMB and betaine wound irrigation solution and gels in hard to heal wounds	24 case studies comprising 52 hard-to-heal wounds from 50 patients. 11 case studies excluded (6 for use of debridement pad as primary treatment, 3 covering biofilm pathway, 1 covering	No statistical methods reported. Pain scores recorded directly via a numeric pain score or binary pain status or indirectly by use of pain medication.	**Solution group** PHMB and betaine irrigation solution alone (n=16 wounds) **Solution and gel group** PHMB and betaine irrigation solution in addition to PHMB and betaine gel (n=36 wounds) Soak times with cleansing solution varied according to	**Reasons for using PHMB/betaine** • Wound duration (n=20 >1 month, n=15 >3 months) • Fail to heal due to infection (n=14) • Postoperative/trauma complications including wound dehiscence (n=7)	**Limitations** • Retrospective pooled analysis of 24 case studies with no specific detail of setting or demographics. • Noted that authors observed large wound areas

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
study (secondary data analysis)	Wounds were considered hard to heal if: • They were determine chronic or complex by the original study author • >6 weeks in duration • Presenting with signs of complications (infection, suspected biofilm or necrosis) **Primary Outcome** Not clearly stated Outcomes appear to be • Proportion of wounds achieving partial healing • Impact on complete wound healing for	burns, 1 insufficient data) Wound and patient characteristics were reported where available: • Number of patients and wounds • Type of wound • Previous treatment history • Age of wound • Wound details (malodour, exudate, slough and size) • Pain level (analgesia use) • Dressing change details • Duration of new treatment • Patient quality of life. **Inclusion** • Use of PHMB and betaine wound irrigation		wound condition, with the majority stating 5–10 minutes.	• Complicated healing by secondary intention (n=38) Duration of cases ranged from 9 days to 10 months. Treatment was followed to complete wound healing for 12 (23%), the reason for ending observation was not given for the other 77%. **Wound Healing** Wounds ,<1 month duration excluded from analysis N=23 wounds included • Complete healing in 12 wounds (10 treated with solution and gel; 2 with solution alone • 26.1% of healed wounds were healed within 2 months • Of the remaining 11 wounds, 8 demonstrated	up to 300cm^2 which had been unhealed for up to 20 years. • Non-comparative although does try to make some comparisons between solution+gel and solution alone • Small sample size • Narrative/Descriptive results – no statistical analysis • Treatment plans not reported (soaks, irrigation etc) • Duration of study not reported **Applicability** • UK based study with very

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
	wounds treated to >1 month	solution alone or in addition to PHMB and betaine gel **Exclusion** • Acute, non-complex wounds • Wound pathway without primary data • Insufficient data • Burns • Primary focus of debridement pad use **Setting** Not reported			improvements and wound size reduction and 3 had no details **Wound Area** Reported for 8 wounds • >90% reduction observed in 5 wounds within 3-6 months • Mean wound size reduction of 75.6% **Initial Improvements** N=33 (63%) wounds, for others only endpoint data available. • Earliest initial improvement was observed within 2 days in the solution + gel group and within 4 weeks in the solution alone group Considering both groups together, initial wound improvements were observed	limited patient reported outcomes. • Mix of solution+gel and solution alone likely to be indicative of wider UK practice • Population is applicable to scope although some patients with applicable wounds (burns) were excluded. **Funding/CoI** One author employee at B. Braun, 2 authors received consulting fees from B. Braun.

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• Within 1 week for 19% (10/52) of wounds • By week 4 for 63% (33/52) of wounds **Pain Score** • Pain was reported for 21 wounds prior to PHMB/Betaine. • 18 (86%) reported reduction in pain of which 2 were pain free • 2 patients previously unable to tolerate compression for leg ulcers were able to initiate compression • 3 wounds were not followed up • 1 wound reported increased pain and stopped treatment. • 8 patients used pain medication at outset with 4 reducing their use and 2 stopping medication **Malodour, exudate, slough**	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• 5/6 wounds (1 not followed up) reported improvements in odour with 3 reporting resolution • 20/20 wounds reported improvement in exudate with 10/20 fully resolved • 16/16 wounds reported slough removed **Dressing Changes** Data for 14 (27%) wounds (13 solution + gel). • Before treatment, dressings were changed an average of 4.68 times per week (SD 2.14) • Follow-up data for 6 wounds indicated a mean reduction in dressing change frequency of 55% • After treatment dressing change frequency was 2.25	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					times per week (SD 0.88) • Reduction was observed an average of 16.5 days (SD 8.8) after treatment started **Patient Quality of Life (QoL)** • N=10 patients indicated improvements in QoL • 7 patients reported improvements in mobility during course of treatment • Psychological improvements were noted including ○ Improved morale ○ Resumption of social activities ○ Able to engage in family life ○ Go abroad	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					○ Attend social activities	
Bellingeri (2016) **Country:** Italy **Data collection** June 2010 to December 2013 **Study Design Comparative:** randomized controlled trial	To investigate the clinical efficacy of a propylbetaine-polihexaide (PP) solution versus normal saline (NS) solution in patients with pressure ulcers (PUs) or vascular leg ulcers, assessing inflammatory signs and wound size. **Primary Outcomes:** Assessed using the validated 13 item Bates-Jensen Wound Assessment Tool (BWAT) – Reduction in scores indicates improvement. Assessment of wound inflammation was performed through the analysis of a score obtained	N=320 eligible patients with PU or vascular leg ulcer of which 289 randomized. **Demographics** Average age: saline group 77.2 (±15.3), Pronotsan group 79.8 (±12.1); female/male: saline group 81(55.5%)/65(44.5 %); Prontosan group 85(59.4%)/58(40.6 %) **Inclusion:** • Aged ≥18 years • Inpatients, outpatients or hospitalised at home for at least 24 hours • A least one PU category II or II	**Sample size** 165 patients per group to demonstrate a power of 90% and significance level of 5% **Randomization & Allocation** Third party random generated number list & sealed envelope **Primary Outcome** Wound size measured using sterile rule and gridded acetate sheets **Statistical Tests** Two-tailed students t-test	**Intervention** Propylbetaine-polihexanide (Prontosan irrigation solution) (n=143) Irrigation (20-30ml) followed by 10 minute soak **Comparator** Saline (n=146) Irrigation (20-30ml) followed by 10 minute soak	Follow-up was completed for • 141 patients in the Prontosan arm • 139 in the saline arm No significant difference in baseline characteristics including gender, age, Braden scores for PU's, BMI and comorbidities. • 67% vascular leg ulcers (venous and mixed origin) • 25% Pressure Ulcers • Distribution of wound type was similar in both groups • No significant difference in the initial BWAT scores.	**Limitations** Study is underpowered Comparison may not be reflective of NHS practice for the use of saline as clinical experts suggest that soaking with saline would not routinely be done. Risk of selective reporting bias • BWAT results for each item, at each time point are not reported • P values are not reported for all significant time points The narrative results are unclear

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
	from five BWAT items specifically linked to inflammation Pictures of wound taken at each weekly assessment **Secondary Outcomes:** Visual analog scale (VAS) for pain	as described in the NPUAP/EPUAP • Braden score ≥10 for patients with PU or the presence of a lesion of vascular origin • Size of lesion: <80cm^2 (10cmx10cm dressing to cover it) **Exclusion** • Terminally ill patients • Systemic or topical antibiotics and/or antiseptics with 10 days of recruitment • Braden score <10 • Systemic corticosteroids, immunosuppressants or radiotherapy	Analysis was Intention to Treat **Follow-up** Assessment in all patients at T0 (recruitment) T1 (day 7) T2 (day 14) T3 (day 21) T4 (day 28)		**Wound Improvement** Significant changes between T0 and T4 observed for: • Reduction in total BWAT score of overall wound evolution indicating better progression of wounds in the Prontosan group compared with the saline group (p=0.0248) • Reduction in average total BWAT score was significantly better at T4 versus T0 in the Prontosan group • BWAT average inflammatory score indicates a significantly better progression of wounds in the Prontosan group (p=0.03) • Reduction in the average BWAT scores for inflammatory signs	in relation to what they are reporting. The aim of the study was to report a comparison between saline and Prontosan at different time points. The results however appear to report a combination of between groups (saline versus Prontosan) and within groups (Prontosan only) results. **Applicability** Applicable to NHS setting **Funding/CoI** No CoI to declare. B.Braun supplied materials and paid ethics committee fees

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Difficult to reposition or unable to place on pressure redistributing mattress **Setting** 6 centres in either hospital wards or outpatient clinics			that was significantly better at T4 than at T0 in the Prontosan group (n p-value) **Pain** • Pain scores were similar for both groups • Average score was 3.0 • Minimal to no change during follow-up • No significant difference in pain associated with study wounds or dressing changes or in pain suffered between dressing changes **Adverse Events** No treatment related adverse events were reported.	
Durante (2014) **Country** Italy	To evaluate the effects of a polyhexadine and propyl betaine based	N=124 patients with chronic wounds **Demographics**	**Statistical Tests** • Descriptive statistics including mean,	Application of Prontosan wound gel in combination with secondary dressing (alginate/hydrofibre with in	Patients with no positive evolution after two weeks of treatment stopped the study and	**Limitations** • Not a comparative study

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
Data collection Not Reported **Study Type** Comparative: before and after	gel for wound cleansing in the treatment of chronic wounds according to common usage in clinical practice. Effects of treatment applied in combination with a secondary dressing after appropriate cleansing **Outcomes** *Not clearly stated, appear to be:* • Reduction in wound size • Evolution of the wound bed and edges and appearance of surrounding skin • Pain during dressing changes • Microbiological examination of the wound	• 60% female • 217.2 days average wound duration • 33.9% venous insufficiency • 15.3% perigastrostomy • 12.9% pressure wounds **Inclusion** • Wounds caused by chronic venous insufficiency or autoimmune disease • Diabetic wounds in the lower limbs • Pressure sores • Perigastromy wounds • Scleroderma, connective tissue pathologies or microvascular injuries. **Exclusion**	median, standard deviation, frequency, percentages • Paired data to compare difference in pain scores between baseline and final visit. **Follow-up** 60 days or complete healing	cavity wounds, non-adherent dressing for flat wounds), followed by mechanical debridement if necessary. Compression or bandage selected by clinician. If multiple wounds, only the largest wound was treated.	were treated with other therapies, number not reported. Factors affecting healing included: • Diabetes (21%) • Obesity (16.9% • Vascoconstrictor drugs (11.3%) • Malnutrition (17.7%) **Wound Healing** Significant reduction in mean • Maximum length: -17.5±21.4cm ($p<0.0001$) • Minimum length: -15.5±21.1cm ($p<0.0001$) • Wound area: -8.3±16.7cm^2 ($p=0.0001$) **Wound bed improvement** • Patients with increase in re-epithislializing wounds from 0.8% at baseline to 26.6% at final visit	• Unclear what the treatment timings were throughout the study • Numbers in final analysis not reported. **Applicability** • Prontosan gel used which may not be widely used in the UK NHS setting. • Prontosan used in combination with debridement and secondary dressings which is likely reflective of wound management protocols **Funding/CoI** Not reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
	Treatment visits were day 7, 15, 30, 45 and 60 days but no later than eventual complete wound healing. Pain assessed using VAS or FLACC Scale in newborn babies and children under 3 years	• Acute wounds • Arterial ulcers or diabetic foot • Concomitant presence of other serious infectious diseases, cardiovascular, respiratory, neurological, psychiatric, neoplastic, endocrine, terminal state • Ongoing treatment with antineoplastic agents, immunosuppressants, corticiosteroids • Malnourished patients not receiving artificial nutrition • Pregnant or breastfeeding women • Patients showing			• Patients with presence of biofilm reduced from 23.4% at baseline to 1.6% at final visit • Patients with intact periwound skin increased from 17.7% to 75.8% and intact wound edges from 28.2% to 75.8% • 74% of wounds were non-exuding at final visit compared with 14.5% at baseline **Debridement** No substantial change in type of debridement other than reduction in autolytic debridement from baseline (41% to 27%) **Microbiological Cultures** Baseline visit indicated presence of *Staphylococcus aureus* (4 patients),	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		hypersensitivity to one or more of the constituents of the studied drugs. **Setting** Not reported			*Pseudomonas aeruginosa* (1 patient), *P. aeruginosa* + *S. aureus* (2 patients), *Stenotrophomonas maltophilia* + *Staphylococcus hominis* (1 patient), *Escherichia coli* + *S. aureus* (1 patient). *P. aeruginosa* + *Candida albicans* (1 patient), *Serratia marcescens* + *C albicans* (1 patient). Final visit indicated presence of *Staphylococcus aureus* (4 patients) and *Pseudomonas aeruginosa* (1 patient). **Pain Score** Average VAS/FLACC score decreased from baseline to final visit: • VAS: -4.67±2.7; 95% CI -5.36 to –3.98 (p<0.0001) • FLACC: -12±4; 95% CI -10.22 to -7.75 (p<0.00005)	

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					Adverse Events No adverse events of side effects (local or systemic) were reported.	
Horrocks (2006) **Country** UK **Data collection** Not reported **Study Type** Non-comparative: case series	To undertake an evaluation of patients in the community with chronic wounds previously cleansed and irrigated for >1 month with saline. **Objectives (outcomes) listed as** • Removal of biofilm: normal wound bed becoming visible within 3 weeks • Reduction in wound size • Compare use of antibiotic/silver prior to and during use of Prontosan • Patient comfort • Ease of application	N=10 patients with chronic wounds. **Demographics** Age range: 32-85 years; female/male: 6/4 male; wound duration; <1 year to > 5years. Wounds included: VLU, mixed aetiology LU, pressure ulcers, buttock wound, abdominal wound. **Inclusion** • Aged over 18 years • Chronic wound of >1 month that had been treated with saline • Saline discontinued	**Statistical tests** Not reported, descriptive results only **Follow-up** Not reported	Prontosan solution ± Prontosan gel **Wound Care** Irrigate with Prontosan followed by 10 min soak If using gel, apply thin film Use of appropriate conventional wound product Note: unclear if reporting what they specifically did or as follow on to the product information and IFU	• 7/10 patients showed dramatic improvements within 3 weeks with 6/7 no longer requiring use of silver products or antibiotics • Elimination of biofilm and reduction of exudate levels were reported by staff • Previously malodourous wounds had no odour • Visits by community nurses reduced from daily to alternate days or twice weekly visits • All patients reported elimination or reduction in wound pain	**Limitations** • No comparator • Retrospective review • Small sample size • Number of patients using solution + gel not reported – cannot report on results for Prontosan solution alone • Outcome reporting is limited (no statistical analysis) • Conclusions state that Prontosan is safe and cost effective but no cost

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
	• Note any adverse reactions	• Wound appeared to contain biofilm • No other change to patient care/regimen **Setting** Community			• 1 patient withdrawn due to non-concordance with treatment regimen • 2 patients did not report any significant outcome after 3 weeks and were withdrawn	effectiveness outcomes are reported. **Applicability** UK setting in a relevant population and setting (community setting) **Funding/CoI** Not reported
Möller (2018) **Country** Germany **Data collection** January 2005 to March 2007 **Study Type** Non-comparative: case series	Not clearly stated: To evaluate the use of Prontosan in wound management as part of standard care **Outcomes** • Wound Evaluation (healing, improvement, no improvement) • Wound Infection	N=953 patients **Demographics** Female/male: 571/382; mean age >65 years No detailed inclusion/exclusion criteria reported. **Setting** Outpatient wound clinic	**Statistical tests** Not reported, descriptive results only **Follow-up** Not reported	• Prontosan solution for irrigation of all wounds ay every dressing change • Additional application of Prontosan gel if there was no/moderate exudation • Hydrofibre/foam dressing and other dressings used as appropriate to wound type Cleansing effect of irrigation solution and supportive removal of non-vital tissue components by gel were evaluated separately and in combination	**Wound type** • 62% - Diabetic foot syndrome • 10% - leg ulcer (CVI stage III) • 8% decubitis grade II or higher • 16% of patients were treated for post-operative disturbances of wound healing • 4% had reactions to radiotherapy **Wound healing** At treatment outset, • 41% of patients had wound infection	**Limitations** • Retrospective review of patient records • No comparator • No formal statistical analysis despite large sample size • Detailed methods reporting is lacking • Unclear if peer reviewed publication • Translation from German

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• 11% had heavily contaminated wounds These patients were given systemic antibiotics as well as combination treatment. • 8% of patients were given infection treatment prophylactically • Two thirds of patients with diabetic foot had wound infections at treatment outset but these persisted for maximum 5 days after treatment • 3% developed infection during treatment compared with 40% before the use of Prontosan • 620/953 patients reported a great or complete improvement in wound odour **Safety and tolerability**	language provided by the company, the EAC cannot verify the accuracy of the translation **Applicability** • Although not UK based, the treatment protocol for the included patients appear relevant. • Both Prontosan irrigation solution and gel are used which is relevant to the decision problem but the results are not reported separately if patients were treated with irrigation solution alone. • Population is relevant to the

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• 1% of treated patients reported a slight burning sensation	decision problem **Funding/CoI** Not reported
Moore 2016 **Country** USA **Data collection** 2011 to 2013 **Study Type** Non-comparative retrospective chart analysis	To investigate the number of days to wound closure, change in absolute wound size and antibiotic initiation following application of Prontosan **Outcomes** • Time to wound closure • Absolute change in wound size • Initiation of antimicrobial therapy	N=49 patients (70 wounds) who had complete wound closure defined by complete epithelialisation. **Demographics** Age • ≤49 years (16.3%) • 50-79 years (63.3%) • ≥80 years (20.4%) • Female (55.1%) • Mean BMI 30kg/m^2 (SD 7.5) Comorbidities included hyperlipidemia (42.9%),	**Wound Management** Prontosan irrigation solution or wound gel applied to the wounds at regular clinic visits per standard of care **Statistical Tests** Descriptive statistics: Mean, standard deviation, median and range **Follow-up** Followed up as needed but at a minimum once monthly from baseline to complete epithelialisation	Intervention: Prontosan wound irrigation solution and Prontosan wound gel	**Wounds** n=19 Surgical wounds n=17 Trauma wounds n=16 Venous leg ulcers n=7 Burns n=6 Diabetic Ulcer n=5 Pressure Ulcer **Wound Closure** Days to wound closure varied according to aetiology: Mean days to wound closure: • 67±38 days for surgical wounds • 34±22 days for trauma wounds • 38±24 days for venous leg ulcers • 44±17 days for burns • 91±26 days for diabetic ulcers • 44±17 days for pressure ulcers	**Limitations** • Retrospective • Small sample size • Non-comparative • Full inclusion/exclusion not reported • Details of Prontosan use not reported beyond its use as part of standard care **Applicability** • Not a UK based study • Not clear how Prontosan was used (soaks, cleansing, single applications)

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		hypertension (53.1%), type 1 diabetes (14.3%), type 2 diabetes (14.3%), obesity (8.2%), peripheral vascular disease (8.2%), venous insufficiency (18.%) Number of co-morbidities • 27% had no comorbidities • 28% one comorbidity • 18% had one or more comorbidity No detailed inclusion/exclusion criteria reported. Inclusion limited to patients with complete wound closure demonstrated by complete epithelialisation **Setting** Not reported			Change in absolute wound area varied on aetiology: Mean change in absolute wound area: • 2170±5501 mm^2 for surgical wounds • 545±697 $mm^2$for trauma wounds • 198±256 $mm^2$for venous leg ulcers • 449±507 $mm^2$for burns • 850±1207 $mm^2$for diabetic foot ulcer • 552±726 mm^2pressure ulcer • Antimicrobial therapy was initiated in 5/49 (10.2%) patients, all in surgical and trauma categories. • 2 patients had wound related injuries: 1 periwound inflammation 29	**Funding/CoI** Funding for study provided by BBraun One author receives grant/research support and is a consultant for BBraun Two authors receive grant/research support from BBraun

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					days after initial Prontosan administration and 1 periwound itchiness 71 days after Prontosan administration	
Ricci 2018 **Country** Italy **Data collection** Not reported **Study Type** Comparative: before and after	To evaluate the activity of a polyhexanide propylbetaine (PP) solution in wound bed preparation. **Outcomes** • Wound score - Falanga • Wound photographic relief • Infection score - Cutting and Harding • Pain - VAS	N=70 patients **Demographics** Group A: 75.95 (32-95) years; females/ males:26/14; aetiology: VLU n=16, ALU n=7, mixed ulcer n=8, pressure ulcer n=1, DFU n=2, other n=6 Group B: 80.53 (52-93) years; females/males: 19/11; aetiology: VLU n=10, ALU n=4, mixed ulcer n=7, pressure ulcer n=3, DFU n=2, other n=4 **Inclusion** • Aged >18 years	**Statistical tests** Not reported, descriptive results only **Follow-up** Group A: 2, 5, 10 or 15 mins Group B: 14 days	Group A (n=40): Cleansing with single application of PP (10ml) for 2, 5, 10 or 15 mins – 10 patients for each time point Group B (n=30): Soak with PP (10 mins), removed without cleansing – once a day for 14 days	**Group A – single application** **Wound bed score** All patients • No change at 2 min or 5 min time periods compared with baseline • 4/10 cases showed reductions in score when treated for 10 minutes (2 C-B; 2 B-A) • 5/10 reductions when treated for 15 minutes (3 B-A; 2 C-B) Number of wounds with a change in wound bed score by wound type • Venous leg ulcer (5/16)	**Limitations** • Study appears to be a before and after study comparing baseline and treatment however it is not clearly stated. • Non-comparative study • Small sample size in each of the groups, with smaller sample sizes for each of the time points in group A • Descriptive results (no

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Chronic wound (>6 weeks) of defined aetiology • Wound bed preparation (WBD) tissue score of B or C • WBP exudate score of 1 or 2 • Contaminated or colonised but no other level of infection **Exclusion** • Patients <18 years • Acute wounds • Undefined aetiology • Neoplastic wounds • Allergy to any treatment components **Setting** Not reported			• Arterial leg ulcer (1/7) • Mixed ulcer (1/8) • Pressure ulcer (0/1) • Diabetic foot ulcer (0/2) • Other (1/6) **Group B – daily application for 14 days** **Wound bed score** • 16 cases were classified as B at enrolment. 12 cases had evolved from B to A, 3 remained unchanged, 1 worsened from B to C • 14 cases were classified as C at enrolment. 2 evolved to A, 9 to B and 3 remained unchanged. • Exudate scores were unchanged **Infection Score**	statistical analysis) **Applicability** • Not a UK based study however wound treatment approach consistent with UK practice • Population and interventions are relevant • Use of Prontosan in Group A (single applications) may not be relevant however do suggest that the longer application times (10 and 15 minutes) are required for effect. **Funding/Col**

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					• No patient had a score higher than 2 on enrolment • At the end of observation, 1 patient recorded 2 positive signs and 5 cases reported 1 positive sign **Pain Score** • Pain score was evaluated in 26 patients and showed an average reduction of 47% **Periwound skin evaluation** • Improvement in the parameter of periwound skin was observed in 29/30 cases and worsened in one case	Author is consultant for B. Braun
Valenzuela (2008) **Country** Spain **Duration**	To evaluate the effectiveness of the application of a 0.1% polyhexanide product (Prontosan Gel) for wound cleansing and	N=142 patients with chronic wounds – no more than two wound lesions per patient included in the study.	**Randomization & Allocation** Principal investigator randomly assigned eligible patients using a table of	Intervention Prontosan Gel (n=78) Comparator Saline, if debridement was necessary, autolytic	**Demogrpahics** • No statistically significant differences between the groups in relation to sociodemographics	**Limitations** • Not clear from the study what the specific outcomes were • No blinding in the study

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
September to December 2006 **Study Type** Comparative: randomized controlled trial	bacterial control in chronic wounds To investigate the evolution of bacterial build-up in the wound bed and the size of wounds being studied To investigate how polyhexanide gel behaves as a debridement option **Outcomes** Not specified but several variables measured relating to bacterial presence, evolution of wound surface.	**Demographics** No specific details provided **Inclusion** • Aged ≥18 years • At least one chronic wound • Presence of granulation tissue and/or soft devitalised tissue • Remain in study for 2 week follow-up **Exclusion** • Pregnancy • Local or systemic antibiotic treatment during last week of treatment • Devitalised tissue taking >33% of lesion area	random numbers, no allocation details provided. **Treatment** Control Group: cleansed by dabbing with saline, autolytic debridement with hydrogel if necessary. Polyurethane secondary dressing Experimental Group: cleansed by dabbing with saline, Prontosan gel applied. Polyurethane secondary dressing **Sample Size** • 67 subjects were required in each group to detect a difference equal to or higher than 20% of	debridement by means of a hydrogel was used (n=64) Once dressing removed ulcer bed was cleaned by dabbing with saline solution. Secondary dressing of polyurethane foam used. Treatment administered every 24-48 hours as required.	(details not reported) • There was a higher number of women in both groups **Microbiological Cultures** • No significant difference between the groups at the beginning of the study (p value not reported). • There were significant variations in the cultures between the groups (p=0.004). Note, the EAC is unclear what result this is reporting due to the translation. **Lesion Size** • Mean absolute reduction was 19.71cm^2 (95% CI: 3.79-24.31) with Prontosan and 5.65cm^2 (95% CI -	• Short follow-up, unclear if wounds were followed to complete healing but unlikely • This is a translation of a Spanish language paper provided by the company. The EAC cannot verify the accuracy of the translation and in some cases cannot verify the accuracy of the results reporting. **Applicability** • Population, intervention and comparator relevant to the scope • Not a UK based study however wound

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
		• Presence of necrotic plaques Allergy to study components **Setting** Not specified	bacterial build-up • A 10% follow-up loss rate was estimated **Statistical Tests** Descriptive and inferential statistical analysis. Chi squared test and student t-test were used Intention to treat analysis. **Follow-up** 2 weeks		0.17 to 11.47) in the control group (p=0.013) • Mean percentage reduction in the Prontosan group was 43.64% ± 35.07% compared with 17.3%±35.07% in the control group (p=0.000). **Specific Wound elements** • Surface of lesion decreased significantly from baseline in the Prontosan group compared with control group (p=0.013) • % granulation tissue increased significantly from baseline in the Prontosan group compared with the control group (p=0.001) • % slough reduced significantly from	treatment approach appear consistent with UK practice • Prontosan gel is the intervention in this study, while relevant to the scope, it is possible that Prontosan gel is not widely used in the UK **Funding/CoI** Not reported

Study ID	Aims and Objectives	Patient Population	Methods	Interventions/Comparators & Treatments	Results	EAC Comments
					baseline compared with the control group (p=0.002)	

Abbreviations: CFU: colony forming units; CoI: conflicts of interest; FLACC: Face, Legs, Activity, Cry, Consolability; FTSG: full thickness skin grafting; IFU: instructions for use; N/A: not applicable; NS: normal saline; NPUAP: National Pressure Injury Advisory Panel; EPUAP: European Pressure Advisory Panel ; PHMB: Polyhexamethylene biguanide; PU: pressure ulcer; SSI: surgical site infection; STSG: split thickness skin graft; TBSA: total body surface area; WBD: wound bed preparation; VAS: Visual Analogue Scale;VLU: venous leg ulcer

Appendix C Critical Appraisals

Quality assessment of company included RCTs (n=4) assessed by the Cochrane Risk of Bias tool (Sterne 2019)

Risk of Bias Domain	Bellingeri (2016)		Romanelli (2010)		Valenzuela (2008)		Wattanaploy (2017)	
	Company	EAC	Company	EAC	Company	EAC	Company	EAC
Bias arising from the randomization process	low risk	low risk	low risk	some concerns	low risk	some concerns	low risk	some concerns
Bias due to deviations from intended interventions	low risk	low risk	low risk	some concerns	low risk	some concerns	low risk	some concerns
Bias due to missing outcome data	low risk	low risk	low risk	low risk	low risk	low risk	low risk	low risk
Bias in measurement of the outcome	low risk	low risk	low risk	low risk	some concerns	low risk	some concerns	some concerns
Bias in selection of the reported result	low risk	low risk	some concerns	some concerns	low risk	some concerns	some concerns	some concerns
Overall risk of bias	low risk of bias	low risk of bias	some concerns	some concerns	some concerns	some concerns	some concerns	some concerns

Quality assessment of additional RCTs included by the EAC assessed by the Cochrane Risk of Bias tool (Sterne 2019)

	Risk of Bias Domain					
Study	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement outcome	Selection reported result	Overall risk of bias
Assadian (2018)	high risk	Some concerns	low risk	low risk	some concerns	**High risk of bias**
Borges (2018)	Some concerns	high risk	high risk	low risk	some concerns	**High risk of bias**
Harding (2012)	Some concerns	Low risk	Low Risk	Low Risk	Low Risk	**Some concerns**
Saleh (2016)	Some concerns	Some concerns	low risk	low risk	low risk	**Some concerns**

Assadian (2018)

Reference & Sources	Assadian (2018) Journal article	**Aim**	assess the effect of assignment to intervention (the 'intention-to-treat' effect)
Experimental	12 treatment comparisons Includes prontosan	**Comparator**	saline
Outcome assessed for risk of bias	Difference in the quantitative number of microorganisms per 1cm^2 of wound surface harvested before and after a 20 minute wet-to-moist cleansing		
Results	• Using 0.9% NaCL (saline) did not significantly reduce the planktonic bacterial burden on wounds (p=0.761). • Using Prontosan did not significantly reduce the bacterial burden (p=0.051)		
Domain 1	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**	Patients were randomized to one of the 12 wound irrigation solutions investigated, using a computerised, randomisation programme, dynamic allocation and stratification by wound size. No detail on concealment method or if 3rd party	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Differences include more females who had more VLU and MLU wounds. However the baselines characteristics are not given for each treatment group so unclear as to whether there were differences between treatment groups	PY
	Risk-of-bias judgement		High Risk

Domain 2	Signalling questions	Comments	Response options
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Both the patient and the wound care-givers were aware which irrigation solution was being used	Y
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NI
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Data for all	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
	Risk-of-bias judgement		Some concerns
Domain 3	**Signalling questions**	**Comments**	**Response options**
Missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?		Y
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
	Risk-of-bias judgement		Low risk
Domain 4	**Signalling questions**	**Comments**	**Response options**
Risk of bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Swab technique	N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	neither the microbiologist processing samples, nor the individual conducting the statistical analysis, had any	N

		knowledge on the assigned treatment arm.	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
	Risk-of-bias judgement		Low risk
Domain 5	**Signalling questions**	**Comments**	**Response options**
Risk of bias in selection of the reported result	**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**		NI
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		NI
	5.3 ... multiple eligible analyses of the data?		NI
	Risk-of-bias judgement		Some concerns
Overall risk of bias	**Risk-of-bias judgement**		High Risk

Borges (2018)

Reference & Sources	Borges (2018) Journal article	**Aim**	assess the effect of assignment to intervention (the 'intention-to-treat' effect)
Experimental	prontosan	**Comparator**	saline

Outcome assessed for risk of bias	Primary outcome not specified – for this assessment : bacterial load		
Results	No significant difference in reduction of bacterial load between solutions.		
Domain 1	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**	Randomization was performed with a random number table in a horizontal sequence from left to right, if the last digit was even, the wound was assigned to the control group and if it was odd, then it was assigned to the PHMB group. No detail on concealment method or if 3rd party	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
	Risk-of-bias judgement		Some concerns
Domain 2	**Signalling questions**	**Comments**	**Response options**
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	**2.1. Were participants aware of their assigned intervention during the trial?**	Concealment or blinding was performed whenever possible; this included the dermatologist, who removed wound tissue fragments from the venous leg ulcers; the wound ostomy continence nurse, who performed the cleansing of all the wounds; the study participant, and the professionals who carried out the microbiological analysis and electron microscopy.	N
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Only those with data analysed so not ITT and no indication that imputed data	N
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	Patients who had absence of bacteria in the first wound tissue fragment biopsied were eliminated from the study, resulting in 19 participants in the control group and 8 participants in the PHMB group	Y
	Risk-of-bias judgement		High risk
Domain 3	**Signalling questions**	**Comments**	**Response options**
Missing outcome data	**3.1 Were data for this outcome available for all, or nearly all, participants randomized?**		N
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		PN
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	Related to outcome as those that were eliminated from study had absence of bacteria at baseline and more eliminated in control group	Y
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	Related to outcome as those that were eliminated from study had absence of bacteria at baseline	PY
	Risk-of-bias judgement		High risk
Domain 4	**Signalling questions**	**Comments**	**Response options**
Risk of bias in measurement of the outcome	**4.1 Was the method of measuring the outcome inappropriate?**	**Biopsy and microbial analysis**	N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Concealment or blinding was performed whenever possible; this included the dermatologist, who removed wound	N

		tissue fragments from the venous leg ulcers; the wound ostomy continence nurse, who performed the cleansing of all the wounds; the study participant, and the professionals who carried out the microbiological analysis and electron microscopy.	
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
	Risk-of-bias judgement		Low risk
Domain 5	**Signalling questions**	**Comments**	**Response options**
Risk of bias in selection of the reported result	**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**		NI
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		NI
	5.3 ... multiple eligible analyses of the data?		NI
	Risk-of-bias judgement		Some concerns
Overall risk of bias	**Risk-of-bias judgement**		High Risk

Harding 2012

Reference & Sources	Harding Clinical study report (2012) CT.gov report	**Aim**	assess the effect of assignment to intervention (the 'intention-to-treat' effect)
Experimental	Prontosan Wound Solution and Gel	**Comparator**	Normal Saline and Placebo Gel
Outcome assessed for risk of bias	Healing of Target Ulcer at V6/EOS		
Results	Prontosan: 8/17 (47.1%) Saline: 5/17 (29.4%) Comparison: 17.6% (-14.5%, 49.8%) p=0.4813 (Table 6-44)		
Domain 1	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**	created by a computer program. Not clear if remote allocation	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Differences in numbers of males and females in each group Variation in duration of leg ulceration	PY
	Risk-of-bias judgement		Some concerns
Domain 2	**Signalling questions**	**Comments**	**Response options**
Risk of bias due to deviations from the intended interventions	**2.1. Were participants aware of their assigned intervention during the trial?**	Participant, Care Provider, Investigator – note that CIC study report states only double blind (investigators and patients)	N
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N

(effect of assignment to intervention)	**2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?**		NA
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	ITT with details of missing outcome data	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
	Risk-of-bias judgement		Low risk
Domain 3	**Signalling questions**	**Comments**	**Response options**
Missing outcome data	**3.1 Were data for this outcome available for all, or nearly all, participants randomized?**	Prontosan: 17/17 Saline: 15/17	Y
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
	Risk-of-bias judgement		Low risk
Domain 4	**Signalling questions**	**Comments**	**Response options**
Risk of bias in measurement of the outcome	**4.1 Was the method of measuring the outcome inappropriate?**	Healing of ulcer	N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Investigators blinded	N

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
	Risk-of-bias judgement		Low risk
Domain 5	**Signalling questions**	**Comments**	**Response options**
Risk of bias in selection of the reported result	**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**		Y
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
	5.3 ... multiple eligible analyses of the data?		N
	Risk-of-bias judgement		Low risk
Overall risk of bias	**Risk-of-bias judgement**		Some concerns

Saleh (2016)

Reference & Sources	Saleh (2016) Journal article & clinical trials registration: NCT02253069	**Aim**	assess the effect of assignment to intervention (the 'intention-to-treat' effect)
Experimental	Skin graft sutured, tie-over dressing soaked with Prontosan applied	**Comparator**	Comparator

			Skin graft sutured, tie over dressing soaked with sterile water applied
Outcome assessed for risk of bias	As per CT.gov: Measuring colony forming units in swabs collected from wounds pre-,intra- and postoperatively (7 days after surgery1)		
Results	No significant difference in bacterial load levels measured • before surgery • end of surgery • at 1 week after surgery		
Domain 1	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**	Software used to generate randomisation lists, allocation details not provided or if 3rd party	N
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
	Risk-of-bias judgement		Some concerns
Domain 2	**Signalling questions**	**Comments**	**Response options**
Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	**2.1. Were participants aware of their assigned intervention during the trial?**	States that double blind but not specified who but does state 'overall assessment by the blinded principal investigator classifying a wound as infected or noninfected' and 'Bacterial samples were blindly collected from each patient using Eswabs' so these could be the 'double blind'	**PN**

	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PY
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NI
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	ITT	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
	Risk-of-bias judgement		Some concerns
Domain 3	**Signalling questions**	**Comments**	**Response options**
Missing outcome data	**3.1 Were data for this outcome available for all, or nearly all, participants randomized?**	All	Y
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
	Risk-of-bias judgement		Low risk
Domain 4	**Signalling questions**	**Comments**	**Response options**
Risk of bias in measurement of the outcome	**4.1 Was the method of measuring the outcome inappropriate?**	Swabs and quantitative analysis of CFU	Y
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	'Bacterial samples were blindly collected from each patient using Eswabs'	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
	Risk-of-bias judgement		Low risk
Domain 5	**Signalling questions**	**Comments**	**Response options**
Risk of bias in selection of the reported result	**5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	CT.gov registration	Y
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
	5.3 ... multiple eligible analyses of the data?		N
	Risk-of-bias judgement		Low risk
Overall risk of bias	**Risk-of-bias judgement**		Some concerns

Appendix D Impact of alternative survival analysis approaches for modelling, Andriessen

From the published data (Andriessen 2008), a Kaplan Meier graph (figure 1) can be derived, as is also reported by the study authors and the company.

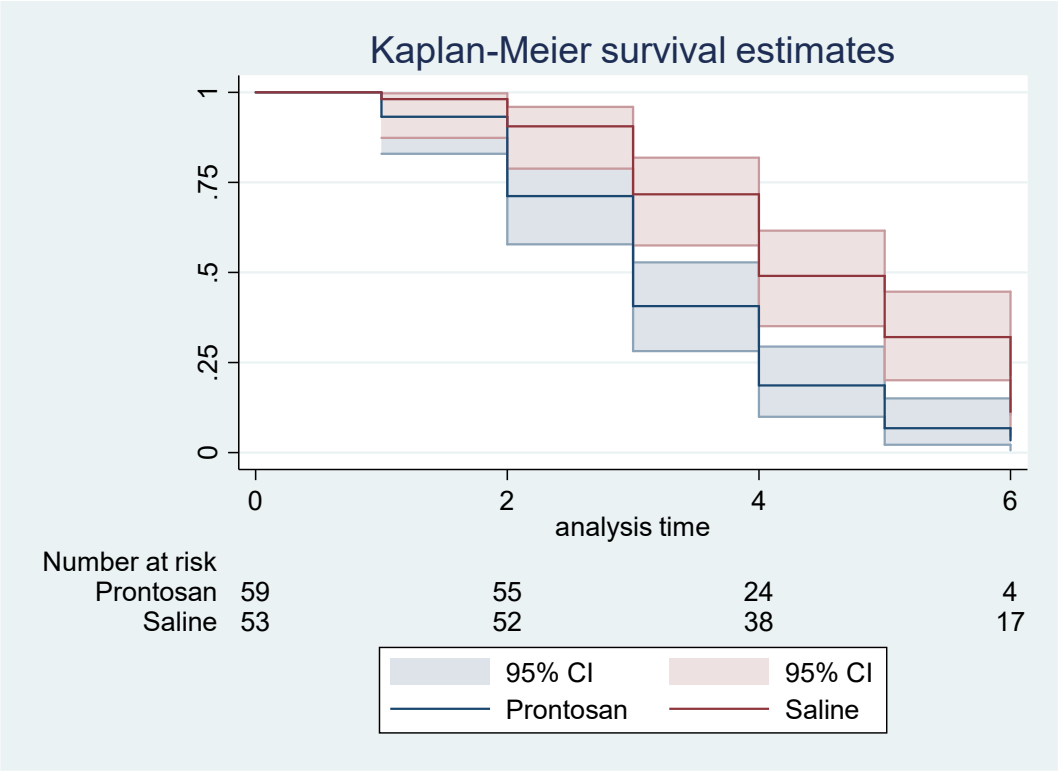


Figure 1: Kaplan-Meier graph from Andriessen (2008)

This data was used to fit an exponential curve, replicating the company procedures. The resultant curve together with the K-M graph are shown below.

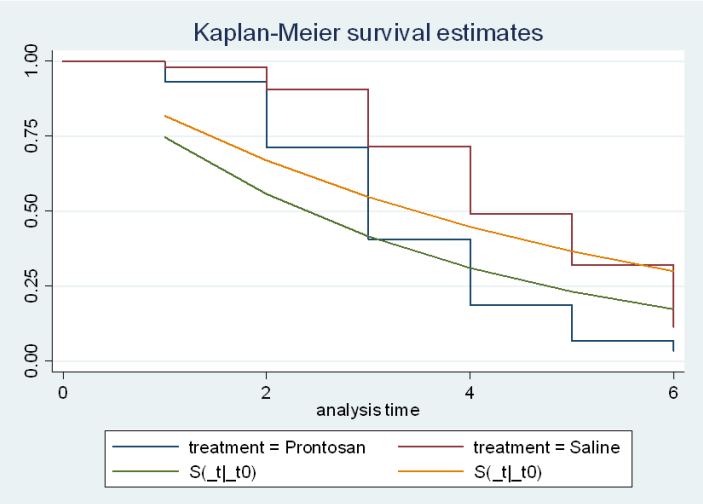


Figure 2: Kaplan Meier graph with exponential curve

The model is structured to use constant transition probabilities, however the EAC also investigated the use of a Weibull model to explore the fit to the original data, as shown in figure 3.

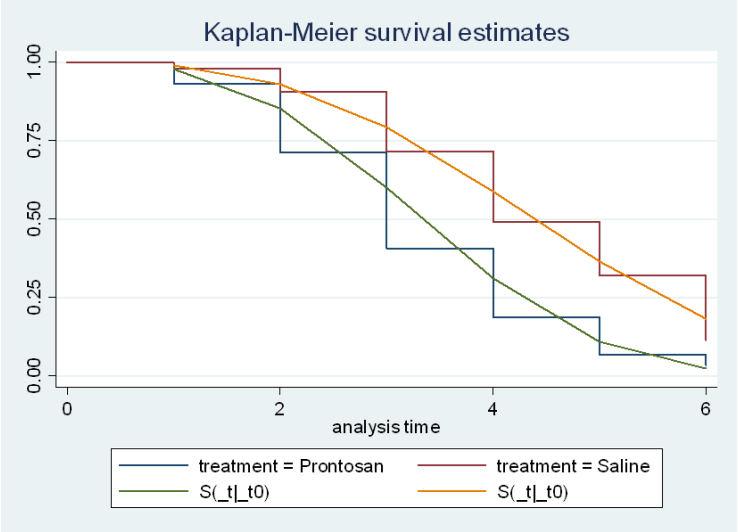


Figure 3: Kaplan Meier graph with Weibull curve

The AIC value (where lower values indicate a better fit) for each curve and the calculated mean time to healing are shown in table 1

Table 1: Comparison of results from exponential and Weibull models

	AIC value	Mean Time to healing (months)		
		Prontosan	Saline	Difference
Kaplan-Meir		3.31	4.42	1.11
Exponential	250.6086	3.42	4.98	1.56
Weibull	139.3978	3.38	4.44	1.06

The EAC consider that Weibull would be a better fit, but agree that it is not supported by the current model structure. The EAC explored the potential impact of the different mean times to healing by considering the cost of the “open” state for the difference in time to healing and also by using these mean time to healing values in the wound bed preparation model.

Table 2: Exploration of cost impact, using exponential and Weibull models

	Time to healing	Estimation of change in results using cost of "open" state		Estimation using wound bed model		
	Difference (months)	(Time) x (cost_open £512.73)	Change relative to submitted method	Prontosan	Saline	Cost saving per person
Kaplan-Meir	1.11	£569.13	£230.73	£1,975.03	£2,495.58	£531.15
Exponential	1.56	£799.86	0	£2,040.66	£2,811.76	£783.03
Weibull	1.06	£543.49	£256.36	£2,016.79	£2,506.87	£500.72

It can be seen that the Weibull model is likely to result in a reduced cost saving. The wound bed preparation was used to estimate the size of the reduction, however inclusion of the Weibull parameters in the wound closure model would give somewhat different results due to movement in and out of infected states, longer time horizon and costs associated with infected and healed states that don't exist in the wound bed preparation model.

Appendix E Stress testing economic models

Stress testing:Andriessen (2008) data				
Scenario	**Cost of Prontosan**	**Cost of Comparator**	**Cost difference**	**Notes**
Base case	£3,342.80	£4,461.06	-£1,118.27	Taking the base case from Andriessen, including half cycle correction.
The number of patients equal to 0.	£0	£0	£0	As expected (Cell changed is Results /D7)
The number of patients equal to 1000.	£3,342,799.51	£4,461,064.61	-£1,118,265.10	
Cost of Prontosan solution + Gel = £0	£3,342.80	£4,461.06	-£1,118.27	Calculations don't follow through. No clear location for sources data. Changed prices in Resource use / P11:P15, but no impact on cost modelled.
Cost of Prontosan Solution + Gel = £0	£3,232.69	£4,461.06	-£1,228.37	Cost of zero entered into Resource use B10. Cost of gel is zero, and therefore cost for Prontosan arm decreases, but main costs are for staff time and other care, so impact is not large.
Cost of Prontosan solution + Gel = £100				
Cost of Prontosan solution + Gel = £500	£5,096.42	£4,461.06	£635.35	Cost of £500 entered into Resource use C10 (outside limits set for B10).
Cost of Saline = £0	£3,342.80	£4,446.33	-£1,103.53	Very small impact
Cost of Saline = £500	£3,342.80	£5,702.73	-£2,359.93	Set each component to be £500, each treatment cost = £229.70 for open wound
Change prontosan monthly healing rate from 25% to 2%	£7,551.54	£4,461.06	£3,090.47	As would be expected, prontosan costs increase, as more wounds stay in open. Very few are in infected at end of one year though, even though over 70% are open all the way through, so few change from open to infected.
Add 50% infection rate to previous row	£13,368.84	£4,461.06	£8,907.78	As expected, costs for prontosan increase, and graphs show increased numbers in infected state
Cost of wound stage "open" = 0	£973.05	£1,417.68	-£444.63	Costs for open now just for prontosan and solution. Still a cost saving due to infection
Cost of wound stage "infected" = 0	£2,825.18	£3,335.93	-£510.75	Now costs are being saved in open stage. Only goes cost incurring if both are =o

Cost of wound stage “open” and “infected” = 0	£455.43	£292.54	£162.88	As expected, now cost incurring
Cost of wound stage “healing” = 0	£3,006.76	£4,183.25	-£1,176.50	As expected, very small impact
Cost of wound stage “open” = £5,000	£19,610.32	£25,352.86	-£5,742.54	As expected, large cost saving, as more time spent in this stage by saline arm
Cost of wound stage “infected” = £5,000	£4,097.50	£6,101.54	-£2,004.04	Fewer patients in infected, plus also smaller change from submitted value.
Cost of wound stage “healed” = £5,000	£42,197.65	£36,582.95	£5,614.70	Very cost incurring, as more patients spend time in healed state in Prontosan arm.
Prontosan tp set to saline values	£4,607.91	£4,461.06	£146.84	Even where there is no clinical benefit being modelled, the marginal cost is very small.
Prontosan tp for open to healed set = saline	£4,071.67	£4,461.06	-£389.39	Still some cost saving, due to infection state
Prontosan tp for infection to open set = saline	£3,624.42	£4,461.06	-£836.65	Relatively small impact, small number of infected wounds
Prontosan infection rate set to saline	£3,506.96	£4,461.06	-£954.10	As above

Stress testing: wound bed model						
Scenario	**Cost of Prontosan**	**Cost of Comparator (Saline)**	**Cost difference**	**Cost of comparator (Tap water)**	**Cost difference**	**Notes**
Base case	£705.68	£1,840.59	-£1,134.90	£1,833.48	-£1,127.80	
The number of patients equal to 0.	£705.68	£1,840.59	-£1,134.90	£1,833.48	-£1,127.80	The totals do not change as expected. They are not linked correctly to the technology cost cell and are only linked to the cell for gel price per patient, which by definition will not change dependant on number of participants
The number of patients equal to 1000.	£705.68	£1,840.59	-£1,134.90	£1,833.48	-£1,127.80	As above
Cost of Prontosan Saline + Gel = £0	£671.33	£1,840.59	-£1,169.26	£1,833.48	-£1,162.15	Small change. Most of the costs are healthcare
Cost of Prontosan Saline + Gel = £100	£749.17	£1,840.59	-£1,091.41	£1,833.48	-£1,084.31	As above
Prontosan Time to wound prep days =100	£2,441.78	£1,840.59	£601.19	£1,833.48	£608.29	Cost saving depend on reducing duration of treatment.
Saline Time to wound prep days =200	£705.68	£4,663.84	-£3,958.16	£4,645.81	-£3,940.13	Larger cost saving as costs of saline increase.
Cost of saline sachet = £1000	£705.68	£2,033.48	-£1,327.80	£2,033.48	-£1,327.80	Small increase in cost saving

Appendix F Changes made by EAC to economic models

Changes to Wound bed preparation model

W/sheet	Cell	Description	Result
cost of therapy	G8	cost of pack of solution should be 0.62	
Resource data	D74, E74, K74	inflation rates corrected to PSSRU values	-£1,127.02
Resource data	f43:F47	updated to take average o/p costs	-1047.20086
Resource data	B61	2019 o/p cost changed to weighted average of all non-consultant face to face.	-972.5846562
Resource data	F52:53	Change to only band 5-6 nurses, others are not going out doing routine visits	-915.0941862
Resource data		Update to include costs of progressing wounds	
	R12	add 347 observations for progressing	
	S12, V12	copy formulae from row 13 to calculate costs and visits	
	R,S,V16	update to include row 12	-832.5444346
Resource data	B54:E54 and B60:C60	calculations altered to reference cells above, no change in output value	-£832.54
Resource data	T,U,V16	corrected to include progression state costs and visit numbers	-£821.78
Resource data	N3:8	Add hospital costs back in.	-£907.35

Changes to Wound closure model

w/sheet	cell	description	results		
cost	D62, E62, K62	inflation rates corrected to PSSRU values	3310.248893	4407.258902	-1097.01
cost	f35:F39	updated to take average o/p costs	3094.79385	4135.679768	-1040.89
cost	B51	2019 o/p cost changed to weighted av of all non-consultant face to face.	2896.27535	3886.011725	-989.736
cost	F43:F44	Change to only band 5-6 nurses, others are not going out doing routine visits	2769.89913	3712.878004	-942.979
			3201.89521	4105.012635	-903.117
cost	K41:45	Update to calculate number of visits using weighted method calculate total visits, observations and get weighted average (O45)	2769.89913	3712.238187	-942.339
	D21	link to O45 for weighted average			
resource use	B44:E44 and B50:C50	calculations altered to reference cells above, no change in output value	2769.89913	3712.238187	-942.339
Transition probability	c8	changed to link to correct cell	2768.789708	3712.238187	-943.448
resource use	P11	change from 6.71 to 6.55	no change, unused cell		
resource use	P14	32.89 changed to 32.10			
resource use	P15	12.29 changed to 11.99	2756.283594	3712.238187	-955.955
Base case	H3:I16	re-calculation of half cycle correction	2756.283594	3712.238187	-955.955
	Q3:P16	re-calculation of half cycle correction	3187.115813	4104.337492	-917.222
Result	C15:16	link to new results cells in base case page	2753.797601	3706.830087	-953.032
resource use	P11	Returned to submitted value post fact check	no change, unused cell		
resource use	P14	Returned to submitted value post fact check			
resource use	P15	Returned to submitted value post fact check	2755.8226	3706.830087	-951.0075

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Prontosan for acute and chronic wounds

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Decision problem and claimed benefits from scope

1 The technology

Prontosan (B Braun) is a range of topical solutions and gels used for cleansing and moistening acute and chronic wounds. Prontosan is available as:

- Prontosan Wound Irrigation Solution, used for wound irrigation or applied to gauze as a soak, 350ml bottle, 40ml single-use pods and 1,000ml bottle for instillation.
- Prontosan Wound Gel, applied to the wound bed during dressing changes after wound cleansing and before application of secondary dressing. The 30ml bottle is suitable for use in deep and tunnelling wounds, wound cavities and difficult to access wounds.
- Prontosan Wound Gel X (extra thick gel), 50g or 250g tube, applied to the wound bed during dressing changes, after wound cleansing and before application of secondary dressing. It is suitable for use in flat or larger surface area wounds such as leg ulcers.

The solution and gels contain an antimicrobial polyhexanide (0.1% polyhexamethylene biguanide) and a betaine surfactant (0.1% undecylenamidopropyl betaine). The company claim that Prontosan is the only wound cleansing solution or gel that contains these 2 active ingredients which work in combination to disrupt and prevent biofilm from the wound bed as well as cleansing and removing slough, devitalised tissue and other wound debris.

Prontosan received a CE mark in February 2009 as a class III medical device. The CE mark covers both Prontosan wound irrigation solution and wound gels (see below) and is valid until May 2024.

2 Proposed use of the technology

2.1 Disease or condition

Prontosan is intended for use in acute and chronic wounds when they require cleansing, rinsing or moistening. The company's instructions for use state that Prontosan can be used in a range of wound types including:

- Acute non-infected and infected wounds such as trauma wounds (skin lacerations, bites, cuts or crush injuries) and post-operative wounds.
- Chronic non-infected and infected wounds including pressure ulcers, leg ulcers and diabetic foot ulcers.
- Thermal, chemical and post-radiation wounds including burns.

2.2 Patient group

The population who may benefit from this technology is large. It is estimated that in the UK, over 2 million people per year have wounds that require treatment. A cohort analysis of 1,000 NHS patients that have wounds suggested that about 39% of wounds do not heal within the first year and may need additional therapy (Guest et al. 2015).

2.3 Current management

Care of acute or chronic wounds aims to improve wound condition, promote healing and minimise the risk of further complications. If the wound is suspected of being infected, a microbiological sample is usually taken, and an antibiotic prescribed to treat the organism causing the infection. Other treatment options include cleansing, debridement (autolytic, mechanical, or surgical) and the use of dressings.

Clinical experts note that the decision to cleanse and treat wounds is made based on clinical need following wound assessment. Furthermore, clinical experts say there are no specific wound types that would be cleansed at every dressing change.

The current treatment options for cleansing acute and chronic wounds are sterile saline or water. Clinical experts note that Ringer's solution is not routinely used in the NHS to cleanse wounds but there is a dressing which contains Ringer's solution available and that this would be used if clinically indicated for debridement.

Dressings are selected on a case-by-case basis to promote healing and manage exudate. Chronic wounds may be treated with advanced dressings that usually work by simple physical or chemical means, typically by controlling moisture levels (for example, alginate, film, foam, hydrocolloid and hydrogel dressings).

There is no national/NICE guidance on wound care in general. NICE has published 3 clinical guidelines that include recommendations on wound care for specific types of wounds but only 1 of them includes any specific guidance on wound cleansing:

- NICE guideline on surgical site infections: prevention and treatment (NG125, last updated 2020) recommends the use of sterile saline for wound cleansing up to 48 hours after surgery and the use of tap water for wound cleansing after 48 hours if the surgical wound has separated or has been surgically opened to drain pus.
- NICE guideline on diabetic foot problems: prevention and management (NG19, last updated 2019)
- NICE clinical guideline on pressure ulcers: prevention and management (CG179, 2014)

NICE has published MTG guidance on 9 wound care technologies but none of them are direct comparators for Prontosan.

A national wound care strategy programme (NWCSP) has been commissioned by NHS England and Improvement to improve the prevention and care of pressure ulcers, lower limb ulcers and surgical wounds. So far, the NWCPS has published recommendations on the care of lower limb ulcers

and surgical wounds. The NWCSP recommendations on surgical wound cleansing align with the NICE guidance linked above. In the lower limb ulcers guidance, the NWCSP recommends that immediate and ongoing care for all foot and leg wounds should include 'Wound bed cleansing, debridement, peri-wound and limb skin cleaning and emollient, as required'. The following explanatory notes are also included regarding wound cleansing and debridement:

> It is good practice to cleanse the wound bed, peri-wound (around the wound) and the limb and apply emollient to moisturise the surrounding skin. The method of cleansing will depend on the situation in which care is being undertaken and the individual needs of the patient. While debridement may be required for leg and foot wounds, in most cases, this will not form part of initial and necessary care.

2.4 Proposed management with new technology

The company proposed that Prontosan is used in place of saline or water, for wound cleansing. The company note that the irrigation solution can be used for irrigating (rinsing) or soaking the wound depending on desired clinical outcome. Prontosan Gel X or Gel is applied to the wound bed and left in situ. The company has outlined 3 clinical scenarios where Prontosan could be used as part of chronic wound management:

- Granulating, non-sloughy wounds – irrigate to a 5 min soak with Prontosan solution and use of Prontosan gel or gel X should be considered
- Wounds with light to moderate slough – 5 to 10 min soak with Prontosan solution and Prontosan gel or gel X applied before dressing
- Wounds with local-spreading infection – 10 to 15 min soak with Prontosan solution and Prontosan gel or gel X applied before dressing

For acute wound treatment the company has also outlined 3 clinical scenarios:

- Suture, post-operative trauma wounds - irrigation with Prontosan solution until visibly clear of debris

- Patient at high-risk of wound infection – 1 to 5 min soak with Prontosan solution and use of Prontosan gel should be considered
- Burns (first/second/third degree) and/or infected wounds – 1 to 15 min soak with Prontosan solution depending on wound severity and Prontosan gel applied before dressing

3 Company claimed benefits and the decision problem

Details of the company's claimed benefits and the decision problem are described in Appendix C. The company did not propose any changes to the decision problem. The strengths and limitations of the evidence the company submitted to support the decision problem are discussed in the following sections.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified 15 full text published studies from its literature search. The company also included 3 abstracts and 3 ongoing or unpublished studies. The EAC included 16 full text published studies and 2 unpublished full text studies as key evidence. An additional 4 posters/conference abstracts are included for information and supporting evidence. The rationale for the selection of these studies is in section 4.1 and 4.2 of the EAC assessment report. Of the included studies, 9 were comparative (7 RCTs and 2 observational studies) and 9 were non-comparative (see table 1).

Table 1 Included studies and excluded studies

Studies included by both EAC and company	
Publication and study design	15 studies included by both • 5 RCTs (Bellingeri et al. 2016; Harding* 2012; Romanelli et al. 2010; Valenzuela & Perucho 2008; Wattanaploy et al. 2017) • 1 comparative non-concurrent retrospective analysis (Andriessen 2008)

	• 3 prospective non-comparative observational studies (Kiefer et al. 2018; Oropallo* et al.; Ricci et al. 2018) • 6 retrospective non-comparative studies (Atkin et al. 2020; Ciprandi et al. 2018; Durante et al. 2014; Horrocks et al. 2006; Möller et al. 2008; Moore et al. 2016)
Studies in submission excluded by EAC	
Publication and study design	3 studies were excluded by the EAC: • 1 in vitro study (Salisbury* et al. 2020) • 1 meeting report (Collier et al. 2017) • 1 narrative review (Wilkins et al. 2013) Reasons for exclusion included 1) non-clinical study, 2) not peer reviewed and details of methods and patient population not reported, and 3) no systematic review plus 3 studies have been reviewed individually. The remainder of the included studies were animal and in-vitro studies.
Studies not in company submission included by EAC	
Publication and study design	• 2 RCTs (Borges et al. 2018; Saleh et al. 2020) • 1 comparative prospective cohort study (Assadian et al. 2018)
Abbreviations: EAC external assessment center; RCT randomized controlled trial Notes: * unpublished study	

The evidence identified by the company and EAC differed in terms of the study designs, participants, formulations and administration of Prontosan, comparators and outcomes.

Summary of the company's approach to synthesising the clinical evidence

The company critically appraised the studies included in the submission using the Cochrane Risk of Bias tool for randomized trials and CASP checklist for non-randomized studies. The EAC noted that it had reviewed the company's critical appraisals for each study and agrees with the company's overall assessment of the evidence quality.

The company concluded that meta-analysis was not possible due to the diverse nature of the studies. Instead, the company conducted a qualitative

review of the evidence. The qualitative review takes the form of a narrative summary of the results reported on outcome-by-outcome basis. In the section on wound bed condition; slough, malodour, exudate etc., the company states that the published RCTs (Bellingeri 2016; Valenzuela and Perucho 2008) provide the most robust evidence for the outcome of wound bed condition because of study size and design (company submission, section 7, p86). The company did not make any statements on the relative importance of the studies for any other outcomes.

The EAC did not make any comments on the company's overall approach to summarising and synthesising the evidence, although it did take a similar approach in its own evidence review.

Summary of the company's interpretation of the clinical evidence and conclusions

The company's interpretation of the evidence is reported in section 8 of the company submission. It discusses the results reported in its qualitative review with reference to several other publications on wound healing rates and the biological mechanisms that underlie the wound healing process. The company states that chronic wounds often are stuck in the inflammatory phase of healing, with poor wound bed condition. This is defined as wounds having low amounts of granulation tissue and increased exudate levels, slough, and signs of inflammation. The company reaches the following overall conclusion about the clinical effectiveness of Prontosan:

> the evidence supports the expectation that Prontosan will improve wound bed condition leading to improved healing, reduction in infection, and improved patient experience over standard care of saline, Ringer's or potable water (company submission, section 8, p95).

The company presents its conclusions regarding the evidence for specific wound types. These are all in keeping with its overarching conclusion.

The EAC commented on the company's claimed benefits and whether these were met (table 18 in the assessment report, p.71). The EAC stated that the claims made by the company on improved wound bed condition, improved healing rate, reduced markers of infection and improved patient experience were partially supported by the evidence. The quality of the evidence informing these outcomes was variable but overall, the EAC considered that Prontosan appeared to improve wound condition. However, it stated that the evidence for whether Prontosan is better than saline or water is less certain.

Summary of the EAC's approach to synthesising the clinical evidence

The EAC critically reviewed the studies it included using the same checklists as the company. The EAC considered the strength of the evidence to be limited with only 1 RCT (Bellingeri 2018) at low risk of bias. The remaining RCTs were judged to have a high risk of bias or to have some concerns indicating a possible high risk of bias. The results of its critical appraisal are summarised in table 2.

Table 2: EAC's critical appraisal results

Study	Study Design	Wound type	EAC Comments	Conclusion
Venous Leg Ulcers				
Borges (2018)	Randomized controlled trial	Venous Leg Ulcers	Not included in company submission*	High risk of bias
Romanelli (2010)	Randomized controlled trial	Venous Leg Ulcers	Disagreed on some domains but the overall conclusion is same The EAC assumed in data extraction that analysis was per protocol and not ITT but no definitive information so change to 'unknown'	Some concerns
Harding et al (2012) NCT01153633	Pilot randomized controlled trial	Venous leg ulcers	Assessed by company as Low Risk of Bias	Some Concerns
Andriessen (2008)	Comparative non-concurrent retrospective analysis	Venous Leg Ulcers	Agree with company that low quality study. Note that comparator	High risk of bias

Study	Study Design	Wound type	EAC Comments	Conclusion
			was either saline or Ringer's	
Burns				
Wattanaploy (2017)	Randomized controlled trial	Burns	Disagreed on some domains but the overall conclusion is same	Some concerns
Kiefer et al (2018)	Non-comparative prospective clinical study	Burns	Agree with company that low quality study	High risk of bias
Ciprandi et al (2018)	Non-comparative retrospective data review (case series)	Burns	Agree with company that low quality study	High risk of bias
Surgical site wounds				
Saleh (2018)	Randomized controlled trial	Surgical Site Wounds	Not included in company submission See Appendix C for detailed appraisal results	Some Concerns
Mixed wound aetiology				
Bellingeri (2016)	Randomized controlled trial	Mixed wound aetiology	Agree with company that low RoB, tool does not assess power and this study still underpowered	Low risk of bias
Valenzuela (2008)	Randomized controlled trial	Mixed wound aetiology	Disagreed on some domains but the overall conclusion is same Note: add ITT analysis to data extraction table	Some concerns
Assadian (2018)	Comparative prospective cohort study	Mixed wound aetiology	Not included in company submission*	High risk of bias
Ricci (2018)	Non-comparative prospective observational study	Mixed wound aetiology	Agree with company that low quality study	High risk of bias
Durante (2014)	Non-comparative retrospective observational study	Mixed wound aetiology	Agree with company that low quality study	High risk of bias

Study	Study Design	Wound type	EAC Comments	Conclusion
Oropallo et al (unpublished, NCT03369756)	Non-comparative prospective observational study	Mixed wound aetiology	Agree with company that low quality study	High risk of bias
Horrocks (2006)	Non-comparative retrospective case series	Mixed wound aetiology	Agree with company that low quality study	High risk of bias
Atkin (2020)	Non-comparative retrospective case series	Mixed wound aetiology	Agree with company that low quality study	High risk of bias
Möller, Nolte & Kaehn (2008)	Non-comparative retrospective analysis	Mixed wound aetiology	Agree with company that low quality study	High risk of bias
Moore (2016)	Non-comparative retrospective analysis	Mixed wound aetiology	Agree with company that low quality study	High risk of bias
Source: Adapted from EAC report table 12 *See Appendix C of the assessment report for detailed critical appraisal				

The EAC also made the following overarching comments about the limitations of the evidence base:

- Most of the included studies have small sample sizes and some of the larger randomized trials are underpowered which result in increased risk of bias (although for some populations conducting larger studies may not be achievable).
- Prontosan is not used consistently across the studies and not all use is reflective of NHS practice or in line with company instructions for use.
- Outcomes are not always clearly reported and similar outcomes are reported differently across different studies making it difficult to make comparisons/draw conclusions across the evidence base though some limited grouping of results by wound type is possible.

The EAC reached the following conclusions based on its critical appraisal:

- all the studies are relevant to the current decision problem
- in each of the studies, there are elements which will limit the extent to which they are applicable to UK clinical practice.

Similarly to the company, the EAC considered did not consider it appropriate to conduct a meta-analysis due to the heterogeneity of the studies. Instead, it summarised the studies in both narrative and table format, with studies in similar patient populations grouped together and the results reported on an outcome-by-outcome basis.

Studies in patients with venous leg ulcers

The EAC included 5 studies that reported results that were specific to patients with venous leg ulcers, 4 of which were comparative. The data for the comparative studies are presented in table 3 along with the EAC's comments. The data for the non-comparative study are reported in section 5 of the EAC report.

Table 3. Results from comparative studies in patients with venous leg ulcer

Study, design and funding	Participants/ population	Intervention & comparator	Results	EAC comments
Harding et al. (2012) NCT01153633 Pilot RCT Location: UK	34 outpatients with venous leg ulcers Wounds were present for ≥4 weeks at the start of treatment.	Intervention Prontosan Irrigation solution plus Prontosan wound gel (n=17) Comparator Saline plus placebo gel (n=17) In both groups, wounds were soaked for 15min with either Prontosan solution or saline. Follow up 12 weeks	Wound healing (ITT) In the Prontosan group 8/17 (47.1%) wounds healed compared with 5/17 (29.4%) in the saline group (P=0.4813). The treatment difference was -17.6% (95% CI -14.5-49.8). Secondary infection during Study (ITT) Prontosan group: 4/17 (23.5%) compared with saline group: 3/17 (17.6%) Number of different microorganisms post-treatment (mean) (ITT) Prontosan: 0.8 (SD=0.9) Saline: 1.2 (SD=1.1)	This is an unpublished study provided by the company (not peer-reviewed, accessible for wider review). The company assessed this study as low risk of bias, but the EAC had some concerns about the randomization process because of the difference in number of males and females in each group and the variation in duration of leg ulceration. This study has a small sample size and was extended because of recruitment issues.

			Change in pain (VAS score) (mean)(ITT) Prontosan: -9.5 (SD=19.5) Saline: -9.0 (SD=23.6)	
Romanelli et al. (2010) RCT Location: Italy Partially funded by B. Braun AG, author received financial support for clinical consulting from B. Braun Medical AG.	40 outpatients with chronic venous leg ulcers in an outpatient wound clinic of a dermatology department Wounds were present for >8 weeks at the start of treatment.	Intervention Prontosan irrigation solution (n=20) Comparator Saline (n=20) Patients treated every other day with Prontosan or saline plus standard wound care (polyurethane foam and elastic compression) Follow up 4 weeks (treatment duration)	Wound healing Wound size did not differ significantly between the 2 groups (Prontosan and Saline) from baseline to study end (p values not reported) Bacterial burden Prontosan group showed significantly better control of bacterial burden at the end of the study (p values not reported) Pain Significantly better pain control at 4 weeks in patients treated with Prontosan solution compared with saline solution ($p<0.05$)	This study has a small sample size and sample size calculation was not reported. Population, comparator and intervention are relevant. Wound treatment approach appeared to be consistent with UK practice.
Borges et al. (2018) RCT Location: Brazil Financial support from FAPEMIG	44 outpatients with venous leg ulcers Wounds were present for >8 weeks at the	Intervention Prontosan irrigation solution (n=22) Comparator Saline (n=22)	Bacterial Load (CFUs/g) After a single irrigation, both Prontosan and saline reduced the bacterial load compared with baseline but there was no significant difference in reduction of bacterial load between solutions.	High risk of bias because of some concerns around the randomization process, deviation from the intended intervention selection of reported results and missing outcome data.

	start of treatment.	In both groups wounds were treated with 1 minute irrigation under continuous pressure Follow up No follow-up – biopsy taken before and after cleansing	Wound characteristics There were no significant differences between the groups and the effect of the wound duration, wound area and necrosis.	Study had a small sample size and is likely underpowered, but no sample size calculations were provided. Likely limited applicability to NHS setting as wounds irrigated for 1 minute with no soak applied.
Andriessen et al. (2008) Retrospective comparative case series Location: Germany	112 outpatients with venous leg ulcers Wounds were present for ≥3 months at the start of treatment.	Intervention Prontosan Irrigation Solution (n=59) Comparator Saline or Ringer's Solution (n=53) In both groups wounds were cleansed for 15 minutes with a wet phase and short resting (dry) phase to restore periwound skin integrity (15 mins). Follow up To ulcer closure or 6 months	Wound healing At 6 months 97% (57/59) of wounds in Prontosan group were healed compared to 89% (47/53) in saline/Ringer's group Mean time to healing was 3.31 months (SE 0.17) with Prontosan versus 4.42 months (SE 0.19) with saline/Ringer's solution ($p<0.0001$) Wound infection 3% (2/59) in the Prontosan group and 13% (7/53) in the saline/Ringer's group experienced infection	Low quality study with high risk of bias. This study used retrospective comparisons and the control group had mixed interventions (saline or Ringer's) combined. Population group is relevant however full inclusion criteria were not defined. The results were primarily narrative/ descriptive with limited statistical analysis.

Abbreviations used:
ITT, intention to treat; SD, standard deviation; SE, standard error; VAS, visual analogue scale, EAC external assessment centre; RCT randomized controlled trial.

Studies in patients with burns

The EAC included 4 studies that reported results that were specific to patients with burns, 1 of which was comparative. The data for the comparative study are presented in table 4 along with the EAC's comments. The data for the non-comparative studies are reported in section 5 of the EAC report.

Table 4. Results from comparative studies in patients with burns

Study, design and funding	Participants/ population	Intervention (& comparator)	Results	EAC comments
Wattanaploy et al. (2017) Prospective RCT Location: Thailand	46 adult patients with partial thickness burn wounds Burns within 48 hours after injury were included	<u>Intervention</u> Prontosan wound gel X (n=23) <u>Comparator</u> Silver sulphadiazine (n=23) Both groups received daily dressing changes and same standard care, 3-5mm of	<u>Wound healing</u> All patients showed complete epithelialisation of wounds within 3 weeks. Time to healing did not differ significantly between the groups: 17.8±2.2 days (Prontosan) compared with 18.8 days±2.1 days (silver sulphadiazine); p=0.13. <u>Wound infection</u>	The EAC identified some concerns regarding bias arising from the randomization process, deviation from intended interventions, bias in measurement of outcome and selection of reported results. The comparator is out of scope (although the EAC stated silver sulfadiazine is

		Prontosan wound gel X or silver sulfadiazine. <u>Follow up</u> 3 weeks	No infections reported. Six patients (26.1%) in each group had a positive surface swab culture without signs/symptoms of infection. Routine swab cultures a week later were negative. <u>Pain score</u> Pain score was significantly less in the Prontosan group at 4 to 9 days and 12 days after treatment ($p<0.05$) but not on any other treatment day. <u>Treatment satisfaction</u> Staff consistently reported • Prontosan was easier to use when changing dressings • Wound dressing was easier to evaluate with Prontosan Patients reported being satisfied with Prontosan.	an appropriate comparator for burns). Saline is used in both arms for wound cleansing before the application of either Prontosan or silver sulphadiazine. The study has a small sample size and sample size calculations were not provided. Potentially applicable to UK setting.

Studies in patients with surgical site wounds

The EAC included 2 studies that reported results that were specific to patients with surgical site wounds, 1 of which was comparative. The data for the comparative study are presented in table 5 along with the EAC's comments. The data for the non-comparative studies are reported in section 5 of the EAC report.

Table 5. Results from comparative studies in patients with surgical site wounds

Study, design and funding	Participants/ population	Intervention & comparator	Results	EAC comments
Saleh et al. (2018) RCT Location: Sweden and Singapore Funding from Swedish government and research council.	40 patients with skin malignancies excised Wound duration at the start of the study not specified	<u>Intervention</u> Prontosan irrigation solution (n=20) <u>Comparator</u> Sterile water (n=20) Skin graft sutured, tie-over dressing applied; soaked with Prontosan or sterile water. <u>Follow up</u> 7 days post-surgery	<u>Wound infection</u> Ten wounds were assessed as infected of which 8 were in the intervention (Prontosan) group giving a statistically significantly higher rate of infection (p=0.028) No significant difference in bacterial load levels were measured before surgery, at the end of surgery and at 1 week after surgery	This study has a small sample size and there are some concerns about the randomization and blinding process. Limited outcome comparisons were reported and the EAC considers only the SSI outcome reporting likely to be of relevance. The EAC also noted that the method of Prontosan and sterile water use may have limited applicability to UK practice.

Mixed population studies

The EAC included 10 studies that reported results for mixed populations, 3 of which were comparative. The patients included in the comparative studies all had chronic wounds. The data for the comparative studies are presented in table 6 along with the EAC's comments. The data for the non-comparative studies are reported in section 5 of the EAC report.

Tabel 6. Results from comparative studies of patients with chronic wounds of mixed aetiology

Study, design and funding	Participants/ population	Intervention & comparator	Results	EAC comments
Bellingeri et al. (2016) RCT Location: Italy B.Braun paid ethics committee fees	320 patients with pressure ulcer or vascular leg ulcer of which 289 randomized Wound duration at the start of the study not specified	<u>Intervention</u> Prontosan Irrigation solution (n=143) <u>Comparator</u> Saline (n=146) Both groups irrigation 20-30ml followed by 10-minute soak <u>Follow up</u> 28 days with assessments being done once a week	<u>Wound improvement measured using the Bates-Jensen wound assessment tool (BWAT)</u> *The BWAT is a validated score for wound bed condition. The BWAT contains 13 items that assess wound size, wound depth, wound edges, wound undermining, necrotic tissue type, necrotic tissue amount, granulation tissue, epithelialisation, exudate type, exudate amount, surrounding skin colour, peripheral tissue oedema, and peripheral tissue induration. These items use a modified Likert scale: a score of 1 indicates the healthiest and 5 indicates the most unhealthy attribute for each characteristic. The total BWAT score was obtained by adding the individual scores of each assessment item, thus, the total value ranged from a minimum of 13 to a potential maximum of 65. Assessment of wound inflammation was performed through the analysis of a score obtained from five BWAT items specifically linked to inflammation: exudate type, exudate amount, surrounding skin colour, peripheral tissue oedema, and peripheral tissue induration.*	Low risk of bias, however the study is underpowered. At risk of selective reporting bias: BWAT results for each item, at each time point were not reported; p-values were not reported for all significant outcomes; the narrative results were unclear in relation to what the study aimed to do.

			Significant changes between T0 (baseline) and T4 (day 28) observed for: • Reduction in total BWAT score indicated better progression of wounds in the Prontosan group (from 26 at T0 to 14 at T4) compared with the saline group (from 26 at T0 to 22 at T4) (p=0.0248) • Reduction in average total BWAT score was significantly better at T4 versus T0 in the Prontosan group (no p-value) • 'Inflammation BWAT score' indicates a significantly better progression of wounds in the Prontosan group (p=0.03) • Reduction in the average Inflammation BWAT scores was significantly better at T4 than at T0 in the Prontosan group (no p-value) <u>Pain</u> Pain scores were similar for both groups. Average score was 3.0. Minimal to no change during follow-up No significant difference in pain associated with study wounds or dressing changes or in pain suffered between dressing changes	
Valenzuela et al. (2008)	142 patients with chronic	<u>Intervention</u>	<u>Wound healing</u> *Lesion size*	Some concerns because of lack of blinding, not clear

RCT Location: Spain	wounds (no more than 2 lesions per patient) Wound duration at the start of the study not specified	Prontosan Wound Gel (n=78) <u>Comparator</u> Saline (n=64) <u>Follow up</u> 2 weeks	Mean absolute reduction was 19.71cm2 (95% CI: 3.79-24.31) with Prontosan and 5.65cm2 (95% CI -0.17 to 11.47) in the control group (p=0.013) Mean percentage reduction in the Prontosan group was 43.64% ± 35.07% compared with 17.3%±35.07% in the control group (p=0.000). % granulation tissue increased significantly from baseline in the Prontosan group compared with the control group (p=0.001) <u>Microbiological cultures</u> No significant difference between the groups at the beginning of the study (p value not reported). % slough reduced significantly from baseline compared with the control group (p=0.002) % purulent exudate reduced significantly from baseline in the Prontosan group compared with control group (p=0.005) <u>Pain</u> *Prontosan group*	what the specific outcomes were and short follow up period. This is a translation of a Spanish language paper provided by the company. The EAC cannot verify the accuracy of the translation. Prontosan gel is the intervention in this study, while relevant to the scope, it is possible that Prontosan wound gel is not widely used in the UK

			Baseline: 50 (65.8%) 2 weeks: 15 (20.3%) *Control group* Baseline: 36 (57.1%) 2 weeks: 20 (35.7%) No significant difference between the intervention and control group (p=0.049).	
Assadian et al. (2018) Comparative prospective cohort study Location: Switzerland	260 patients with a total of 299 chronic wounds treated with a range of different approaches Wounds were present for >3 months at the start of treatment.	<u>Intervention</u> Prontosan irrigation solution (n=33 patients/36 wounds) <u>Comparator</u> Saline (n=12 patients/14 wounds) Wounds treated with a 20-minute wet-to-moist cleansing <u>Follow up</u> No post treatment follow up	<u>Reduction of bacterial bioburden after a single application</u> • Using 0.9% NaCL (saline) did not significantly reduce the planktonic bacterial burden on wounds (p=0.761). • Using Prontosan did not significantly reduce the bacterial burden (p=0.051)	This study is judged to be high risk of bias because of concerns related to the randomization process, deviation from intended interventions and selection reported results. This study has a small sample size, only 45 patients (50 wounds) were relevant to the scope. Likely limited applicability to NHS setting as only a single application of Prontosan was used.

Summary of the EAC's interpretation of the clinical evidence and conclusions

The EAC considered that most of the evidence was applicable to the UK but raised some concerns, specifically around the use of a single application of Prontosan and the use of Prontosan wound gel without the irrigation solution.

- The EAC reached the following conclusions about the evidence:
- even though there are weaknesses in the available evidence, the use of Prontosan products as an option for chronic wound management is supported
- the evidence for whether Prontosan products are more effective than water or saline however is limited
- based on the limited comparative evidence as well as clinical expert input that not all wounds will need cleansing at every dressing change, it is unlikely that Prontosan will replace saline or water
- the evidence for acute wounds is very limited and therefore less certain though there is some evidence that using Prontosan for burn wounds is beneficial.

4.2 Summary of economic evidence

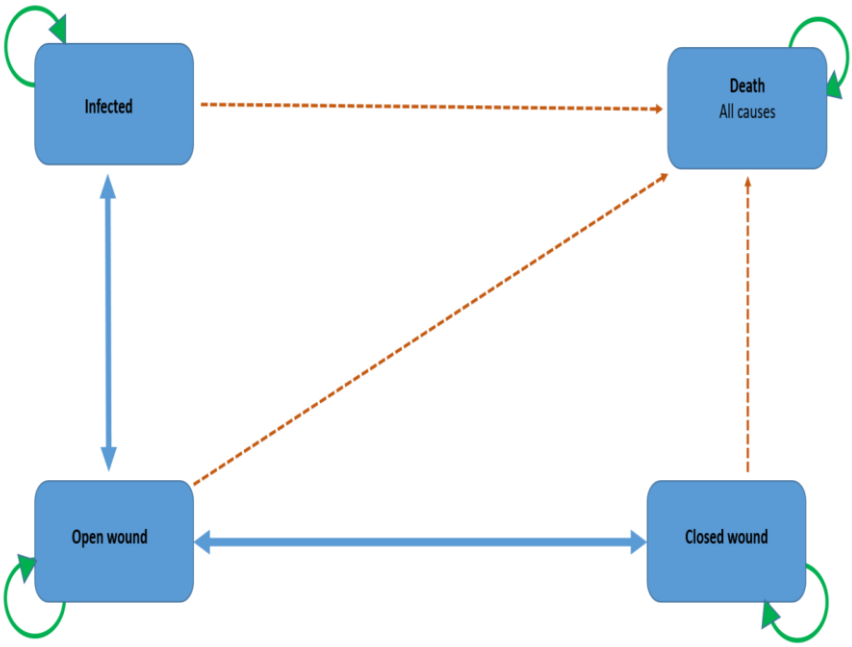
The company submission included a separate search strategy for economic evidence for Prontosan that identified 9 studies, which they excluded. The EAC undertook a combined search for clinical and economic evidence and found no economic evidence relating to the use of Prontosan.

De novo analysis

The company submitted 2 separate models, with different structures, both for chronic wounds (e.g., venous leg ulcers, pressure ulcers). No cost modelling was submitted for acute wound care (e.g., burns, surgical wounds). Some costs and resource values are the same for both models.

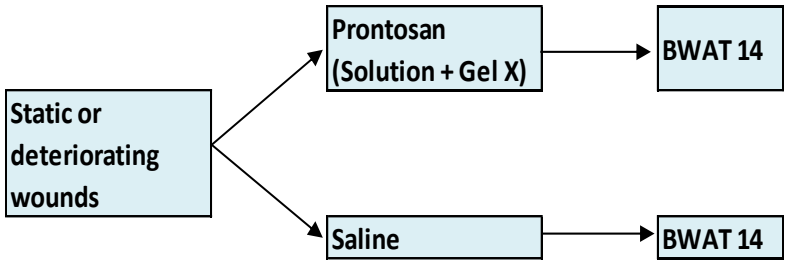
The first model is a Markov wound closure model with a one-year time horizon and an NHS and personal social services perspective (Figure 1). The company note the model structure could be appropriate for all chronic wounds, however, due to the limitations of the evidence base, many of the clinical inputs, and some of the cost inputs, are specific to a population with venous leg ulcers. The EAC noted that the clinical pathways are likely to be similar for other types of chronic wounds, although the healing time may be different. The model structure is not intended for patients with acute wounds and is unlikely to capture the appropriate pathways for these groups. The company did not include amputation in the model as it is more commonly associated with diabetic foot ulcers. Key assumptions for this model are summarised in table 21 of section 9.3 of the assessment report.

Figure 1. Markov wound healing model structure (from company submission)



The second model compares the costs associated with using Prontosan wound irrigation solution versus saline to achieve a healthy wound condition defined by a BWAT score of 14. As noted in table 6 above, the BWAT is a validated measure of wound bed condition and scores range from a minimum of 13 to a potential maximum of 65. A score of 14 indicates 75% epithelialisation. This model is for chronic wounds and the clinical inputs used are taken from a study in patients with pressure ulcers or vascular leg ulcers. There is an assumption that these wounds are on a pathway to healing and will not deteriorate. No additional cost or modelling is included for deteriorating or recurring wounds, or for additional treatment until healing. The time horizon is until a BWAT score of 14 is reached, which is 4.1 or 11.3 weeks in Prontosan and saline, respectively. Key assumptions for this model are described in table 26 of section 9.4 of the assessment report.

Figure 2. Wound Bed Preparation Model Structure (adapted from company submission)



Wound closure model

Model clinical parameters

The model includes clinical parameters related to wound healing, infection, wound recurrence and infection resolution.

- The company submitted two alternative data sets for wound healing (Andriessen 2008 and Harding 2012). The EAC considered that there were no other suitable data sources. The EAC decided that Andriessen 2008 (retrospective analysis, n=112, follow up 6 months) was a more suitable data source than Harding 2012 (pilot RCT, n=34, follow up 12 weeks) because of the larger number of participants and longer follow up.

- The company also submitted two alternative data sets for infection rate; the same two studies by Andriessen 2008 and Harding 2012 were used, with the monthly transition probabilities being derived from the number of infections reported during the study period. The EAC noted that for Harding 2012 the comparator experienced slightly fewer infections that the Prontosan group, but that the study numbers were low.

- The probability of recurrence of healed leg ulcers was taken from Gohel 2005 and the EAC considered this to be a reasonable data source.

- The probability of infection resolution was taken from Valenzuala et al. (2008). The EAC noted that the results are reported as bacterial culture and not clinical infection, so this should be treated with caution. No alternative data sources were identified. Full details of the clinical parameters and variables used and the EAC's opinion on the appropriateness of these can be found in section 9.3 (page 85) of the assessment report.

Costs and resource use

In the company submission, the costs and resources were calculated per dressing change visit and used to give a monthly cost for each model state (healed, open and infected) (table 6 and table 7).

The cost for Prontosan wound gel X were included in the model as shown in table 6. For both Prontosan and saline, multiple product sizes were considered and a cost per dressing was calculated for each. The company used the average cost.

The cost per healthcare state was taken from Harding, Posnett and Vowden (2013) (observational study, n=827 leg ulcers) because they reported a weekly cost per 'leg ulcer' and the cost was validated against other papers (Phillips et al. 2020; Guest, Fuller, and Vowden 2018; Guest, Fuller, and Vowden 2020). In Harding, Posnett and Vowden (2013), the costs were grouped into categories of healed, progressing, static, deteriorating or infected. The company used the reported data to split the costs further into three types: staff and outpatient costs, hospital admissions, and other costs.

The staff costs reported by Harding, Posnett and Vowden (2013) were updated by the company to 2019 prices using PSSRU 2019, with an assumption of 20 minutes for community visits and 15 minutes for practice nurse visits.

The EAC noted that the costs in Harding, Posnett and Vowden (2013) were inflated already from 2000 to 2008/09. The EAC decided to alter the staff costs in its base case to include only bands 5 and 6, as higher bands are

unlikely to be doing community visits. Additional minor changes to calculations for staff costs are listed in appendix F of the assessment report (p184).

The company removed hospital admission costs from the monthly healthcare cost, because of the low number of hospitalisations experienced by people with venous leg ulcers. The EAC considered this a reasonable approach, and that inclusion of hospital admissions would increase the cost saving due to Prontosan. Other costs included in the company model were for dressings, antibiotics, analgesics and investigations. These were inflated using pay and prices index (PSSRU 2019), and the EAC made some very minor corrections in the values used for inflation.

The company provided resource use per dressing change and the EAC accepted these as accurate (table 7).

Table 6. Cost parameters used in the company's wound closure model and changes made by the EAC

Parameter	Unit	Company base-case	EAC base-case	Source
Prontosan irrigation solution ampule	40ml unit	£0.62	Unchanged	Drug Tariff, Jan 2021
Prontosan irrigation solution bottle	350ml	£5.03	Unchanged	Drug Tariff, Jan 2021 (£0.57 per dressing)
Mean cost per Prontosan irrigation	40 ml	£0.60	Unchanged	UK PCA data 12 months to November 2020, company submission.
Prontosan Wound Gel	30ml	£6.71	Unchanged (Drug Tariff: £6.55)	Drug Tariff, Jan 2021 This is unused in model
Prontosan Wound Gel X	50g	£32.89	Unchanged (Drug Tariff: £32.10)	Drug Tariff, Jan 2021. (£2.51 per dressing)
Prontosan Wound Gel X	250g	£12.29	Unchanged (Drug Tariff: £11.99)	Drug Tariff, Jan 2021. (£1.34 per dressing)

Mean cost per Gel X dressing	10g	£1.97	£1.93	
Saline				
Irripod solution sachet	20ml	£0.24	Unchanged	Drug Tariff, Jan 2021
Steripod solution sachet	20ml	£0.20	Unchanged	Drug Tariff, Jan 2021
Normasol solution sachet	25ml	£0.26	Unchanged	Drug Tariff, Jan 2021
Mean cost per Saline irrigation	20-25ml	£0.23	Unchanged	
Monthly health care cost per state				
Health care cost, open		£635.76	£512.73	Harding (2013), cost for static, progressing and deteriorating wounds, inflated to 2018/19 prices, excluding hospital admissions. EAC corrections: see text
Health care cost, infected		£2,034.15	£1,847.05	Harding (2013), cost for severe wounds, inflated to 2018/19 prices, excluding hospital admissions. EAC corrections: see text
Health care cost, healed		£42.87	£34.36	Harding (2013), cost for healed wounds, inflated to 2018/19 prices, excluding hospital admissions EAC corrections: see text

Table 7. Resource use in the company's wound closure model and changes made by the EAC

Parameter	Company value	EAC value	Source
Resources per Dressing			

Mean wound size	54.1cm^2	unchanged	No change following discussion with experts
Gel thickness	2mm	unchanged	No change following discussion with experts, but thicker gel is considered in sensitivity analysis
Gel used per dressing change	10g	unchanged	The gel required for area and thickness is 10.8 cm$^{3.}$ This is assumed to be 10g of gel.
Prontosan Solution	40ml	unchanged	Either a 40ml sachet or 40ml from a bottle of 350ml
Saline solution	20-25ml	unchanged	A single sachet may be 20 or 25ml
Dressings per month			
Open	11.48	10.42	Harding (2013), based on cost of nursing visits and hourly cost of nursing staff. EAC corrections for staff costs and weightings.
Infected	14.18	13.75	
Healed	0.34	0.30	

Wound bed preparation model

Model clinical parameters

Clinical inputs were taken from Bellingeri et al. (2016). The EAC noted some concerns about the data, but no alternative data source was identified so the clinical inputs remained unchanged by the EAC (see table 27 of the assessment report).

Costs and resource use

Costs and resources were calculated per dressing change visit and used to give a weekly cost for each model state. The details of the health care, saline and Prontosan costs are the same as for the Markov model with the following exceptions:

- For Prontosan and saline, several product sizes were considered, and separate scenarios were used for different combinations, whereas in the wound closure model the company had taken an average. The EAC accepted this approach as it has a very minor impact.

- The cost per healthcare state were based on data from the same paper as was used to calculate the costs used in the wound closure model (Harding, Posnett and Vowden (2013)). As noted above, this paper reported a weekly cost per 'leg ulcer' grouped into categories of healed, progressing, static, deteriorating or infected. The company used an average of static and deteriorating costs to calculate the weekly cost of health care. The EAC considered that an improvement to BWAT 14 would include a progressing state, and therefore considered it appropriate to use a weighted average of static, deteriorating and progressing costs. The company have used the reported data to split the costs further into three types: staff and outpatient costs; hospital admissions; other costs.

- The company did not include hospital admission costs in the monthly healthcare costs in this model (which is the same as in the wound closure model), however, the stated reason for this was the low number of hospitalisations experienced by people with venous leg ulcers. As this model is for mixed aetiology wounds, the EAC has included hospital admission costs (inflated to 2019 costs), resulting in a small increase in cost saving. The EAC made the same minor corrections for inflation for other costs as reported in the Markov model.

Table 8 and table 9 summarises the cost and resource parameters in the company model and changes made by the EAC.

Table 8: Cost parameters used in the company's wound bed preparation model and changes made by the EAC

Parameter	Unit	Company value	EAC value	Source
Prontosan				
Prontosan irrigation solution sachet	40ml unit	£0.62	Unchanged	Drug Tariff, Jan 2021
Prontosan irrigation solution bottle	350ml	£5.03	Unchanged	Drug Tariff, Jan 2021 (£0.57 per dressing)

Parameter	Unit	Company value	EAC value	Source
Prontosan Wound Gel X	50g	£32.89	Unchanged	Drug Tariff, Jan 2021. (£2.51 per dressing)
Prontosan Wound Gel X	250g	£12.29	Unchanged	Drug Tariff, Jan 2021. (£1.34 per dressing)
Saline				
Irripod solution sachet	20ml	£0.24	Unchanged	Drug Tariff, Jan 2021
Steripod solution sachet	20ml	£0.20	Unchanged	Drug Tariff, Jan 2021
Normasol solution sachet	25ml	£0.26	Unchanged	Drug Tariff, Jan 2021
Mean cost per Saline irrigation	20-25ml	£0.23	Unchanged	
Weekly cost of healthcare				
Health care cost, weekly (monthly)	£162.60 (£704.61)	£118.32 (£512.73)		Harding (2013), cost for static, progressing and deteriorating wounds, inflated to 2018/19 prices, excluding hospital admissions. EAC corrections: see text

Table 9: Resource use in the company's wound bed preparation model and changes made by the EAC

Dressings per month			
Dressings per week (monthly)	2.74 (11.89)	2.40 (10.42	Harding (2013), based on cost of nursing visits and hourly cost of nursing staff. EAC corrections for staff costs and weightings.

Results

The company's base case results are reported in table 10 below. The EAC replicated all the company's base case analyses using its preferred inputs, the

results of these analyses are also shown in table 10 below. Prontosan was cost saving in all these analyses.

The EAC considered that the wound closure model with clinical inputs from Andriessen 2008 (most suitable data source) provided the most robust estimates as this model allowed for improvement, deterioration and recurrence of wounds which reflects clinical realities for chronic wounds and therefore selected this as its base case. This model estimated a cost saving from the use of Prontosan compared to saline of £951.01 per patient over a time horizon of 1 year.

Table 10. Summary of results for company and EAC economic analyses

Cost category	Company's base-case			Results using EAC's preferred inputs		
	Prontosan	**Saline**	**Cost saving per patient***	**Prontosan**	**Saline**	**Cost saving per patient***
	Markov wound closure model (Andriessen 2008)					
Healthcare cost	£3,223.41	£4,446.33	£1,222.92	£2,647.10	£3,693.37	£1,046.27
Technology	£119.39	£14.73	-£104.65	£108.72	£13.46	-£95.26
Total	**£3,433.04**	**£4,461.06**	**£1,118.26**	**£2,755.82**	**£3,706.83**	**£951.01 [EAC base case]**
	Markov wound closure model (Harding 2012)					
Healthcare cost	£5,052.85	£6,396.27	£1,343.42	£4,234.16	£5,368.82	£1,134.66
Technology	£175.61	£20.66	-£154.96	£160.88	£18.93	-£141.95
Total	**£5,228.46**	**£6,416.93**	**£1,188.47**	**£4,392.05**	**£5,387.75**	**£992.71**
	Wound bed preparation model					
Healthcare cost	£671.33	£1,833.48	£1,162.15	£537.94	£1,469.17	£931.23
Technology	£34.87	£7.12	-£27.75	£30.56	£6.24	-£24.32
Total	**£706.20**	**£1,841.28**	**£1,134.40**	**£568.49**	**£1,475.40**	**£906.91**

Sensitivity analysis

Wound closure model

The company's sensitivity analysis for the wound closure model with the Andriessen 2008 and Harding 2012 data included:

- a threshold analysis to determine the level of improved healing rate required for Prontosan to break even in cost with saline
- one-way sensitivity analyses for clinical, resource and cost variables
- a bivariate analysis varying the costs of both Prontosan and saline.

The company's threshold analysis indicated an increased healing rate for Prontosan of 9-12% is required if the costs of treatment are to breakeven with costs of cleansing with saline. The company note that the increased healing rate for Prontosan compared with saline predicted by the model were considerably higher; when the clinical inputs were derived from Andriessen 2008 the predicted increased healing rate was 46%, when the clinical inputs were derived from Harding 2012, the predicted increased healing rate was 66%.

The company's one way sensitivity analysis tested the impact of varying key clinical and cost inputs. Specifically, it tested the following:

- Varying the healing rate transition probability in the Prontosan arm based on the upper and lower bounds of the confidence intervals reported in the clinical studies that informed this parameter
- Varying the infection rate and infection resolution transition probabilities by 30% and 25% respectively
- Varying resource use costs in line with the 95% confidence intervals reported in Harding, Posnett and Vowden 2013
- Varying the technology costs as follows:

- Prontosan: lowest cost = available cost of Prontosan; upper cost was average cost of Prontosan +100%.

- Saline: lowest cost £0.00; upper cost = cost of saline +100%

The analyses revealed that Prontosan remains cost saving over saline when resource, infection rate and infection resolution rate are varied. Prontosan also remains cost saving compared with saline when healing rate is varied using the Andriessen 2008 data. However, some uncertainty around impact of varying healing rate using the Harding 2012 data was identified (Figure 4). The company noted these results are not surprising due to small study population in the Harding study (n=37) resulting in large error and 95%CI estimates, whereas for the larger study by Andriessen 2008 (n=119) the 95%CI (0.989) was very close to crossing 1, indicating significant impact of Prontosan on healing rate.

Figure 3 – Tornado plot showing results of company sensitivity analysis varying transition probabilities derived from Andriesson (2008), cumulative half cycle (source: company submission, figure 6)

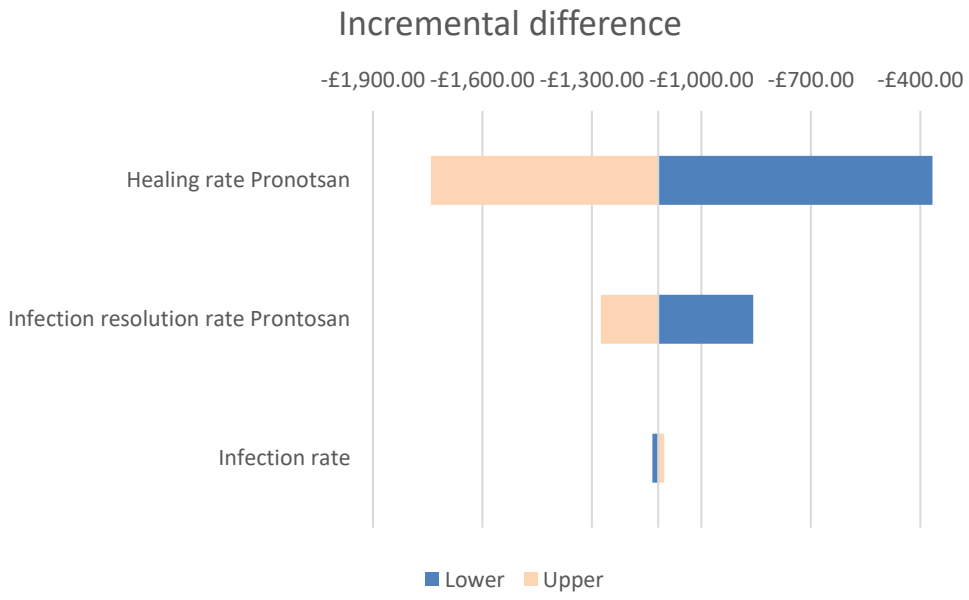
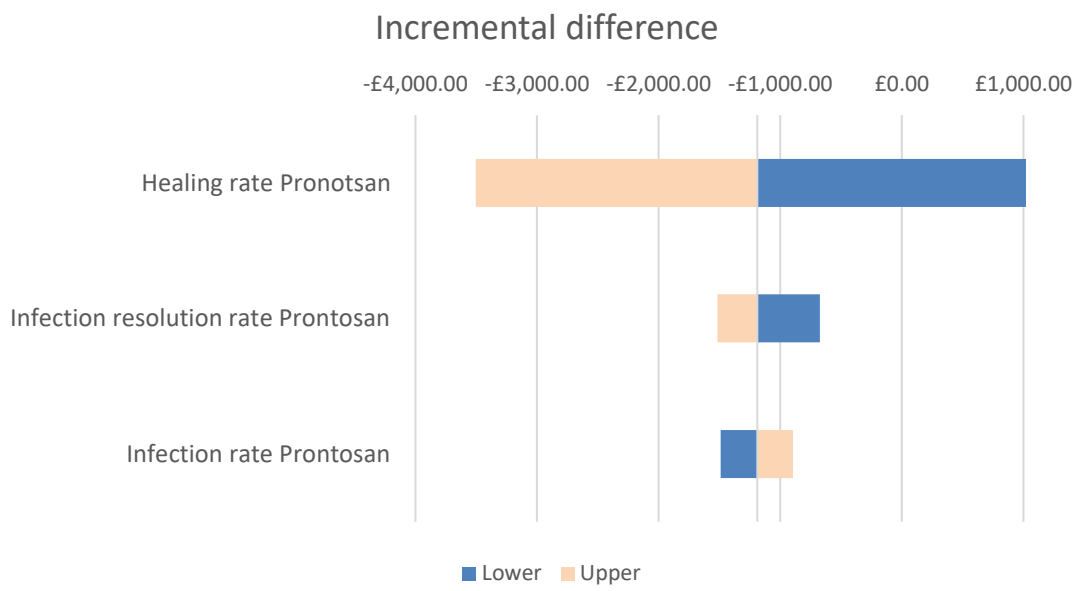


Figure 4 – Tornado plot showing results from company sensitivity analysis varying transition probabilities derived from Harding (2012), cumulative half cycle (source: company submission, figure 6)



The company's bivariate analysis showed that Prontosan still remained cost saving when used until wound closure, with the assumption of no cost for the current treatment and a 100% increase in Prontosan products. The company stated that this showed that it is therefore highly unlikely that savings would be reduced through any increase in costs of Prontosan or changes to comparator costs.

The EAC noted that the model does not have the functionality to re-run these analyses so the EAC explored the impact of key variables using the updated EAC base case (wound closure model populated with the Andriessen 2008 data).

The EAC found that if the transition probabilities for healing with Prontosan are set to be equivalent to those for saline, the model remained slightly cost saving due to the reduction in infections. Where all transition probabilities are set to the values for saline the EAC base case is slightly cost incurring.

The EAC noted the key drivers identified in the company model are the time to healing, reduced time in infected state and costs of healthcare visits and this remained unchanged in the EAC base case. The EAC noted that the cost saving was because of the reduction in visits for dressing changes, and the healthcare resource associated with these visits in the Prontosan arm. The EAC stated the model is robust to variation of key drivers, because of the large costs of these visits relative to the costs of saline or Prontosan products.

Wound bed preparation model

The company's sensitivity analysis for the wound bed preparation model included one way sensitivity analysis on time to BWAT 14 score, costs of Prontosan and saline products, and weekly health care costs. When each of the parameters were varied by the upper and lower limits, Prontosan remained cost saving.

The EAC stated that the sensitivity analyses showed that that identified savings were driven by reducing the time taken for the wound to reach a healthy wound state following Prontosan treatment compared with saline and costs of healthcare visits.

Summary of the company's interpretation of the economic evidence and conclusions

The company's overall conclusion regarding the economic evidence is that it supports the case for Prontosan as an option for treatment of venous leg ulcers until wound closure and for the treatment of stagnant and deteriorating wounds to improve wound condition.

Summary of the EAC's interpretation of the economic evidence and conclusions

The EAC considered the Markov wound healing model populated with the data from Andriessen 2008 to be the most appropriate and that, while the structure might be suitable for all chronic wounds, many of the clinical inputs, and some of the cost inputs were specific to venous leg ulcers. Although the

EAC stated a preference for using the Andriessen 2008 data to populate the model, it also noted that the incremental cost savings per person for both wound closure models were very similar when the Harding 2012 data were used instead. It noted that the methods used to extrapolate the observed data over the 1-year time horizon impact the results and that use of alternative extrapolation approach is likely to lead to a moderate reduction in the overall cost saving due to Prontosan. It would however remain clearly cost saving.

The EAC also noted that although both models included costs for the use of Prontosan solution and gel X at every dressing, the clinical data used to inform the wound closure model comes from studies that use only Prontosan solution (Andriessen 2008) or Prontosan solution and Prontosan gel (Harding 2012). The time to healing or wound progression is a much larger driver in the models than the cost of the products. The selection of different Prontosan products is a clinical decision and should not be influenced by the modelling approach.

The EAC stated that the key drivers of the model were the time to healing and the cost of wound care during this process. The same drivers were also found in the wound bed preparation model.

The EAC noted no modelling was submitted for burns or acute surgical site wounds. A non-Markov model may be more suitable in these populations where deterioration of wound condition and recurrence of wounds are less common, however there is very little available evidence to populate it.

The EAC stated the key limitations are that the models rely on clinical evidence which is comparative, but not of high quality. Despite these limitations, the models are robust to variation in the clinical inputs, requiring only a small impact on time to healing or reduction in infections to remain cost saving. The modelling supports the company claims that use of Prontosan leads to a reduced number of visits and a reduction in the associated resources.

5 Ongoing research

The EAC identified 13 ongoing studies that mentioned Prontosan of which 3 were considered potentially relevant to the decision problem. The company submission included details of 1 additional ongoing case series that was not identified by the EAC searches. One study is based in the UK. Details of these 4 studies can be found in table 19 (section 8.2) in the EAC assessment report.

The EAC notes that the potential impact on the current evidence base is uncertain. Two ongoing studies are large randomised trials of which 1, the NEWfeet trial, is of particular interest as it is a UK-based trial. Results from this trial will inform the effectiveness of Prontosan solution compared with electrolised water for patients with diabetic foot ulcers. This will be an addition to the evidence base as there currently is no evidence for diabetic foot ulcers specifically.

6 Issues for consideration by the Committee

Clinical evidence

1. The population in the decision problem is very broad (adults and children with acute or chronic wounds) but evidence is only available for some groups.

    - One study (Ciprandi 2018) was identified that included children who were being treated in hospital for burn wounds. Wound duration at the start of the study was not specified.

    - 3 studies (Wattanaploy 2017, Kiefer 2018 and Moore 2016) were identified that only included adults with burns. In Wattanaploy 2012 burns within 48 hours after injury were included. For Kiefer wound duration at the start of the study was not specified. The patients in Moore 2016 were described as having chronic, non-healing wounds.

- 15 studies included adults with chronic wounds. Most of the data reported in these studies relates to patients with pressure or venous leg ulcers.

The clinical experts confirmed that the population in the decision problem is appropriate. Specifically, they noted that Prontosan is suitable for a wide range of wound types and settings and for both adults and children. The clinical experts' initial comments on the extent to which wound care and wound outcomes differ across subgroups were as follows:

- They largely agreed that it was appropriate to generalise evidence from chronic wound types because most chronic wounds are treated in a similar way and have similar prognosis. However, they raised specific concerns around vascular wounds. In these wounds, a poor blood supply is going to impact wound healing and if the blood supply cannot be improved, and the experts stated that the product used to treat the wound will not matter.

- One expert noted that key factors related to delayed wound healing include age, vascular disease, immunosuppression, presence of infection, pain, lifestyle, BMI, nutrition, mobility, practitioner skill, pressure, and wound site.

Given the data gaps for some populations, the committee may wish to consider if the results from studies in specific subgroups be generalised to other subgroups/the overarching population.

2. The intervention in the decision problem includes all Prontosan products (irrigation solution/gel/gel X). Evidence has been identified for all three products but in some studies irrigation solution or gel is used alone, in other studies a combination of solution and gel is used. In addition, the methods of administration differ across studies. The clinical experts noted there are 3 types of appropriate uses of Prontosan products depending on wound condition and clinical need. These include using

Prontosan wound irrigation solution alone, Prontosan wound gel or gel X alone, or Prontosan wound irrigation solution plus wound gel or gel X. Currently Prontosan wound irrigation solution is the most used product. Clinical experts agreed that the soak using the irrigation solution is the most important element. The clinical experts also agreed that typically a Prontosan soak would take between 5-15 minutes depending on wound condition, but most soaks were 10 minutes. They noted that it was feasible to incorporate a 10-minute soak into the standard timeframe for a dressing change. One expert stated that the gel would be used to support and maintain the irrigation/soak process.

The EAC noted that the studies by Borges 2018, Saleh 2020, Assadien 2018 may be of limited relevance to clinical practice because of the way the intervention was delivered. The EAC considers that the use of Prontosan irrigation solution or saline for irrigation followed by 10-minute soak as in Bellingeri (2016), Prontosan soak times of 5-10 minutes (Atkin 2020) and Prontosan soak times of 10 mins followed by gel if necessary (Horrocks 2006) to be most applicable to NHS practice. The committee may wish to consider whether all studies looking at any Prontosan formulation or mode of administration should be used to inform decisions about the clinical effectiveness of Prontosan.

3. The decision problem includes 3 comparators – water, saline and Ringer's solution. 9 of the studies included by the EAC were non-comparative. One study (Andreissen 2008) has been identified where patients in the control arm received saline or Ringer's solution. The EAC noted no comment can be made on the efficacy of Prontosan compared with saline or Ringer's solution specifically based on the results in this study. One study in adult patients with burns (Wattanaploy 2017) compared Prontosan to a comparator not listed in the decision problem (silver sulphadiazine, a thick white creamy dressing material). Silver sulphadiazine is an antibiotic and is intended to kill bacteria or prevent its growth. The EAC consider this an appropriate comparator to Prontosan for patients with burns. The clinical experts confirmed that:

- saline and water are both currently used for wound cleansing in the NHS
- Ringer's solution is rarely used in practice in their experience
- No comments were made on using silver sulphadiazine to treat burns. One expert said that there is no standard of care in burn wound cleansing or management of chronic wounds. It varies from plain water, saline, antiseptics, antimicrobials, and mechanical methods including surgery.

The committee may wish to consider whether results from studies with no comparator arm, or the studies by Andreissen 2008 and Wattanaploy 2017 can inform decisions about the relative clinical effectiveness of Prontosan and other wound cleansing treatments used in the NHS.

4. Most of the evidence was of low quality and at high risk of bias. Specifically, the EAC concluded that 12 studies were at high risk of bias and 5 were at some risk of bias and one was at low risk of bias. It noted that all studies had some limitations, regardless of design/risk of bias (see section 4.1). The committee may wish to consider if the evidence is appropriate for decision making.

Cost evidence

1. No useful published economic studies were identified.

2. The company submitted 2 de-novo economic models, a wound closure Markov model and a simple wound bed preparation cost comparison model. The EAC review highlighted some limitations with the models but overall, its assessment suggests that the company have made best use of the available data. The EAC stated that the key drivers of the wound closure model were the time to healing, reduced time in infected state and the cost of wound care. In the wound bed preparation model, the key drivers of the model were the time to wound bed improvement

and the cost of wound care. The EAC made the following comments about the uncertainty of the inputs for these key drivers:

- Wound closure model – wound healing and infection rates
    i. Andriessen (2008) is a retrospective comparative case series of 112 patients with venous leg ulcers and a follow up time of 6 months. The EAC considered that Andriessen 2008 was a more suitable data source due to the larger number of participants and longer follow up. However, the study was at high risk of bias because of potential selection and reporting bias.

    ii. Harding (2012) is a small UK pilot RCT study with 34 patients. The shorter follow-up period of 12 weeks meant that there was greater reliance on extrapolation for the calculation of transition probabilities for wound healing. There were some concerns around the randomisation process.

- Wound bed preparation model – wound bed improvement rates
    i. Bellingeri (2016) is an RCT in 289 patients with pressure ulcers or vascular leg ulcers at low risk of bias. The follow up was 28 days, and wounds were assessed for BWAT wound healing score. The company used an excel trendline to extend the graphs to reach a mean score of BWAT for both arms. Although there were concerns about the data, no improved data source has been identified.

3. All of the company's base case results showed that Prontosan was cost saving compared to saline. One of the company's sensitivity analyses for the wound closure model showed that treatment with Prontosan could be cost incurring up to £1000/per year.

4. The EAC chose the wound closure Markov model, with clinical inputs from Andriessen 2008 as the EAC base case. It considers its base case results robust enough to inform decisions about the cost savings associated with using Prontosan in people with venous leg ulcers only.

5. The wound bed preparation model is underpinned by a study that has fewer methodological limitations than either of the studies tested for the wound closure model. The study used a surrogate outcome (at least 75% epithelisation), but it is a recognised validated wound assessment tool. No additional cost or modelling is included for deteriorating or recurring wounds, or for additional treatment until healing.

6. The committee can decide if it wants to base its decision on the costs associated with Prontosan on one or more of the models that have been submitted. It may wish to consider the relevance of the model structures to clinical practice or the limitations of the evidence included in each model.

7 Authors

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Juliet Kenny, Health Technology Assessment Adviser

NICE Medical Technologies Evaluation Programme

April 2021

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- O'Connell S, Knight L, Morgan H, et al. Prontosan for acute and chronic wounds, March 2021.

B Submissions from the following sponsors:

- B. Braun Medical Limited

C Related NICE guidance (published)

- Leg ulcer infection: antimicrobial prescribing. (2020) NICE guideline.
- Surgical site infections: prevention and treatment (2020) NICE guideline NG125
- Diabetic foot infection: antimicrobial prescribing. (2019) NICE guideline.
- Diabetic foot problems: prevention and management (2015) NICE guideline NG19. Last updated: January 2016
- Pressure ulcers: prevention and management (2014) NICE guideline CG179

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NICE Guideline [CG179]: Pressure ulcers: prevention and management. url: https://www.nice.org.uk/guidance/cg179 [last accessed: March 2021]

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Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Patricia Littlewood

Lead Tissue Viability Clinical Nurse Specialist, Frimley Health Foundation Trust. Nursing & Midwifery Council.

Mark Collier

Nurse Consultant and Associate Lecturer (Tissue Viability), Independent with affiliations to the Universities of Lincoln and Hertfordshire. Nursing & Midwifery Council.

Katie Bennett

Wound Care Lead Nurse, Westbury Group Practice. Royal College of Nursing.

Heather Hodgson

Lead Nurse Tissue Viability, NHSGGC. Nursing & Midwifery Council.

Mr Haitham Khalil

Consultant Oncoplasty and Reconstructive Surgeon, University Hospitals Birmingham. American Society of Plastic Surgeons, British Association of Surgical Oncology and Association of Breast Surgery.

Dr Fania Pagnamenta

Clinical Academic Nurse Consultant (Tissue Viability), Newcastle upon Tyne Hospitals NHS Foundation Trust. Nursing & Midwifery Council.

Kimberley Wilde

Advanced Podiatrist, Manchester Foundation Trust. Health Professions Council.

Denise Woodd

Independent Clinical Nurse Specialist in Wound Care and Leg Ulcers, NHS Portsmouth CCG and Solent NHS Trust. Nursing & Midwifery Council, Royal College of Nursing and Leg Ulcer Forum.

Baljit Dheansa

Consultant Burns and Plastic Surgeon, Queen Victoria Hospital. British Burns Association, British Association of Plastic, Reconstructive and Aesthetic Surgeons.

Please see responses to the expert advisor questionnaire (EAQ) included in the committee pack for full details.

Appendix C: decision problem and claimed benefits from scope

The benefits to patients claimed by the company are:

- Quicker wound healing and fewer wound care service visits needed.
- Improved quality of life.
- Improved wound bed condition: reduced pain, wound exudate, odour, and slough.
- Reduced infection and markers of infection.

The benefits to the healthcare system claimed by the company are:

- Reduced need for wound care services (including community wound care) and associated costs because of fewer dressing changes and faster healing time.
- Reduced need for antibiotics, antimicrobial dressings and pain medication.

Population	Adults and children with acute or chronic wounds
Intervention	• Prontosan Wound Irrigation Solution • Prontosan Wound Gel • Prontosan Wound Gel X
Comparator(s)	• Saline • Water • Ringers solution

Outcomes	The outcome measures to consider include:
	• Proportion of wounds with complete closure
	• Time to complete wound closure
	• Other outcomes related to wound characteristics including wound size, volume and area
	• Number of dressing changes and use of antimicrobial dressings and other consumables
	• Incidence of wound infection evidenced by
	  ○ Adverse events and/or use of antibiotics (related to wound infection)
	  ○ Reduction in clinical signs of infection
	• Changes to wound bed condition including slough, exudate, granulation and oedema
	• Staff time

	• Antibiotic use • Analgesic use • Length of hospital stay • Number of follow on treatments including GP, nurse and hospital visits • Number of surgical debridement procedures • Number of amputations or skin grafts • Colonisation with antimicrobial resistant pathogens Patient and carer related outcomes: • Health-related quality of life • Patient-related outcomes such as pain scores, discomfort and wound odour, or level of satisfaction • Carer's level of satisfaction • Mortality rates • Device-related adverse events.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	• Burns • Diabetic foot ulcers • Leg ulcers • Pressure ulcers • Post-operative wounds (with and without surgical site infection) • Trauma wounds • Infected wounds of any aetiology • Recurrent infections • Wound duration • Wound size • Children or adolescents
Special considerations, including those related to equality	Older people, people with diabetes, people with restricted mobility and people with darker skin tones are more likely to have chronic or non-healing wounds. Age, disability, and race are protected characteristics

Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Category 1 pressure ulcers are identified by visual assessment of a non-blanching area of redness. In people with darker skin tones, it may not be possible to identify pressure ulcers by visual assessment. People with certain family origins are also more prone to poor wound healing due to receiving poorer quality care and have an increased risk of developing conditions that may cause poor healing outcomes (such as diabetes).	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Prontosan for acute and chronic wounds

1 Technology

1.1 Description of the technology

Prontosan (B Braun) is a range of topical solutions and gels used for cleansing and moistening acute and chronic wounds. Prontosan is available as:

- Prontosan Wound Irrigation Solution, used for wound irrigation or applied to gauze as a soak, 350ml bottle, 40ml single-use pods and 1,000ml bottle for instillation.
- Prontosan Wound Gel, applied to the wound bed during dressing changes after wound cleansing and before application of secondary dressing. The 30ml bottle is suitable for use in deep and tunnelling wounds, wound cavities and difficult to access wounds.
- Prontosan Wound Gel X (extra thick gel), 50g or 250g tube, applied to the wound bed during dressing changes, after wound cleansing and before application of secondary dressing. It is suitable for use in flat or larger surface area wounds such as leg ulcers.

The solution and gels contain an antimicrobial polyhexanide (0.1% polyhexamethylene biguanide) and a betaine surfactant (0.1% undecylenamidopropyl betaine). The company claim that Prontosan is the only wound cleansing solution or gel that contains these 2 active ingredients which work in combination to disrupt and prevent biofilm from the wound bed as well as cleansing and removing slough, devitalised tissue and other wound debris.

1.2 Relevant diseases and conditions

Prontosan is intended for use in acute and chronic wounds only when they require cleansing. The types of wounds that may be encountered include:

- Acute non-infected and infected wounds such as trauma wounds (skin lacerations, bites, cuts or crush injuries) and post-operative wounds.
- Chronic non-infected and infected wounds including pressure ulcers, leg ulcers and diabetic foot ulcers.
- Thermal, chemical and post-radiation wounds including burns.

The population who may benefit from this technology is large. It is estimated that in the UK, over 2 million people per year have wounds that require treatment. A cohort analysis of 1,000 NHS patients that have wounds suggested that about 39% of wounds do not heal within the first year and may need additional therapy.

1.3 Current management

Current treatment options for cleansing acute and chronic wounds include sterile saline or water. Care of acute or chronic non-healing wounds aims to improve wound condition, promote healing and minimise the risk of further complications. If the wound is suspected of being infected, a microbiological sample is usually taken and an antibiotic prescribed to treat the organism causing the infection. The wound is treated with regular cleansing and debridement (autolytic, mechanical, or surgical, as required by the wound) and then a dressing is applied. An appropriate dressing is selected to promote healing and manage exudate on a case-by-case basis. Chronic wounds may be treated with advanced dressings that usually work by simple physical or chemical means, typically by controlling moisture levels (for example, alginate, film, foam, hydrocolloid and hydrogel dressings).

The following publications have been identified as relevant to this care pathway: NICE's guidelines on surgical site infections, diabetic foot problems and pressure ulcers.

1.4 Regulatory status

Prontosan received a CE mark in February 2009 as a class III medical device. The different sizes and preparations of Prontosan are covered under the CE mark.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Quicker wound healing and fewer wound care service visits needed.
- Improved quality of life.
- Improved wound bed condition: reduced pain, wound exudate, odour, and slough.
- Reduced infection and markers of infection.

The benefits to the healthcare system claimed by the company are:

- Reduced need for wound care services (including community wound care) and associated costs because of fewer dressing changes and faster healing time.
- Reduced need for antibiotics, antimicrobial dressings and pain medication.

2 Decision problem

Population	Adults and children with acute or chronic wounds
Intervention	• Prontosan Wound Irrigation Solution • Prontosan Wound Gel • Prontosan Wound Gel X
Comparator(s)	• Saline • Water • Ringers solution
Outcomes	The outcome measures to consider include: • Proportion of wounds with complete closure • Time to complete wound closure • Other outcomes related to wound characteristics including wound size, volume and area • Number of dressing changes and use of antimicrobial dressings and other consumables • Incidence of wound infection evidenced by

	○ Adverse events and/or use of antibiotics (related to wound infection) ○ Reduction in clinical signs of infection • Changes to wound bed condition including slough, exudate, granulation and oedema • Staff time • Antibiotic use • Analgesic use • Length of hospital stay • Number of follow on treatments including GP, nurse and hospital visits • Number of surgical debridement procedures • Number of amputations or skin grafts • Colonisation with antimicrobial resistant pathogens Patient and carer related outcomes: • Health-related quality of life • Patient-related outcomes such as pain scores, discomfort and wound odour, or level of satisfaction • Carer's level of satisfaction • Mortality rates • Device-related adverse events.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	• Burns • Diabetic foot ulcers • Leg ulcers • Pressure ulcers • Post-operative wounds (with and without surgical site infection) • Trauma wounds • Infected wounds of any aetiology • Recurrent infections • Wound duration • Wound size • Children or adolescents
Special considerations, including those	Older people, people with diabetes, people with restricted mobility and people with darker skin tones are more likely to have chronic

related to equality	or non-healing wounds. Age, disability, and race are protected characteristics	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Category 1 pressure ulcers are identified by visual assessment of a non-blanching area of redness. In people with darker skin tones, it may not be possible to identify pressure ulcers by visual assessment. People with certain family origins are also more prone to poor wound healing due to receiving poorer quality care and have an increased risk of developing conditions that may cause poor healing outcomes (such as diabetes).	

3 Related NICE guidance

Published

- Leg ulcer infection: antimicrobial prescribing. (2020) NICE guideline.
- Surgical site infections: prevention and treatment (2020) NICE guideline NG125
- Diabetic foot infection: antimicrobial prescribing. (2019) NICE guideline.
- Diabetic foot problems: prevention and management (2015) NICE guideline NG19. Last updated: January 2016
- Pressure ulcers: prevention and management (2014) NICE guideline CG179

In development

NICE is developing the following guidance:

- Diabetic foot ulcers - new treatments. NICE guideline. Publication date TBC

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association for Perioperative Practice
- Association of Breast Surgery
- Association of Surgeons of Great Britain and Ireland
- British Association of Paediatric Surgeons
- British Association of Plastic Reconstructive and Aesthetic Surgeons
- British Obesity and Metabolic Surgery Society
- British Obesity Surgery Society
- British Pain Society
- Community Practitioners' & Health Visitors Association
- Primary Care Diabetes Society
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Obstetricians and Gynaecologists
- Royal college of Surgeons
- Society of Vascular Nurses
- Surgical Dressing Manufacturers Association
- The Vascular Society
- Tissue Viability Society

NICE National Institute for Health and Care Excellence

Adoption report: GID-MT551 Prontosan for acute and chronic wounds

Summary

Adoption levers identified by contributors

- Easy to use and convenient
- Good patient experience and potential for self-administration
- Positive contributor experience
- Clinical confidence in the evidence supporting control of biofilms
- Ampules are small and easy to store
- May be cost saving in reducing wound infections

Adoption barriers identified by contributors

- Perceived requirement for long soak time for the solution (10 minutes)
- Multiple wound care products and strategies available for the intended indication.
- Protocols would be needed in multiple care pathways to optimise use.
- More expensive than alternatives (water or saline)
- Some poor clinical acceptance of use for foot ulcers in place of sharp debridement
- Concern about microbial resistance if used for all wounds.
- Emergence of similar products with perceived shorter cleaning times

1 Introduction

The adoption team has collated information from healthcare professionals working within NHS organisations 8 of whom have experience of using Prontosan Wound: Irrigation Solution; Gel X and Gel. This report has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption. It does not represent the opinion of NICE or MTAC.

2 Contributors and respective usage

Details of contributing individuals and usage of Prontosan are listed below.

Job title	Prontosan Use
Lead Tissue Viability Specialist Nurse	Used solution as a soak in the past. Used on wounds known to be infected or at risk of serious wound infection. Changed to alternative product with a shorter soak time and was part of the washing product range from another company with which the trust had a contract.
Vascular Nurse Consultant	The irrigation solution (as a soak) and Gel X are used for chronic wounds where other treatment has been optimised (e.g off loading, compression) and bioburden is suspected (odour, pain, exudate). (4-5 years)
Wound Care Practice Nurse	Irrigation solution (as a soak) and Gel X are used as part of the local wound cleaning pathway. Used for wounds that are non healing, require debridement, or are recurrently infected. (7 years)
Advanced Podiatrist	All Prontosan technologies are used but most commonly the irrigation solution is used as a soak for diabetic and ischaemic foot ulcers in high risk patients (are those with a current ulcer that have complications such as a poor vascular supply, severe loss of feeling, immunosuppressed). (8 years)
Tissue Viability Lead Nurse for Acute and Community	The irrigation solution (as a soak and for irrigation) and Gel X are used for a variety of wounds including C-section surgical wounds, postnatal perineal tears and episiotomies which are not healing as expected, infected or the person is at high risk of wound infection. (since it was first available to the NHS) The irrigation solution and Gel X are included in the wound cleaning pathway and maternity guidance. (12 years)
Lead Clinical Nurse Specialist Tissue Viability	Irrigation solution is used in VAC veraflo technology when irrigation setting is in use. For wounds with slough and pus. (4 years)
Community Matron (Tissue Viability & Infection Prevention)	Not routinely used. Previously used the solution as a soak for chronic wounds with re-occurring local infections. Discontinued use in favour of a similar product with a shorter soak time and to simplify patient wash protocols by using products from the same company. Gel X used specifically for chronic wounds with narrow cavity which cannot be packed.
Diabetes Specialist Podiatrist	Used solution as a soak in the past for foot ulcers with slough that was hard to remove. No benefit seen, returned to using sharp debridement.
Consultant Orthopaedic Consultant	Not used

3 Current practice

The three Prontosan products are marketed for use in a broad range of acute and chronic wounds at different stages of wound care.

Although variation exists in practice, consensus from contributors, supported by national guidance, is that acute wounds should not routinely be cleaned during healing. Surgical wounds are left to heal unless there is an unexpected delay in healing or surgical site infection.

One contributor made the distinction between cleaning the wound edge and the wound bed as the type of cleaning and purpose would be different. Chronic wounds should not be routinely cleaned or treated with antibacterial products, unless clinically required for one or more of the following reasons:

- delayed healing
- signs of localised infection
- localised redness
- exudate
- odour
- visible debris.

Wound cleaning and dressing changes should be as infrequent as possible, and a healthy wound bed should not be disturbed.

There is variation in practice around use of (potable) water or saline to clean wounds. This depends on the setting of use (for example access to a clean water supply) and the wound and patient characteristics (e.g if bone is exposed or a patient has compromised immunity).

Contributors advised that early intervention is required once the wound is not healing as expected to prevent further deterioration.

4 Practical application of Prontosan in practice

Tissues viability nurses, podiatrists, practice nurses, district nurse and acute hospital nurses were identified as the professionals most likely to use Prontosan products. All contributors described directing these at the wound bed. The frequency of wound dressing change is guided by the nature of the wound and not the specific product. One contributor suggested that if Prontosan reduces bioburden this should reduce the amount of wound exudate and the frequency of dressing changes. Apart from the single use Prontosan solution ampules, all products have a shelf life of 8 weeks from opening. Contributors did not report any product wastage because of shelf life.

Prontosan Wound Irrigation Solution

The irrigation solution is commonly used as a soak on sterile gauze and placed on the wound for 10 minutes as recommended in the product instructions. Contributors believed soaking for less than 10 minutes would lead to suboptimal results. However, the company said that soak times should be adapted to suit the wound ranging from irrigation to a 15-minute soak for severe wounds. Soaking is repeated at every dressing change. Where a soak is difficult to use due to wound position or if frequent wound cleaning is required due to incontinence, the solution is used as a wash.

Achieving sufficient soak time is reported as a barrier to adoption particularly in an acute hospital setting due to pressures on nursing time. Two contributors reported changing to an alternative wash which they said has a shorter recommended soak time. In community settings this is less of an issue with contributors applying the soak and using this time to undertake the assessment and discuss treatment with the patient.

The solution is available in ampules (40ml) and large bottles (350ml) with contributors using both.

The ampules are more useful:

- in acute settings where use was infrequent, taking up less storage space

- in deep cavities where the product could be applied directly onto the wound bed
- where portability is important as they are compact
- to control volume used for self-caring patients.

The 350ml bottles are more useful where longer term use is expected or for multiple eligible patients. If one bottle is used for several patients, the soak is prepared in a separate clinic room adhering to all infection and prevention protocols.

If wound debridement is required, this is done after the soak. Most contributors reported this to be easier and less painful when using the Prontosan soak. If no other Pronotsan products are used after the soak, the most appropriate dressing for the wound is chosen.

One contributor uses the Prontosan irrigation solution with the V.A.C. Veraflo system for negative pressure wound therapy. Relevant attachments are provided by the company (B.Braun) who report this use to be rare.

Prontosan Wound Gel and Prontosan Wound Gel X

Contributors reported the standard gel (30-ml bottle) is rarely used because it is less viscous and likely to run off the wound.

The thicker Gel X (available in 50g and 250g tubes) is more popular and is described as having a consistency like toothpaste with better wound adherence. A dressing is not always required with Gel X because of its wound adherence. If needed contributors recommend a simple non adherent dressing. Which will not soak up the gel or affect its action.

5 Reported benefits

The potential benefits of adopting Prontosan solution and gels, as reported to the adoption team by the healthcare professionals using the technology are:

- good patient experience – the solution is soothing and moisturising
- loosens slough and debris making manual debridement easier and less painful
- removes biofilm leading to reduced exudate (and associated dressing changes)

- improved wound healing
- reduced incidence of wound infections and referrals to tissue viability services
- reduced use of more costly advanced dressings
- Gel X can stay in place without the need for a secondary dressing
- no reported side effects or allergic reactions to the products

6 Insights from the NHS

Patient selection and wound care pathway

Contributors use Prontosan irrigation solution and gels for chronic non-healing leg ulcers, foot ulcers, pressure ulcers, perineal wounds and dehiscing surgical wounds including Caesarean sections. Some use was also reported in burns. Patients are selected when biofilms are considered to be a contributing factor to delayed healing and all other modifiable factors have been addressed for example:

- offloading in diabetic foot ulcers
- compression for venous leg ulcers
- no improvement observed from advanced dressing.

The products are also selected for use in wounds assessed as 'high risk' either because of the type of wound, included repeated previous infections, or the age or clinical condition of the patient. One contributor would not use a Prontosan gel on a very 'wet' wound.

Contributors agreed that Pronotsan technologies should be used as part of an agreed wound care pathway to ensure appropriate patient selection and optimised use. This could include when to review the impact and if appropriate consider discontinuation.

There is variation in approaches on using both the solution and gel at each dressing change. The solution is used in nearly all dressing changes but the criteria for choosing Gel X varied. Gel X tends to be used for more severe wounds and in wounds where a longer effect is required because dressing changes are more than 48 hours apart (contributors perceived the effect of the Prontosan solution, used at

the dressing change, will stop after 48 hours).. It is also used instead of advanced dressings for some deep cavities where the dressing will not make contact with the wound bed. Once wounds start healing use of the gels decreases.

Clinician confidence/acceptance

Contributors reported an increase in clinical awareness of the evidence on the effect biofilms have in slowing wound healing. This has led to an increase in clinical confidence in the use of Prontosan. More evidence around wound type and patient selection would be welcomed.

Clinicians using Prontosan routinely reported ease of use, improved wound healing and high patient acceptance. Clinical resistance to changing practice is considered to be a barrier to adoption. One contributor reported that sharp debridement is more effective than the solution for removing slough on foot ulcers.

No negative side effects were reported contributors however, concern was expressed about the risk of microbial resistance if it were to be used routinely on all wounds.

One clinician highlighted that there was a potential risk for confusion between the ampules for the Prontosan solution and saline for intravenous use. The company said that the ampules state not for injection and have unique branding and labelling.

Contributors reported that during the current COVID-19 pandemic, some patients have been able to self-administer the Prontosan solution and Gel X as face to face appointments have been reduced.

Cost and procurement

Contributors considered cost to be a barrier to adoption when water or saline are the alternatives. Having Prontosan on local formularies is a lever to adoption especially within community settings. Once on the formulary Prontosan can be prescribed and ordered through NHS Supply Chain.

Some contributors thought Prontosan offered cost savings through reducing: use of advanced dressings, incidence of wound infections, referrals to tissues viability services and improving wound healing.

Procurement in acute trusts can depend on existing contracts for other products. Two contributors said their services moved from using the Prontosan solution to use another wound irrigation product from a company which provides a variety of patient wash products to their trusts.

Training

Prontosan products are reported to be easy to use with minimal training required. The company provides free training to staff within account holding organisations.

Several contributors highlighted the importance of emphasising soak time to ensure the recommended time is achieved.

Contributors said that training and education for clinical staff about biofilms would be useful to help them understand when it is appropriate to use Prontosan. Additionally, a good understanding of its place in the local care pathway is important to ensure potential cost savings can be fully realised.

Contributors have taught several patients to use the Prontosan solution to care for their wound and reported that this is not challenging.

Patient experience

All contributors said patients were very positive about this technology. It has caused no additional pain, is reportedly soothing and debridement is less painful after a Prontosan soak. Having their wounds cleaned when there is visible debris, dried exudate, or blood on the wound or they are smelly and sloughy was considered to be important to patients.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID-MT551 Prontosan for acute and chronic wounds

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	B. Braun Medical Limited
Submission date	8th February 2021
Regulatory documents attached	Please list regulatory documents submitted (e.g. CE certificate, instructions for use, etc.) CE certificate for Prontosan: Medical Devices for Wound Bed Preparation Instructions for Use for Prontosan Wound Irrigation Solution Instructions for Use for Prontosan Wound Gel Instructions for Use for Prontosan Wound Gel X

Contains confidential information	Yes - highlighted in yellow and turquoise

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	Adults and children with acute or chronic wounds	Enter text.	Enter text.
Intervention	• Prontosan Wound Irrigation Solution • Prontosan Wound Gel • Prontosan Wound Gel X	Enter text.	Enter text.
Comparator(s)	• Saline • Water • Ringer's solution	Enter text.	Enter text.
Outcomes	The outcome measures to consider include: • Proportion of wounds with complete closure • Time to complete wound closure • Other outcomes related to wound characteristics including wound size, volume and area • Number of dressing changes and use of antimicrobial dressings and other consumables • Incidence of wound infection evidenced by o Adverse events and/or use of antibiotics (related to wound infection) o Reduction in clinical signs of infection • Changes to wound bed condition including slough, exudate, granulation and oedema • Staff time • Antibiotic use • Analgesic use • Length of hospital stay • Number of follow on treatments including GP, nurse and hospital visits • Number of surgical debridement procedures	Enter text.	Enter text.

	• Number of amputations or skin grafts • Colonisation with antimicrobial resistant pathogens Patient and carer related outcomes: • Health-related quality of life • Patient-related outcomes such as pain scores, discomfort and wound odour, or level of satisfaction • Carer's level of satisfaction • Mortality rates • Device-related adverse events.		
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	Enter text.	Enter text.
Subgroups to be considered	• Burns • Diabetic foot ulcers • Leg ulcers • Pressure ulcers • Post-operative wounds (with and without surgical site infection) • Trauma wounds • Infected wounds of any aetiology • Recurrent infections • Wound duration • Wound size • Children or adolescents	Enter text.	Enter text.

Special considerations, including issues related to equality	Older people, people with diabetes, people with restricted mobility and people with darker skin tones are more likely to have chronic or non-healing wounds. Age, disability, and race are protected characteristics	Enter text.	Enter text.

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	Prontosan
Approved name	Prontosan
CE mark class and date of authorisation	Class III medical device 20.02.2008

Version(s)	Launched	Features
400403	02.03.2009	*Prontosan Wound Irrigation Solution 350ml bottle*
400412	09.05.2009	*Prontosan Wound Irrigation Solution 40ml ampoule*
400484	22.08.2011	*Prontosan Wound Irrigation Solution 1000ml bottle*
400517	08.06.2012	*Prontosan Wound Gel X 50g*
400508	08.04.2011	*Prontosan Wound Gel X 250g*
400505	20.02.2009	*Prontosan Wound Gel 30ml*

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit/ benefit observed in literature	**Supporting evidence**	**Rationale**
Patient benefits		
Improved wound bed condition: reduced wound odour, exudate and slough etc.	Bellingeri et al (2016) Atkin et al (2020) Horrocks (2006) Moore (2016) Valenzuela and Perucho (2008) Durante et al (2004) Bradbury and Fletcher (2011) Ricci (2018) Romanelli et al (2010) Oropallo et al (unpublished)	Chronic wounds are often stuck the inflammatory phase of healing, with poor wound bed condition e.g. low amounts of granulation tissue and increased exudate levels, slough and signs of inflammation. Studies report rapid improved wound bed condition (reduced slough, odour, exudate and improved granulation etc.) following Prontosan treatment compared with saline/Ringer's treatment. Demonstrated in 2 RCT's, with other non-comparative studies also demonstrating rapid improvement in wound bed condition once wounds move onto using Prontosan for wound cleansing as part of wound bed preparation.
More rapid wound healing and high healing rate, wound size reduction	Andriessen and Eberlein (2008) Harding (2012 unpublished) Atkin et al (2020) Ciprandi et al (2018) Kiefer et al (2018) Moore et al (2014) Möller et al (2008) Wilkins & Unverdorben (2013) Valenzeula and Percho (2008)	Chronic wounds can persist for many months, even years, becoming stalled often in the inflammatory phase. Wounds progressing to healing show increased granulation tissue and show reduced wound size over a period of time. Prontosan has been demonstrated in studies to have higher, and faster, rates of wound healing compared with saline/Ringer's solution. In other studies with wounds of long duration a high and rapid healing rate, reduced wound size and increased epithelisation is observed after treatment with Prontosan.

Reduced infection rate/ markers of infection	Andriessen and Eberlein (2008) Collier and Hofer (2017) Ciprandi (2018) Kiefer et al (2018) Möller (2008) Moore et al (2014) Ricci et al (2018) Valenzuela and Percho (2008) Wattanaploy et al (2017) Horrocks (2006)	Chronic wounds are at higher risk of infection, due to the duration of being unhealed, poor wound condition and biofilm formation and maturation among other factors. Compared with saline, wounds treated with Prontosan have been shown to have fewer infections in comparative studies. Implementation of Prontosan as standard practice in a UK hospital was linked with a 92% reduction in hospital acquired wound infections in the Trust. In burns low infection rates following treatment with Prontosan are reported.
Pain reduction	Atkin et al (2020) Durante et al (2014) Horrocks (2006) Kiefer et al (2018) Ricci (2018) Romanelli (2010) Valenzuela and Perucho (2008) Wattanaploy et al (2018)	Pain is frequently reported in patients with chronic wounds. In comparative studies with saline, pain was reported to be reduced following Prontosan treatment. In other studies with wounds of long duration initial wound pain was reported to be reduced or resolved after commencing treatment with Prontosan.
General improvement to quality of life e.g. improved mobility and socialising.	Atkin et al (2020) Horrocks (2006) Oropallo et al (Unpublished)	Chronic wounds have a negative impact on patient quality of life. Pain, high levels of exudate and malodour can result in patients limiting social activities, being anxious and having their days revolve around dressing changes. In the elderly, a chronic wound can be debilitating and significantly interfere with how they self-care (Benbow 2008). Prontosan, by improving wound bed preparation, reduces: pain, excessive exudate, slough and malodour - positively impacting patients' quality of life. [redacted], in numerous case studies patients and healthcare workers report positive changes to patients' ability to socialise and recommence recreational activities after treatment with Prontosan.

More effective than saline	Andriessen and Eberlein (2008) Bellingeri (2016) Romanelli (2010) Valenzuela and Perucho (2008)	Standard habitual practice is to irrigate wounds with saline at dressing change. Multiple comparison studies demonstrate improved wound bed condition, wound healing rate and more rapid wound healing when wounds are treated with Prontosan compared with saline. As standard practice is to irrigate with saline at dressing change non-comparative studies reporting on the introduction of Prontosan therefore demonstrate the impact of moving from saline irrigation to Prontosan; reporting improved wound bed condition, wound healing rate and more rapid wound healing, reduced pain and markers of infection.
System benefits		
Freeing up nursing time to care and Reduce resource use: Nursing visits, dressing change frequency and medications and consumables Due to: • Faster wound healing time • High healing rate • Reduced exudate • Reduced pain	Atkin et al (2020) Durante (2004) Horrocks (2006) Moore et al (2014) Bellingeri et al (2016) Andriessen and Eberlein (2008) Valenzuela and Perucho (2008)	The action of Prontosan on slough, wound debris and biofilm improves the wound bed condition; reducing pain, excessive exudate and resulting in more rapid wound healing and a higher rate of healing. Reduced exudate and improved wound condition reduces the number and frequency of dressing changes required (Vowden et al. 2015; Tickle 2015). Improved wound healing and reduced time to healing directly reduces resource use such as nursing time and consumables such as dressings. Analgesic use reduction as a result of reduced pain, as measure by patients; and reduced need for systematic antibiotics due to reduced infection risk and rate.

Cost benefits		
Reducing resource use and nursing visits by: • Faster wound healing time • High healing rate • Reduced dressing changes • Reduced excessive exudate resulting in reduced use of consumable items per nurse visit, dressings etc.	Atkin et al (2020) Durante (2004) Horrocks (2006) Moore et al (2014) Bellingeri et al (2016) Andriessen and Eberlein (2008) Vallejo et al (2018) Valenzuela and Perucho (2008) Möller et al (2008)	More rapid wound healing reduces nursing visits required to manage chronic wounds. In the UK 37.5 million primary care appointments are attributable to wounds (Guest et al. 2015) – this figure has recently been updated to in excess of 82 million in an updated paper (Guest et al. 2020). Improved wound bed condition, such as reduction in excessive exudate and malodour, reduces the need for additional dressing changes to manage poor wound condition. The resource impact of managing chronic wounds in the UK has been documented widely documented (Guest et al. 2017; Guest et al. 2018a; Guest et al. 2018c; Guest et al. 2015; Guest et al. 2020) Prontosan improves wound bed condition, reduces exudate and odour and promotes wound healing which allow for reduced dressing change frequencies, overall nursing visits and associated consumables and costs.
Reduced cost of additional medication reduced: analgesia, antibiotics and antimicrobial dressings	Horrocks (2006) Kiefer et al (2018) Möller (2008) Moore et al (2014) Atkin et al (2020) Durante et al (2014) Ricci (2018) Romanelli (2010) Valenzuela and Perucho (2008) Andriessen and Eberlein (2008)	Reduced pain and reduced markers of infection can reduce the need for prescription analgesics, antibiotics and advanced antimicrobial wound dressings e.g. silver-containing dressings.

Sustainability benefits		
Improved sustainability through reduced treatment duration, fewer clinical appointment and the associated consumables (e.g. aprons, gloves, gauze and dressing etc), reduced medication wrappings.	Atkin et al (2020) Durante (2004) Horrocks (2006) Moore et al (2014) Bellingeri et al (2016) Andriessen (2008) Valenzuela and Perucho (2008)	The annual prevalence of chronic wounds is growing at the rate of 12% (Guest and Vowden 2017), increasing the burden of wound care on NHS resources; recent data has shown an increase in the prevalence of wounds by 71% over 5 years with the annual costs to the NHS of managing wounds increasing at a rate of 8-9% per annum, representing a 48% increase over 5 years (Guest et al. 2020). Faster and higher healing rates will help offset this increasing burden by overall reducing the number of clinical visits and the associated consumables cost.
Reduction in transportation related pollution due to decreased patient visits required.	Atkin et al (2020) Durante (2004) Horrocks (2006) Moore et al (2014) Bellingeri et al (2016) Andriessen and Eberlein (2008) Valenzuela and Perucho	By reducing patient visits for additional dressing changes (at home, clinic, GP or hospital)
Minimises waste due to shelf life once opened	IFU	Bottles and tubes have an 8 week shelf life once opened, preventing waste at dressing change as the same container can be used over multiple dressing changes. Ampoules are single use for when a smaller amount of product is required, further preventing wastage.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

Prontosan Solution, Gel and Gel X contain 0.1% betaine (undecylenamidopropyl betaine), a surfactant, and 0.1% polyhexanide (polyhexamethylene biguanide, PHMB, polihexanide), a broad spectrum antimicrobial. Prontosan Solution and Gels are indicated for the cleansing and moistening of acute and chronic wounds, and for the prevention of biofilm.

Acute wounds follow a well-defined process of healing, chronic wounds often occur when there is a delay in progressing through the stages of healing (Dowsett and Newton 2005), typically persisting in the inflammation stage, which can delay wound healing (Halim et al. 2012). Slough and exudate are produced in response to inflammatory factors present in the wound bed (Parnham and Bousfield 2018; Newton et al. 2017). The presence of slough and exudate in turn further exacerbate the host immune response, creating a recurring cycle of inflammation and consequently more slough and exudate. In order for wounds to progress to healing, the wound must move out of the inflammatory stage of healing (Milne 2015). The presence of slough and excessive exudate within a wound makes proliferation and migration of cells needed for wound healing difficult to achieve, therefore slowing or delaying wound healing. There is increasing evidence of the role slough plays in in supporting and harbouring biofilm (Percival and Suleman 2015; Halim et al. 2012). Biofilms are a cause of inflammation and delay healing by eliciting a prolonged host immune response; they also contribute to: increased slough and exudate, signs of infection, can be a source of acute infection and consensus acknowledges their role in wound-healing stagnation (Percival et al. 2017; Phillips PL 2010; Atkin et al. 2019; Wolcott et al. 2010; Mahmoudi et al. 2019; Vestby et al. 2020; Murphy et al. 2020). Biofilms are an aggregation of multispecies microorganisms protected by extracellular polymeric substances (EPS). Biofilms cannot be readily detected, consensus is that up to 90% of chronic wounds contain a biofilm (Attinger 2011; Schultz et al. 2017; Tyldesley et al. 2019). Once removed biofilms can reform quickly, with mature biofilm presenting within 24-48hrs (Wolcott et al. 2010).The effects of slough, excessive exudate and biofilm within a wound contribute to delayed healing, and must be removed to create an ideal environment for a wound healing (Percival and Suleman 2015; Murphy et al. 2020).

The betaine in Prontosan is an amphoteric surfactant, containing both hydrophilic and hydrophobic structures; hydrophobic sections bind to debris, slough and biofilm; the hydrophilic element allows for removal and washing away due to formation of micelles (Percival et al. 2019). The surfactant's role in wound cleansing is to facilitate the separation of loose non-viable tissue, slough

(desloughing), and biofilm particles from the wound bed; Prontosan provides a wound cleansing effect by softening and lifting wound bed debris such as slough and devitalised tissue (Kaehn and Eberlein 2008, Ricci 2019). To eliminate biofilm, both the microbial component and the extracellular polymeric substances (EPS) of the biofilm structure must be removed (Tyldesley et al. 2019). The EPS offers protection to microorganisms within the biofilm from antibiotics, topical antimicrobial therapies and the host's immune response. Compared to free-floating planktonic microorganisms, those within biofilms are able to persist in wounds treated with antimicrobial dressings and antibiotics due to this protection. Betaine's cleansing action has a disruptive effect on biofilm EPS (Tyldesley et al. 2019). Once the EPS has been disrupted microbes within the biofilm are exposed and no longer protected; the adjuvant ingredient PHMB helps to minimise bioburden. The disruptive action on the EPS and antimicrobial effect together prevents biofilm reformation (Tyldesley et al. 2019). Antimicrobial wound dressings can be used in addition to Prontosan in infected wounds.

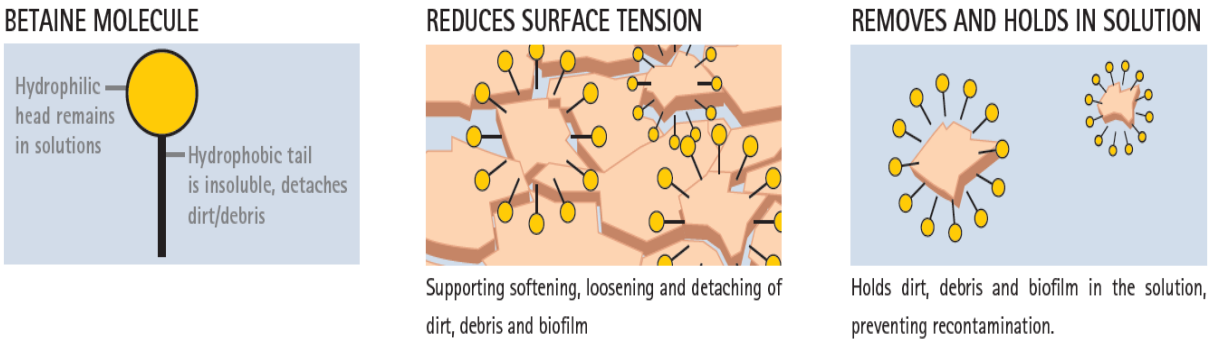


Figure 1 Action of betaine

PHMB is the adjuvant antimicrobial in Prontosan, providing a preservative effect; Prontosan products have an 8 week shelf life once opened (except 40ml ampoules which cannot be recapped). PHMB has been shown to have broad spectrum antimicrobial activity with elimination reported <1 minute (Koburger et al. 2010; Gilbert and Moore 2005; Lopez-Rojas et al. 2017). [redacted]. *In-vivo* porcine wound models show that irrigation of wounds with Prontosan Solution resulted in a significant bacterial reduction compared to control and other wound cleansers (Davis et al. 2017). Evidence of microbial resistance to PHMB has not been detected (Gilbert and Moore 2005; Fabry et al. 2014; Fabry and Kock 2014; Renzoni et al. 2017).

Prontosan Solution can be used as an irrigation in non-complex or acute wounds, or for more complex wounds used on gauze as a soak– dependent on desired desloughing effect; it can be used as part of a combined wound bed preparation strategy and compliments mechanical

debridement, when indicated. Prontosan Gel X and Gel prevent biofilm reformation and continue wound bed preparation between dressing changes. Early intervention strategies are recommended to prevent deterioration of wound condition and to suppress biofilm reformation (Murphy et al. 2020). Prontosan can be used from initial presentation of wounds in any condition up to healing; improving, and preventing deterioration of, wound condition and minimising complications. By removal of slough and devitalised tissue, disruption and prevention of biofilm, Prontosan improves wound bed condition removing barriers to wound healing through effective wound bed preparation which supports and allows the wound to progress to healing.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Chronic unhealed wounds are associated with significant economic and human cost. Increased patient care costs associated with unhealed wounds are 135% more than that of healed wounds. Specifically resource uses for unhealed wounds include: 20% more practice nurse visits, 104% more community nurse visits, 13% more GP visits, 18% more hospital outpatient visits, 40% more drug prescriptions. Unhealed wounds represent an estimated 39% of all wounds in the UK (Guest et al. 2017). Prevalence of wounds has been shown to have increased by 71% over the last 5 years (Guest et al. 2020). Faster time to healing will result in fewer resources used.

The NHS has committed to becoming carbon neutral by 2040 (England 2020). Among the measures taken is a focus on reducing transportation. Prontosan, by improving overall clinical outcomes in chronic/hard-to-heal wounds and speed up the rate of wound healing, has the potential to reduce the frequency and reliance of repeat car journeys both of patients to clinics and those of community based health care workers when treating hard to heal wounds. In addition, faster healing has the potential to reduce resource use of single use items (of dressings, dressing packaging, gauze and other materials used to clean the wound before dressing, PPE) required in the treatment of wounds.

Protecting the environment and conserving natural resources are high priorities for our company. Through management leadership and employee commitment, B. Braun strives to conduct its operations in a manner that is safe for the environment and continually improves environmental performance. An environmental management system has been implemented by B. Braun to ensure observation of the law and sets high standards for this purpose. Beginning at the product development stage, environmentally compatible design, technical safety and health protection are fixed as targets. All employees are encouraged to contribute to these goals through their own behaviour.

Prontosan production is globally managed by B. Braun Medical AG in Switzerland, which as a company has contributed to B. Braun's commitment to work toward the sustained protection of the climate. By voluntary joining the programme of the Swiss Sector Energy Agency since 2010 a reduction of 20 % CO_2 emissions and the optimisation of 15% energy efficiency was achieved during this period.

Raw-materials

B. Braun Medical selects environmentally friendly raw-materials for new products, and constantly improves formulations in order to provide a product portfolio. All ingredients in Prontosan products are degradable according to the Regulation (EC) 648 / 2004. Our Global 2020 environmental report showed reduced use of plastic film by 12.1% in two years and 86% of our waste can be recycled.

Packaging

All packaging materials are PVC-free. The packaging is designed according to the EU directive 94 / 62 / EC which is concerned with minimisation of the creation of packaging waste material and promotes energy recovery, re-use and recycling. The packaging material is minimised in weight to increase environmental sustainability.

Recycling

Containers: made of Low-density polyethylene (LD-PE) while the closures are made of Polypropylene (PP) and labelled accordingly for easy sorting and recycling.
Labels: made of Polyethylene (PE). In-house, just in time label printing reduces the need for corrections and therefore waste.
Carton package: Biodegradable, made from recycled material: FSC-certified
In 2019, B.Braun Medical AG has recycled 15 tons of silicone-coated backing paper, which corresponds to a reduction in CO2 of 30 tons.

B. Braun in Switzerland is certified according to:

- GMP Certificate (Good Manufacturing Practice) for the production site in Switzerland
- ISO 50001 Energy Management
- ISO 9001 Quality Management System
- ISO 13485 to provide medical devices and related services that consistently meet customer
- Requirements and regulatory requirements applicable to medical devices and related services
- ISO 14001 environmental management system and
- ISO 45001 Occupational health and safety management systems
- CO_2 Certificate of the Swiss Private Sector Energy Agency

B. Braun as a distributor in the UK is certified according to:

- ISO 14001 environmental management system
- ISO 9001 Quality Management System
- ISO 9001 Quality Management System

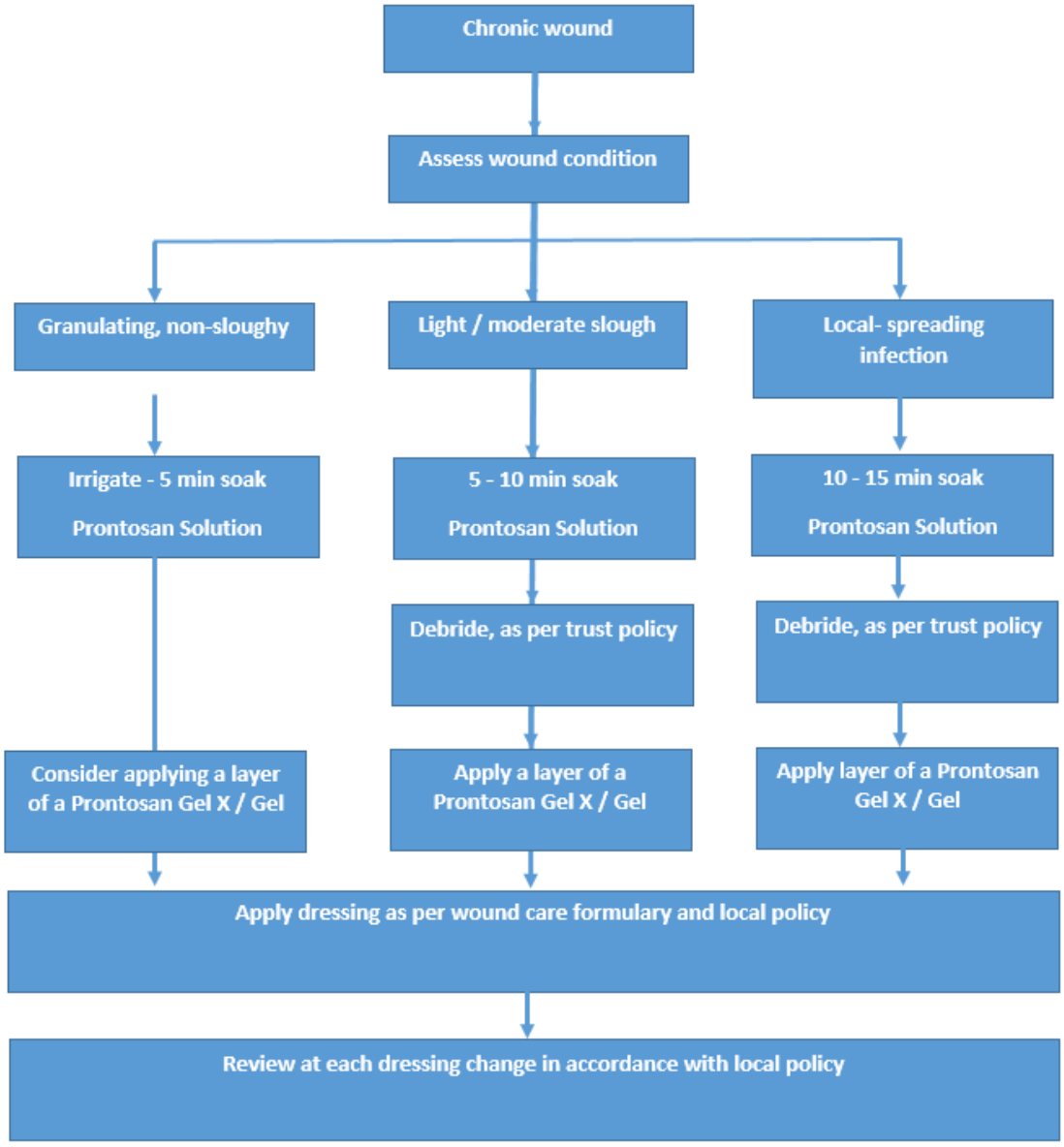
As a global company across all of our therapy fields, procurement at B. Braun has a globally balanced and locally anchored supplier network that is characterised by many years of collaboration, as well as mutual trust and open communication. We select only those suppliers and logistics service providers that meet energy management, compliance and other quality criteria.

3 Clinical context

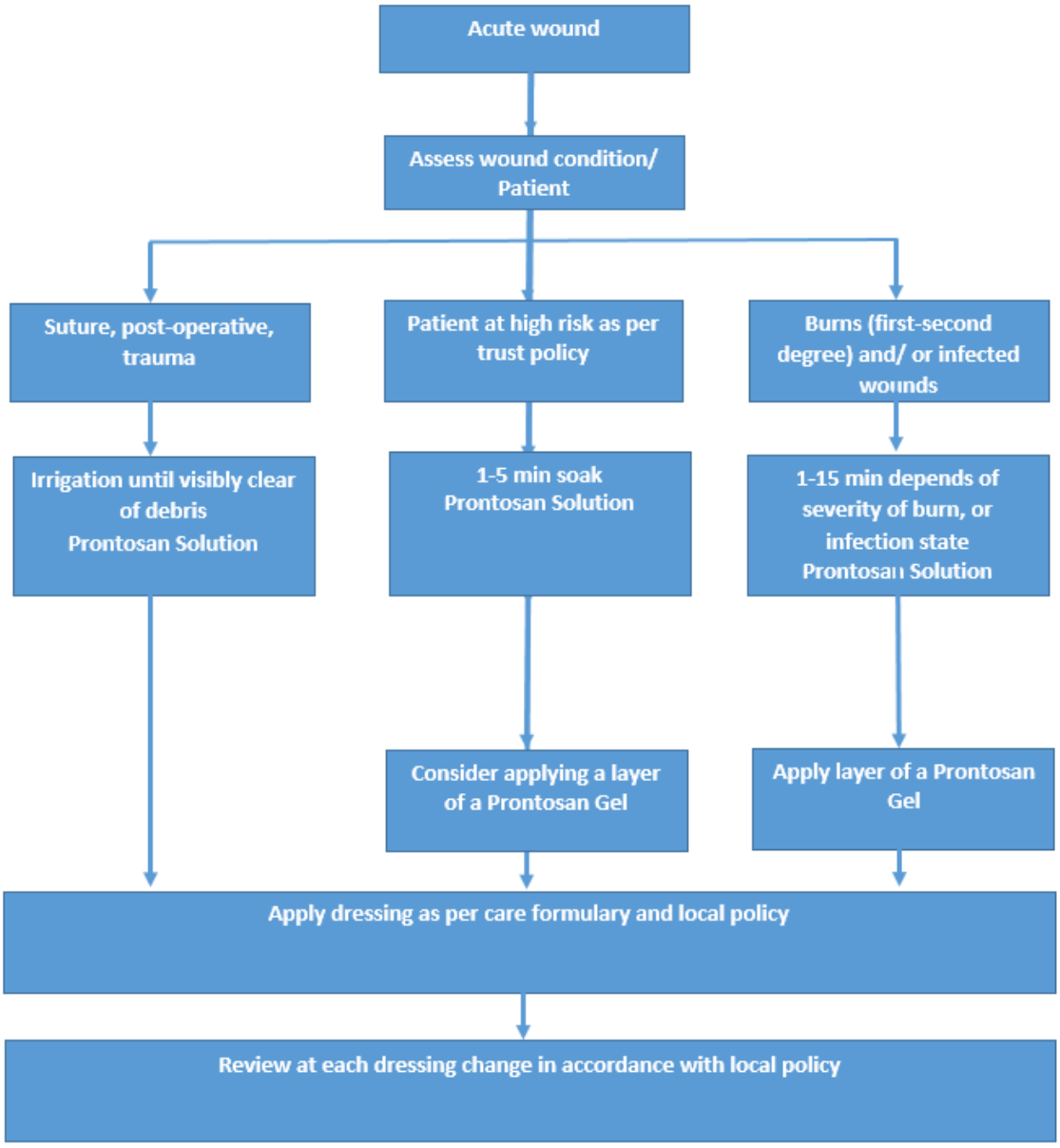
Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

Prontosan Solution is proposed in place of saline, or water, for wound cleansing - either as an irrigation or as a soak depending on desired clinical outcome. Prontosan Gel X or Gel can be left in situ applied to the wound bed beneath a secondary dressing.

PROPOSED WOUND CLEANSING PATHWAY – *Chronic/Hard-to-heal Wounds*

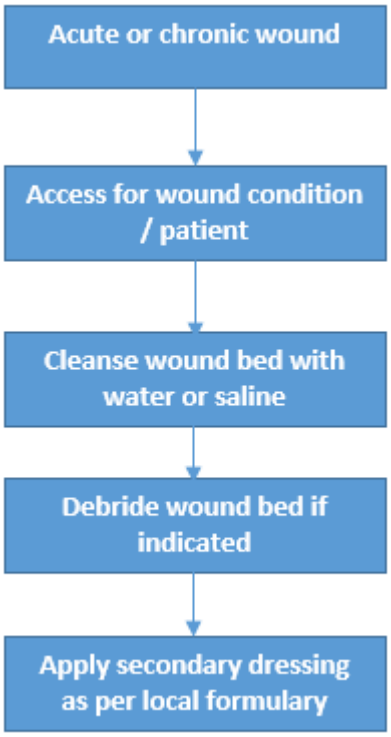


PROPOSED WOUND CLEANSING PATHWAY – *Acute Wounds*



CURRENT WOUND CLEANSING PATHWAY

Current standard practice is to cleanse wounds with saline or water.



Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

B. Braun is committed to partnering with the NHS and supporting product adoption with a comprehensive implementation and training offering. We have a UK-wide dedicated wound care account management team with a named contact for each NHS Organisation. B. Braun works to a proven training and implementation structure, training Health Care Professionals in the acute and community settings on the product features, the benefits to clinician and patient and providing all training materials; such as posters, pathways and ordering code materials. This support extends to all NHS Organisations using Prontosan and ongoing support and 'top-up training' is conducted at regular intervals dependent on the individual needs of each clinical area.

Wound cleansing is a widely utilised practice, the change to Prontosan is anticipated to require minimal practical training and system changes. Saline or water are widely used to irrigate a wound; acute wounds and chronic wounds in a good wound condition can be irrigated with Prontosan therefore no change is required.

It is recommended, for the best clinical outcome, that wounds in a poor wound condition (e.g. infected, persistent slough, visible debris) a soak with Prontosan can be administered for a length of time (0-15 minutes, adjusted for desired de-sloughing effect); as the wound condition improves, with use of Prontosan, the soak times are adjusted down accordingly to suit an improved wound condition. Training covers soak times fitting around other activities at appointment time, by prioritising removal of dressings and the administering of the soak as one of the first actions of a wound dressing change, other necessary steps can be carried out while the soak is in place (such as opening dressing packs, updating patient notes, completing assessments). Adjusted contact times for optimal product performance and clinical benefit are covered as part of basic product implementation, as is use in combination with Prontosan Gel/Gel X and other therapies for wound bed preparation e.g. debridement. This training is supported by multiple training guides and 'how to use' posters (Supplement 1), with example wound images and descriptions next to recommended irrigation or soak times. Bespoke pathway creation is available to ensure consistent practice and reduced variation across the local area (Supplement 2) which can be personalised with local information.

The ease of use of Prontosan allows it to be used in clinician directed self-care, where appropriate and led by the consulting clinician, support with patient support literature is provided.

System changes:

- Replace use of existing cleanser with Prontosan
- Provide advice on use of Gel / Gel X
- Provide advice on irrigation and soaking
- Allow for dressing changes to be reduced based on wound condition

B Braun Medical Ltd are committed to area-wide implementation and ongoing account support and training to capture new staff and embed pathway adherence.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		2489
Number of studies identified as being relevant to the decision problem.		24
Of the relevant studies identified:	Number of published studies (included in table 1).	15
	Number of abstracts (included in table 2).	3
	Number of ongoing studies (included in table 3).	6 (including 2 which do not have results available)

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C

Table 1 Summary of all relevant published studies

PUBLISHED STUDIES				
Author, year, location and data source	**Study design**	**Patient population, setting, and withdrawals/lost to follow up**	**Intervention and comparator**	**Outcomes**
Andriessen & Eberlein (2008), Germany Published study	**Retrospective cohort analysis.** Duration: Until complete ulcer resolution or up to 6 months. All patients received standard compression therapy and 2 layers of short stretch bandages. Bandages were changed on average every 5 days. At each dressing change, wet to dry dressing changes were used, comprising: 15 minute soak in gauze soaked in Prontosan or Ringer's solution, depending on group, followed by 15 minutes with dry dressing followed by moist dressing for both groups.	114 patients, community population presenting with venous leg ulcers. Control group: 14 males and 39 females, mean age of 75 years (range 47-89). Study group: 17 males and 42 females, mean age of 77 years (range 55-93). **Inclusion criteria:** • Wet to dry phase cleaning. • Ulcer present for at least 3 months. **Exclusion criteria:** • Patients with persistent, severe, arterial circulatory disorders. • No follow-up documentation. Patients were followed up at each dressing change (on average every 5 days) until ulcer closure, with a maximum follow up of 6 months.	**Intervention (n=59):** 15 minute soak with Prontosan 0.1% Propylbetaine – polyhexanide irrigation solution. **Comparator (n=53):** 15 minute soak with Ringer's solution or saline.	Number and percentage of wounds healed within 6 months. Frequency of infection, defined as 'the presence of typical clinical signs of infection (e.g. redness, swelling)'.

Atkin, Cooper and Stephenson (2020), UK Published study	**Case series** Combination of multiple case studies in the UK. Solution applied as a “soak” for 5-10 minutes depending on wound condition, applied to the wound at dressing changes. In cases where a gel was additionally applied (on hard-to-heal or complex wounds), this remained in situ between dressing changes. Dressing change frequency was reported for n=14/52 (27%) wounds. Of these, 13 were treated with solution and a gel and the remaining 1 was treated with solution only. Initially, 6 wounds were dressed daily; 3 were dressed on alternate days; 3 were dressed three times per week; 2 were dressed two times per week.	50 patients with 52 wounds in the outpatient setting. Leg/foot ulcer n=20 Post surgery foot wound n=2 Calciphylaxis n=1 Pressure ulcer n=3 Trauma n=3 Buttock wound n=1 Cellulitis n=1 Surgical Site n=3 “chronic/complex” n=15 Inclusion criteria were use of PHMB and betaine wound irrigation solution alone or PHMB and betaine irrigation solution used in addition to a PHMB and betaine gel used on non-healing wounds or complex wounds. Exclusion criteria were: acute / non-complex wounds, wound pathways, insufficient data, burns and primary focus of debridement pad use.	PHMB and betaine wound irrigation solution alone (n=16) or PHMB and betaine irrigation solution used in addition to a PHMB and betaine gel (n=36)	Wound healing rate and time to healing. Pain score. Wound bed condition – malodour, excessive exudate, slough. Dressing change frequency. Patient quality of life.

Bellingeri *et al* (2016), Italy Published study	**Single blinded randomised control trial.** Duration: 28 days. Given the characteristics of the solutions under investigation, it was impossible to perform a double-blind trial. Therefore, to minimise bias, single-blinding was implemented, whereby the investigators assessing wounds did not know which product was being used. At every dressing change, wounds were freely irrigated (syringe 20-30ml, needle 19-20 G), followed by the application of the solution for at least 10 minutes. Patients were followed up every 7 days until day 28. (n=2) in treatment group were lost to follow up. (n=6) in control group were lost to follow up and (n=1) deceased.	289 patients. Wounds included pressure ulcers (n=37 study group; n=35 control group); venous ulcers (n=74 study group; n=66 control group); mixed ulcers (n=27 study group; n=27 control group); traumatic wounds in patients with venous ulcers (n=5 study group; n=18 control group). Control group comprised 65 males and 81 females with a mean age of 77.2 years (SD=15.3); study group comprised 68 males and 85 females with a mean age of 79.8 years (SD=12.1). **Inclusion criteria:** Presence of at least one category II or III pressure ulcer, Braden score of ≥10 for patients with PU or the presence of a lesion of vascular origin, lesion: less than 80cm^2. **Exclusion criteria:** Terminally ill patients**,** treatment with antibiotics, and/or antiseptics within 10 days of recruitment, Braden score <10, treatment with systemic corticosteroids or immunosuppressants or radiotherapy**.** Patients difficult to reposition or impossible to place on a pressure-redistributing mattress. Known or suspected product sensitivity.	**Intervention (n=143):** Propylbetaine-polihexanide 0.1% irrigation solution, Prontosan **Comparator (n=146):** Normal saline	The primary outcome (wound improvement) was assessed through the variation of BWAT scores. Overall BWAT and inflammation BWAT. Pain was assessed with a visual analogue scale. Adverse events were recorded. The safety of the study products was assessed through the incidence of adverse events related to the products under evaluation.

		Patients with diabetic foot ulcers. Wounds with necrotic dry eschars.		
Ciprandi et al (2018), UK, Italy, Russia, Germany and Belgium	**Retrospective systematic data review** Duration: December 2012 and March 2016. Dressings were changed every 2-4 days depending on need. Not all children were necessarily treated with a Prontosan product for the entire healing period. (58.6%) were treated throughout the healing period and a quarter (25.3%) for more than 80% of the time. Soak/irrigation time not specified.	198 Paediatric burns patients (newborns: 0–4 weeks, infants: 5 weeks to 1 year and children older than 1 year old) treated with the Prontosan products at hospital. 74.7% were partial and deep thickness burn. Body parts were thorax (33.3%), hands (29.3%), upper arm (22.2%) and face (20.2%). In 46% of the patients only one site was affected by burn injury; 54% had more than one burn site. Girl 83/198 (41.9%), boy 115/198 (58.1%) **Inclusion criteria:** scald, flame, contact, electric or explosion burns of any degree (First degree: superficial; Second degree sub-divided in superficial partial thickness and deep partial thickness; Third degree: full thickness) with known treatment outcome.	**Intervention (n=198):** Prontosan 0.1% Propylbetaine polyhexanide solution and gel. **Comparator:** None (changes from baseline)	Safety and adverse events. Infections. Level of use of product. Dressing change frequency. Pain. Healing time. Clinical satisfaction.

Collier & Hofer (2017), UK Published study	**Retrospective analysis.** Duration: August 2012 – November 2013 (baseline) and June 2015 – September 2016 (intervention). Previous standard practice at baseline not described. New cleansing pathway including Prontosan implemented.	Hospital patients. All wounds in the Acute Trust within the time periods August 2012 – November 2013 and June 2015 – September 2016. No individual patient follow up was included. Sample size and demographics not stated. **Inclusion criteria:** Acute wounds (surgical and trauma), chronic wounds, chronic granulating wounds, chronic critically colonised/infected wounds. **Exclusion criteria**: Non-wounds.	**Intervention:** Prontosan 0.1% Propylbetaine polyhexanide solution and gel. **Acute surgical wound** – Irrigate wound with Prontosan Solution. **Acute trauma wound** – Soak with Prontosan Solution for 0-5 min. Consider Prontosan Gel X. **Chronic granulating wound** – Soak with Prontosan Solution for 0-5 min. Apply Prontosan Gel X. **Chronic wound** – Soak with Prontosan Solution for 5-10 min. Apply Prontosan Gel X. **Chronic wound critically colonised/infected** – Soak with Prontosan Irrigation Solution for 10-15 min. Apply Prontosan Gel X. **Comparator:** Without Prontosan (saline or tap water, not indicated).	Frequency of health care associated infection for wounds. Frequency of surgical site infection. Percentage change in healthcare associated infection and surgical site infections compared with ‘control’ data prior to implementation of intervention.

Durante *et al* (2014), Italy (6 wound centres) Published study	**Prospective cohort study.** Prontosan Gel was applied after cleansing mechanical debridement where necessary. Prontosan Gel was then directly applied onto the surface or into the wound undermining edge and then a secondary dressing applied. Patients followed up at days 7, 15, 30, 45 and 60, but no later than eventual complete healing. Duration of treatment and dressing change frequency defined by individual investigators.	124 outpatients with chronic wounds. 43 males; 78 females and 3 patients no gender recorded. Mean age 58.9±26.0 years (range 0.3-97.0). No level of drop out stated. Frequency of wound types not specified. **Inclusion criteria:** Wounds caused by chronic venous insufficiency or autoimmune disease. Diabetic wounds in the lower limbs. Pressure sores. Perigastrostomy wounds. Other types of wounds such as scleroderma, connective tissue pathologies or microvascular injuries. **Exclusion criteria:** Acute wounds, arterial ulcers or diabetic foot. Concomitant presence of other serious infectious diseases, cardiovascular, respiratory, neurological, psychiatric, neoplastic, endocrine, terminal state Ongoing treatment with antineoplastic agents, immunosuppressants, corticosteroids. Malnourished patients that are not receiving artificial nutrition (enteral or parenteral). Pregnant or breastfeeding women. Patients showing hypersensitivity to one or more of the constituents of the studied drugs.	**Intervention (n=124):** Prontosan 0.1% Propylbetaine polyhexanide gel in combination with a secondary dressing. **Comparator:** None.	The size of the wounds. Pain assessment. Aspect of the wound bed (clean, granulating, fibrinous, biofilm, restorative, necrotic). Appearance of the periwound skin (intact, macerated, xerotic, oedematous, erythematous). Aspect of the wound edges (intact, eroded, undermined, hyperkeratotic, slipping) Level of exudate (non-exuding, moderately exuding, exuding, very exudative). Presence of bacteria. Secondary dressing type. Frequency of treatment. The tolerability of the treatment.

Horrocks (2006), UK Published study	**Prospective case series.** Previous wound pathway of saline was discontinued; new pathway commenced using Prontosan Solution for irrigation and soaking. Detailed follow-up given for 3 patients. 3 patients withdrew; one patient died due to unrelated factors. Dressing change frequency varied between patients depending on wound condition.	10 adult community patients with chronic wounds of varying duration (1-5 years). Wounds comprised: venous leg ulcer (n=5), mixed aetiology leg ulcer (n=2), grade 4 pressure ulcer (n=1), buttock wound (n=1), and abdominal wound (n=1). Sample comprised 4 males and 6 females, with a mean age of 64.9 (range 32-85). **Inclusion criteria:** Chronic wound exceeding one year. Patient was an adult (over 18 years). Patient had a chronic wound and more than one-month duration of treatment with normal saline. Normal saline was discontinued during the evaluation. Patient had a wound that 'appeared' to contain biofilm. No other change was to be made to wound care regimen or patient's care. **Exclusion criteria:** None stated.	**Intervention (n=10):** Prontosan 0.1% Propylbetaine polyhexanide solution and gel (Prontosan). Prontosan Solution was applied for at least 10 minutes. Prontosan Gel applied as a 3-5mm thick film. **Comparator:** None (changes from baseline).	Wound size reduction over time. Use of antibiotics and silver dressing. Patient comfort. Ease of application. Exudate – descriptive. Malodour – descriptive. Biofilm – descriptive Quality of life - descriptive Frequency of nurse visits. Note any adverse reactions.

Kiefer et al (2018), Germany Published study	**Prospective, multicentre, non-comparative clinical trial.** Duration: 29 days, or until graft has taken if earlier. Every patient received a systemic injection of cephalosporin Immediately after STSG. Prontosan Wound Gel X was applied in a thin layer 3-4mm to entire graft. Gel treatment repeat on day 5 post operatively, continued every other day until day 29, or earlier if complete graft taken. No systemic antimicrobials were administered postoperatively unless the clinical condition of the treated wounds required the use of antibiotics, which would have consequently been rated as a serious adverse event. Dressing changes occurred on postoperative day 3 and then once a day.	50 hospital patients with deep partial and full thickness burns requiring STSG > 18 years old Median 38 years. Males, 70.6%; Females, 29.4% Injury mechanisms were direct flame, contact burns, and scalds. Burn wounds mostly involved the upper or lower extremities (86.9%) and were predominantly deep partial thickness burns (88.2%; full thickness burns: 11.8%). The median size of the meshed skin graft was 110 cm^2 (range 10–950 cm^2) resulting in a markedly higher mean ± standard deviation value of 175.6 ± 191.5 cm^2. The thickness of the graft was **Inclusion criteria:** burns requiring surgical debridement followed by split-thickness skin grafting. Wound size between 10 cm^2 and 1000 cm^2. **Exclusion criteria**: Pregnancy, patients with exposed hyaline cartilage, previous skin graft failure, a total burn surface area of ≥ 70% or infection at the target wound, insulin dependant type 1 diabetes, allergy to ingredietnst site were excluded.	**Intervention (n=50):** Prontosan Wound Gel X. **Comparator:** None.	Time to complete re-epithelialisation. Time to graft take (estimated 5 days post op) Re-epithelisation rate; assessed using photographic software. % epithelialisation; measured by digital assessment. Incidence of infection. Re-operation rate.

Möller, Nolte and Kaehn (2008), Germany Published study	**Retrospective analysis** Duration: 01.01.2005-31.03.2007 (15 months) Data retrospectively collected from patient notes. All patients receiving treatment in the outpatient wound clinic during the specified time frame whose records were complete were recruited. All wounds were irrigated with Prontosan Solution at every dressing change. Wounds with no or moderate exudation were treated with Prontosan Gel or a tamponade moistened with Prontosan Solution. Daily dressing change was no longer necessary; the normal rhythm of three times per week was sufficient.	953 outpatients receiving treatment for chronic wounds during the specified time frame. 571 women, 382 men. Mean age of patients was "over 65". 62% presented with diabetic foot syndrome; 16% with postoperative disturbances to wound healing; 10% with leg ulcer; 8% with decubitus; 4% with radiotherapy damage (oncology patients). **Inclusion criteria:** All patients who were receiving treatment in outpatient wound clinic between the qualifying dates were recruited. **Exclusion criteria:** • Incomplete records. • Treatment outside of the time frame.	**Intervention (N=953)**: Prontosan 0.1% Propylbetaine polyhexanide Solution and Gel. **Comparator**: None (changes from baseline).	Wound progression – wound classified as: Healing. Improvement. No improvement. Wound infection. Wound odour. Frequency of skin irritation. Compatibility with wound coverings. Frequency of infection. Evaluation by patients – odour, pain, tolerability. Evaluation of practicability by user.

Moore, Dobson & Cetnarowski (2016), USA Published study	**Retrospective analysis of one cohort of patients** Duration: 2 years Prontosan Solution and Gel replaced saline as the standard of care for wound treatment. Protocol for use of Prontosan (e.g. soak times) was unspecified. Data from eligible medical records were extracted retrospectively.	Outpatients (n=49) with chronic wounds (n=70) treated at a single centre. Wounds included: burns (n=7); diabetic ulcer (n=7); pressure ulcer (n=5); surgical wound (N=19); trauma (n=17); venous ulcer (n=16). Sample comprised 44.9% males and 55.1% females, with the following age distribution: ≤49 years (16.3%); 50-79 years (63.3%); ≥80 (20.4%). Patients were followed up as needed, but at least once monthly from their initial visit until complete epithelialisation. No patients lost to follow-up. **Inclusion criteria**: Complete wound closure as manifested by complete epithelialisation. **Exclusion criteria:** None stated.	**Intervention (N=9):** Prontosan 0.1% Propylbetaine polyhexanide solution and gel. **Comparator:** None (changes from baseline).	Primary: Healing rate – number of days required for epithelialisation. Secondary: Demographics, BMI, comorbidities, medications, prior treatments, concomitant therapies, adverse events, days to wound closure, change in wound area from baseline to closure and use of antimicrobials were assessed.

Ricci (2018), Italy Published study	**Prospective Observational study** Duration: 14 days (group B), single application (group A) **Group A (cleansing):** removal of dressing and wound evaluation, cleansing with 10ml of Prontosan Solution. Application was with soaked cotton gauze which was then removed at the specified time (2, 5, 10 or 15 minutes). The wound was photographed at the final removal of the gauze. **Group B (debridement):** Gauze soaked with Prontosan Solution was applied to the wound for 10 minutes, after which the gauze was removed and a non-adherent, secondary dressing was applied, in accordance with the site and the aetiological cause of the wound. On days 0, 7 and 14, photographs were taken with a digital camera, and clinical evaluation of the WBP score and the 'Cutting and Harding' score was performed, along with evaluation of the periwound skin. Group B had a 14-day follow-up with no attrition of patients.	70 adult patients with chronic wounds (>6 weeks). Group A: 14 males and 26 females, mean age 75.95 years (32-95). Group B: 11 males and 19 females, mean age 80.53 years (52-93). Varying aetiologies in both groups: venous leg ulcer (n=16 (A), n=10 (B)); arterial leg ulcer (n=7 (A), n=4 (B)); mixed ulcer (n=8 (A), n=7 (B)); pressure ulcer (n=1 (A), n= 3 (B)); diabetic foot ulcer (n=2 (A), n=2 (B)); other (n=6 (A), n=4 (B)). **Inclusion criteria:** >18 years old. Chronic (>6 weeks), defined aetiology. Wound bed preparation tissue score of B or C. Wound bed preparation exudate score of 1 or 2. Wounds contaminated or colonised (but had no other level of infection). **Exclusion criteria** <18 years old. Acute wounds. Undefined aetiology. Neoplastic wounds. Allergy to any components in the treatment.	**Group A (N=40):** Prontosan 0.1% Propylbetaine polyhexanide solution. Treated with a single application of Prontosan Solution at different time durations (2, 5, 10 and 15 minutes) for one single application. **Group B (N=30):** Prontosan 0.1% Propylbetaine polyhexanide solution Treated with Prontosan Solution for 10 minutes, followed by application of an inert dressing at daily dressing changes over 14 days.	Wound Bed Preparation (WBP) score. Change in the Cutting and Harding infection score. Change in exudate according to WBP score. Change in pain score on Visual Analogue Scale. Change in periwound skin area (group B).

Romanelli *et al* (2010), Italy Published study	**Randomised Control Trial** Duration: 4 weeks Patients were treated every other day with the intervention or control wound cleansing solution in association with standard wound care (polyurethane foam and elastic compression). Patients were reviewed weekly. 2 patients lost at follow-up due to change of residence, both from the comparator group. Soak/irrigation time was not specified. Treatment was administered on alternate days.	40 outpatients with chronic venous leg ulcers, 22 males and 18 females, mean age 62 years (55-73). Distribution of patients between groups was not described, the authors state no difference between groups at baseline with regard to age, mean disease duration, mean wound size or pain. **Inclusion criteria:** Painful chronic leg ulcer >8 weeks old; Clinical and instrumental signs of venous insufficiency; Wound size: up to 100 cm^2; Having received compression therapy for at least 2 weeks before inclusion; Patients over 18 years of age. **Exclusion criteria:** Allergy to one of the materials used; Severe systemic diseases; Acute superficial or deep vein thrombosis; Arterial occlusive disease (stages II-IV); Any arterial disease with an Ankle Brachial Pressure Index less than 0.8; Immobile patient/bedridden patient; Pregnancy and period of lactation; Severe lymphoedema of the leg; Diabetes with complications; Well-known hypercoagulability; Thrombophilia with deep vein thrombosis.	**Intervention (n=20):** Prontosan 0.1% Propylbetaine polyhexanide solution. **Comparator (n=20):** Saline.	Wound surface pH. Pain assessment on a visual analogue scale. Wound size.

Valenzuela & Perucho (2008), Spain Published study	**Randomised Control trial** Duration: 2 weeks All patients were treated with the GNEAUPP and AHCPR recommendations for cleansing wounds. No patients lost at follow up.	142 adult patients from multiple outpatient centres with chronic wounds. Two wounds per patient were incorporated. The authors report that there were more females than males in the total sample that the average age was "over 74 years" and that many patients had pathologies related to chronic wounds. While they state that there are no significant demographic differences between groups, specifics are not given. **Inclusion criteria:** Patient aged 18 years or over. Having at least one chronic wound. The lesions to present granulation tissue and/or soft devitalised tissue. Patient to remain in the study for the two weeks of follow-up. **Exclusion criteria:** Being pregnant. Having received a local or systemic antibiotic treatment during the last week of treatment. Devitalised tissue taking up more than 33% of the area of the lesions. Wounds showing necrotic plaques (once debrided they could be incorporated in the study). Being allergic to any of the components of the study product.	**Intervention (N=78):** Cleansing was performed by dabbing saline solution, then Prontosan 0.1% polyhexanide gel administered every 24-48 hours as required by the wound. **Comparator (N=64):** Cleansing by dabbing saline solution; if debridement was necessary, autolytic debridement by means of a hydrogel would be opted for.	Frequency of positive microbiological cultures. Percentage of lesions which reduce their bacterial build up at end compared with start. Wound size reduction. Effect on wound condition: granulation, slough, exudate, pain, oedema and smell.

Wattanaploy et al (2017), Thailand	**Randomised Control Trial** Duration September 2013-May 2015 Both group received daily dressing changes and same standard care, 3-5mm of silver sulfadiazine or PHMB gel applied and covered with gauze. Other treatments for burn patients such as fluid resuscitation, nutrition, and pain control were given equally to both groups as the standard method.	46 Adults with partial thickness burns. **Inclusion criteria:** 18- to 60-year-old patients partial-thickness burns within 48 hours after injury and the burns were more than 10% of total body surface area (TBSA). **Exclusion criteria:** Pregnancy or lactating patient, patient with underlying disease that interfered with wound healing (diabetes mellitus, end-stage renal disease, post radiation, on immunosuppressive drugs, immunocompromised disease). Known hypersensitivity to polyhexanide/ betaine gel or silver sulfadiazine. Patients with impaired consciousness. Patients with endotracheal intubation were also excluded.	**Intervention** (n=23)**:** Prontosan Gel X 0.1% polyhexanide/Betaine gel. **Comparator** (n=23)**:** Silver sulfadiazine.	**Healing time:** time to complete re-epithelialisation **Burn wound infection:** loss of epithelium from a previously reepithelialised surface, have purulent exudate with positive culture, extension of erythema in the uninjured skin surrounding the wound, localized pain or tenderness, or the patients have signs of lymphangitis and/or lymphadenitis. **Bacterial colonization:** Culture from the burn wound surface in the absence of clinical evidence of infection. **Pain during dressing change:** Using numeric visual rating scale 11 or Numeric Rating Scale–11 (NRS-11) **Treatment cost:** Defined as Total cost of admission in the Burn Unit of Siriraj Hospital. **Staff and Patient Satisfactory assessment:** Using 5 grades of satisfaction level: very good, good, average, poor, and very poor.

Wilkins & Unverdorben (2013) Published study	Systematic Literature review Literature search carried out in PubMed, searching for *in vitro* human studies discussing cleaning or cleansing chronic wounds. 31 studies were analysed in detail.	116 published articles, comparing on the basis of: • Improving wound healing. • Effectiveness as an antimicrobial against common wound contaminants *in vitro.* • Toxicity *in vitro.* Patient population not stated. **Inclusion criteria:** The search was performed in February 2012 in PubMed using the following terms: Chronic[All Fields] AND (‘‘wounds and injuries’’[MeSH terms] OR(‘‘wounds’’[All Fields]AND‘‘injuries’’[All Fields])OR‘‘wounds and injuries’’[All Fields] OR ‘‘wound’’[All Fields]) AND (cleaning[All Fields] OR cleansing[All Fields] OR washing[All Fields]) AND ‘‘humans’’[MeSH Terms]. A total of 116 published articles were found, and 31 were analyzed in detail following a preliminary review.	**Intervention:** Standard care plus any wound cleaning agents **Comparator:** PHMB and betaine, Povidone, silver chlorohexidine and alcohols	• Classification of supporting evidence using AACP grading system.

Table 2 Summary of all relevant abstracts / poster presentations

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main results
Poster/abstract	Atkin, Barker & Shirlow (2018), UK	Case series	12 patients with venous and arterial leg ulcers with suspected biofilm or stalled healing. Followed up weekly at outpatient clinic; none lost to follow up.	Prontosan 0.1% Propylbetaine polyhexanide solution (soak time not specified). Application at every dressing change; dressing change frequency not specified.	Baseline	Venous ulcer: 5cm x 3cm reduced to 4cm x 3.5cm after 4 weeks at 3x weekly dressing changes. Arterial ulcer: Pictures only. Mixed ulcer: Pictures only, compared to previous antimicrobial agents 9/12 patients had a reduction in wound size. 8/12 patients had a visible reduction in slough.
Poster/abstract	Cairns *et al* (2012), UK	Case series	15 patients with venous leg ulcers, pressure ulcers and post-surgical sinus sites.	Prontosan 0.1% Propylbetaine polyhexanide solution and gel (soak time and dressing change frequency not specified).	Baseline	2/15 wounds healed in 2 months. Over 50% patients had reduction in exudate. 6/15 reported decrease in frequency and severity of pain.
Poster/abstract	Collier (2016), UK	Case series	Patients across 4 wards with surgical wounds. April 2011 – July 2012 (comparator) and August 2012 – November 2013 (intervention). 1191 positive swabs over 16 month period	Prontosan 0.1% Propylbetaine polyhexanide solution with or without gel (soak time not specified).	Pre new cleansing pathway (saline)	16% reduction in isolates suspected of causing wound infections.

Table 3 Summary of all relevant ongoing or unpublished studies

UNPUBLISHED STUDIES				
Author, year, location and data source	**Study design**	**Patient population, setting, and withdrawals/lost to follow up**	**Intervention and comparator**	**Outcomes**
B. Braun Literature in conjunction with Prof. K. M. Krylov, Russia	Case series Soak/irrigation with Prontosan Irrigation Solution. Prontosan Wound Gel or Gel X left in situ until dressing change. Soak time and dressing change frequency not specified.	27 burns patients with various burns> details provided in detail for 10 cases. Male, 90%; female 10%. Age 38-71. Burns by: fire, 50%; hot water, 10%; hot surface 30%; and colonised donor site, 10%. Body surface are ranged from 3%-18%. Duration of wound prior to treatment ranged from 7-21 days for burns and was 41 ways for colonised donor site. Inclusion and exclusion criteria not discussed.	**Intervention (N=27):** Prontosan Irrigation Solution and Prontosan Gel and Gel X. **Comparator:** Changes from baseline/previous treatment (e.g. povidone-iodine, silver and necrectomy).	Patient reporting on dressing removal: easy and painless. Wound condition: exudation and wound maceration. Wound odour. Skin graft take. Microbial count reduction.

Oropallo *et al* (NCT03369756), USA. Last update January 2020. Terminated. Unpublished clinicaltrials.gov	Open-label interventional study.	43 adult patients with leg wounds located below the knee.	**Intervention (patients n=43, [redacted]):** Prontosan Wound Irrigation Solution and Prontosan Wound Gel (soak time and dressing change frequency not specified). **Comparator:** None	Wound-QoL global score. Body, psyche and everyday life subscores of Wound-QoL. [redacted] Wound size (change from baseline).
Alvarez *et al* (NCT01048307), USA. Last update August 2010. Completed. Results not available. Unpublished clinicaltrials.gov	Randomised, controlled, multi-centre, prospective clinical trial. Efficacy and safety over 3-4 weeks. Dressing changes twice weekly or more.	28 adult outpatients with venous leg ulcers of at least 18 months duration.	**Intervention (n=20)** 15 minute soak with Prontosan Wound Irrigation Solution, followed by placement of a dressing impregnated with Prontosan. **Comparator (n=8)** 15 minute soak with saline solution, followed by placement of a dressing impregnated with saline.	Reduction of bacterial burden (quantitative bacteriology) Reduction in slough and necrotic tissue (clinical score) Amount and quality of granulation tissue (clinical score). Exudate type and amount (clinical score). Reduction in wound size (wound planimetry).

Harding *et al* (2012) (NCT01153633), UK. Last update April 2014. Completed. Results available. clinicaltrials.gov	Randomised, triple-blinded Cleansing with the solution at each dressing change (every 3 days +/- 1 day). Sterile gauze impregnated with solution placed on the wound for 15 minutes. After soak, the wound is then "sparingly covered" with the gel. Dressing fixed to wound with an elastic compression bandage.	34 adult outpatients with venous leg ulcers Mean age 71.6 years (SD=10.1) Female = 55.9% / male = 44.1% Mean duration of wound = 54 months Out patient treatment	**Intervention (n=17):** 15 minute soak with Prontosan Wound Irrigation Solution followed by application of gel **Comparator (n=17):** Saline and placebo gel Dressing changes every 3 days (±1 day)	Percentage change in wound size Healing of target ulcer Absolute change in wound size Number of different microorganisms post-treatment) Change in pain (VAS score) Condition of wound bed
Dancer *et al* (NCT02841969), UK. Last update February 2019. Ongoing, study completion due March 2020. Results not available. Unpublished clinicaltrials.gov	Randomised, double-blinded Both treatments carried out twice per week; inpatients may receive more frequent application (e.g. daily) depending upon wound status.	200 diabetic patients aged 18-65 with chronic, non-healing foot wounds.	**Intervention (projected n=100):** Prontosan Irrigation Solution. **Comparator (projected n=100):** Electrolysed water. Soak time not specified.	Time to complete healing. >50% healing of initial lesion. Avoidance of surgical intervention. Avoidance of debridement or amputation. Requirement for antibiotic therapy. Cost of electrolysed water vs cost of Prontosan.

Ennis *et al* (NCT01554644), USA. Last updated July 2013. Withdrawn. Unpublished clinicaltrials.gov	Randomised, double-blinded	N/A - withdrawn	**Intervention:** Prontosan Irrigation solution and Prontosan Wound Gel. **Comparator:** Saline and inert gel.	Relative % change in wound size area. Change in absolute wound area dimensions. Identification of bacteria present on wound bed at baseline and follow-up. Relative change in bacterial load during treatment period. Change in wound margins determined by colour photography. Number of "non-responders" as measured by wound size change (<50% relative wound size reduction). Change of clinical wound infection during treatment period.

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

<table>
<tr><th colspan="3">RESULTS</th></tr>
<tr><th>Study</th><th>Results</th><th>Company comments</th></tr>
<tr><td>Andriessen & Eberlein (2008)

Published study</td><td>
Table 1. Evolution of ulcer closure for the control group (n = 53).
<table>
<tr><th rowspan="2">Months of treatment</th><th colspan="3">Evolution of ulcer healing (control group)</th></tr>
<tr><th>Patients/month</th><th>%/months</th><th>Cumulated %</th></tr>
<tr><td>1</td><td>1</td><td>2</td><td>2</td></tr>
<tr><td>2</td><td>4</td><td>7</td><td>9</td></tr>
<tr><td>3</td><td>10</td><td>19</td><td>28</td></tr>
<tr><td>4</td><td>12</td><td>23</td><td>51</td></tr>
<tr><td>5</td><td>9</td><td>17</td><td>68</td></tr>
<tr><td>6</td><td>11</td><td>21</td><td>89</td></tr>
<tr><td></td><td>Total</td><td></td><td>%</td></tr>
<tr><td>Ulcer not closed after 6 months</td><td>6</td><td></td><td>11</td></tr>
</table>
Table 2. Evolution of ulcer closure for the study group (n = 59).
<table>
<tr><th rowspan="2">Months of treatment</th><th colspan="3">Evolution of ulcer healing (study group)</th></tr>
<tr><th>Patients/month</th><th>%/months</th><th>Cumulated %</th></tr>
<tr><td>1</td><td>4</td><td>7</td><td>7</td></tr>
<tr><td>2</td><td>13</td><td>22</td><td>29</td></tr>
<tr><td>3</td><td>18</td><td>31</td><td>60</td></tr>
<tr><td>4</td><td>13</td><td>22</td><td>82</td></tr>
<tr><td>5</td><td>7</td><td>12</td><td>94</td></tr>
<tr><td>6</td><td>2</td><td>3</td><td>97</td></tr>
<tr><td></td><td>Total</td><td></td><td>%</td></tr>
<tr><td>Ulcer not closed after 6 months</td><td>2</td><td></td><td>3</td></tr>
</table>
p<0.0001

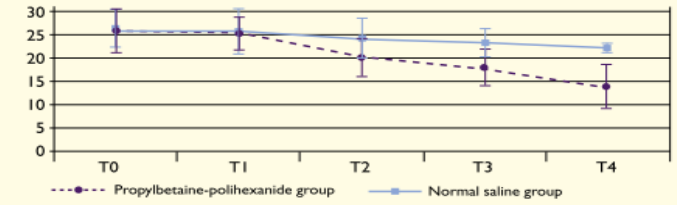
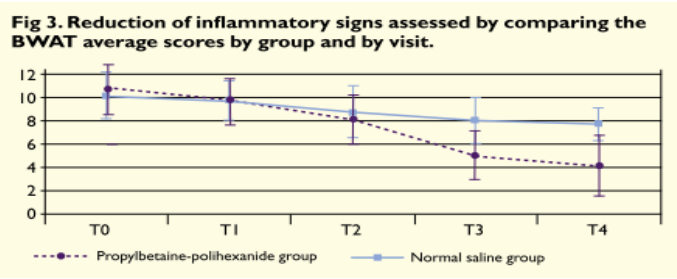
Rate of wound healing:
• Treatment group 57/59 (97%) wound healed by 6 months. Mean healing time for treatment group 3.31 months (SE = 0.17).
• Control group 47/53 (89%) wounds healed by 6 month. Mean healing time control group 4.42 months (SE = 0.19).

Infection rates:
• Treatment group 2/59 cases of infection (3%).
• Control group 7/53 cases (13%).
</td><td>More females than men were participants, though this was the same in both treatment groups.

Lacking detailed demographic data on co-morbidities.</td></tr>
<tr><td>Atkin, Barker & Shirlow (2018)

Poster/abstract</td><td>Venous ulcer: 5cm x 3cm reduced to 4cm x 3.5cm after 4 weeks at 3x weekly dressing changes
Arterial ulcer: Pictures only.
Mixed ulcer: Pictures only, compared to previous treatments 9/12 patients had a reduction in wound size. 8/12 patients had a visible reduction in slough.</td><td>Case study – risk of selection bias.
No comparator.
Minimal data included.</td></tr>
</table>

<table>
<tr>
<td>Atkin, Cooper & Stephenson (2020)</td>
<td>
Wounds treated > 1 month=23, N=12/23 (52%) healed within 10 months
<table>
<tr><th></th><th colspan="2">All Wounds > 1 month treatment (n=23)</th><th colspan="2">Irrigation solution > 1 month treatment(n=4)</th><th colspan="2">Irrigation solution and gel > 1 month treatment (n=19)</th></tr>
<tr><th>Treatment Duration</th><td>Healed</td><td>Cumulative Healed</td><td>Healed</td><td>Cumulative Healed</td><td>Healed</td><td>Cumulative Healed</td></tr>
<tr><td>2 months</td><td>6 (26.1%)</td><td>6 (26.1%)</td><td>0 (0.0%)</td><td>0 (0.0%)</td><td>6 (31.6%)</td><td>6 (31.6%)</td></tr>
<tr><td>3 months</td><td>3 (13.0%)</td><td>9 (39.1%)</td><td>1 (25.0%)</td><td>1 (25.0%)</td><td>2 (10.5%)</td><td>8 (42.1%)</td></tr>
<tr><td>6 months</td><td>2 (8.7%)</td><td>11 (47.8%)</td><td>1 (25.0%)</td><td>2 (50.0%)</td><td>1 (5.2%)</td><td>9 (47.4%)</td></tr>
<tr><td>10 months</td><td>1 (4.3%)</td><td>12 (52.2%)</td><td>0 (0.0%)</td><td>2 (50.0%)</td><td>1 (5.2%)</td><td>10 (52.6%)</td></tr>
</table>
Table 1: Proportion of wounds with treatment duration of > 1 month, healed by treatment time for all wounds and treatment groups.
<table>
<tr><th>Wound area before treatment</th><th>Wound duration</th><th>Wound type</th><th>Treatment group</th><th>Wound area after treatment</th><th>Treatment duration</th><th>Wound area reduction</th></tr>
<tr><td>65 cm^2</td><td>7 months</td><td>Leg ulcer</td><td>Solution</td><td>0 cm^2</td><td>6 months</td><td>100%</td></tr>
<tr><td>35 cm^2</td><td>7 months</td><td>Leg ulcer</td><td>Solution</td><td>0 cm^2</td><td>3 months</td><td>100%</td></tr>
<tr><td>38 cm^2</td><td>6 months</td><td>Infected leg ulcer</td><td>Solution and gel</td><td>16 cm^2</td><td>3.5 months</td><td>58%</td></tr>
<tr><td>15 cm^2</td><td>>1 year</td><td>Leg ulcer</td><td>Solution</td><td>14 cm^2</td><td>1 month</td><td>7%</td></tr>
<tr><td>49 cm^2</td><td>5 months</td><td>Leg ulcer</td><td>Solution and gel</td><td>3 cm^2</td><td>5 months</td><td>94%</td></tr>
<tr><td>120 cm^2</td><td>3 months</td><td>Buttock wound</td><td>Solution</td><td>2 cm^2</td><td>3 months</td><td>98%</td></tr>
<tr><td>Full leg circumference x 8-17cm long</td><td>2 weeks</td><td>Leg cellulitis</td><td>Solution and gel</td><td>0 cm^2</td><td>3 months</td><td>100%</td></tr>
<tr><td>300 cm^2</td><td>Unknown</td><td>Category IV infected pressure ulcer</td><td>Solution and gel</td><td>157 cm^2</td><td>6 days</td><td>48%</td></tr>
</table>
Table 2. Wound area, treatment duration and type of wound for wounds with area measured (n=8)
Initial signs of wound improvement were documented for n=33/52 (63%) wounds:
</td>
<td>
Case studies converted to case series – risk of selection bias in initial case studies.
No comparators.
Variations in outcomes measured in each case study.
</td>
</tr>
</table>

Bellingeri *et al* (2016) NCT 01333670	**Total BWAT score:** Treatment average Total BWAT at T0 = 26. Treatment average Total BWAT at T4 =14 Treatment reduction in average Total BWAT =12 Control average Total BWAT at T0 = 26. Control average Total BWAT at T4 =22 Control reduction in average Total BWAT =4 Significant difference in the reduction of Total BWAT scores between groups (p=0.0248). Also significant difference between Total BWAT at T0 and T4 for Prontosan group; p value not provided. **Inflammation BWAT score:** Treatment average inflammation BWAT at T0 =11 Treatment average inflammation BWAT at T4 =4 Treatment reduction in average inflammation BWAT =7 Control average inflammation BWAT at T0 =10 Control average inflammation BWAT at T4 =8 Control reduction in average inflammation BWAT =2 Significant difference in the reduction of Inflammatory BWAT scores between groups (p=0.03). Also significant difference between Inflammatory BWAT at T0 and T4 for Prontosan group, p value not provided. No change in pain reported across either group, average score of 3 across both groups and time points **Fig 2. Wound improvement assessed by a reduction of average Total BWAT Scores by group and by visit**  **Fig 3. Reduction of inflammatory signs assessed by comparing the BWAT average scores by group and by visit.**  	Text

Cairns *et al* (2012) Poster/abstract	2/15 wounds healed in 2 months. Over 50% patients had reduction in exudate. 6/15 reported decrease in frequency and severity of pain.	Case study – risk of selection bias. No comparator. Minimal data included.
Ciprandi et al (2018) Published Study	Adverse events n=5/198: itching (3 cases), rash (1 case) and hypergranulating tissue (1 case) occurred. No event was severe and all but the latter case (moderate with treatment withdrawal) were mild. N=16/198 patients had clinical signs of infection. In 5 cases, infection was already present before treatment. Therefore 11 patients developed clinical signs of infection during treatment. Antibiotics were given to 8/11 patients. 58.6% were treated throughout the full healing period with Prontosan. 25.3% treated with Prontosan for more than 80% of the time. Dressings were changed on average every 2–4 days. Healing time was 11.5 days for a wound total body surface area (TBSA) of less than 5%. Healing time was 15 days for 5–19% TBSA. Healing time ranged from 8.5 days for superficial burns, 10.9 days for superficial partial thickness burns, 13.5 days for deep partial thickness burns to 17.2 days for full thickness burns Healing time was not directly reported in the questionnaire for this data review. Therefore results are based on the last day of dressing change and when wound was healed or re-epithelised. There was no negative feedback; all physicians were either ‘Satisfied’ with the treatment (73.2%), considered it ‘Good’ or ‘Very good’ (16.2% and 10.6%, respectively).	

<table>
<tr>
<td>Collier & Hofer (2017)

Published study</td>
<td>Percentage change in frequency of Health Care Associated Infection (HCAI) for wounds and Surgical Site Infections (SSI) between control (August 2012-November 2013) and treatment (June 2015-September 2016):

<table>
<tr><th colspan="4">Table 1. HCAI/SSI rates at ULHT (Collier, 2016)</th></tr>
<tr><th>Organisms</th><th>Aug 2012 – Nov 2013</th><th>June 2015 – Sept 2016</th><th>June 2015 – Sept 2016</th></tr>
<tr><td>Other organisms</td><td>33</td><td>0</td><td>-100%</td></tr>
<tr><td>Enterococcus</td><td>6</td><td>5</td><td>-17%</td></tr>
<tr><td>Staphylococcus aureus (MRSA)</td><td>31</td><td>23</td><td>-26%</td></tr>
<tr><td>Escherichia coli/ vulneris</td><td>52</td><td>6</td><td>-88%</td></tr>
<tr><td>Pseudomonas</td><td>68</td><td>2</td><td>-97%</td></tr>
<tr><td>Anaerobic organism</td><td>51</td><td>4</td><td>-98%</td></tr>
<tr><td>Staphylococcus (excluding MRSA)</td><td>221</td><td>6</td><td>-97%</td></tr>
<tr><td>Enterobactor</td><td>23</td><td>1</td><td>-96%</td></tr>
<tr><td>Streptococcus</td><td>42</td><td>2</td><td>-95%</td></tr>
<tr><td>Yeast (undifferentiated)</td><td>17</td><td>0</td><td>-100%</td></tr>
<tr><td>Total</td><td>544</td><td>49</td><td>-92%</td></tr>
</table>
</td>
<td>Retrospective case cohort.
Overlap with Collier 2016 poster/abstract.

Numbers of wounds and surgical sites swabbed in each study time period not disclosed.

Only positive samples reported on.

Overlap with Collier (2016) unpublished study. Only Collier and Hofer (2017) will be used in the full analysis.</td>
</tr>
<tr>
<td>Collier (2016)

Poster/abstract</td>
<td>16% reduction in isolates suspected of causing wound infections.</td>
<td>Overlap with Collier and Hofer (2017) published study. Only Collier and Hofer (2017) will be used in the full analysis.</td>
</tr>
</table>

<table>
<tr>
<td>Durante et al (2014)

Published study</td>
<td>Mean wound length reduction -17.5±21.4 cm, (~70% reduction) versus baseline.

Mean wound width reduction -15.5±21.1 cm (~70% reduction) versus baseline.

Mean wound area reduction -8.3±16.7 cm^2 (~90% reduction) versus baseline.

Reduction in patients undergoing autolytic debridement from 41% to 27%.

Wound bed improvements reduction in fibrinous, necrotic and biofilm (see table) increased number of wounds clean, granulating and re-epithelializing (see table).

At final visit 75% patients had intact periwound skin and wound edges compared with Baseline (18% periwound and 28% wound edges).

Reduced exudate (present in 74% at base line and 15% at final visit).

Average VAS/FLACC score decreased by approximately 80% from baseline to the final visit.

Average reductions VAS: -4.67±2.7 (V95% CI: from -5.36 to -3.98) FLACC: -12±4 (95% CI: from -10.22 to -7.75).

<table>
<tr><td colspan="3">The debridement of the bottom of wound, the periwound skin, edges of the wound and the level of exudate at baseline and at the final visit</td></tr>
<tr><td></td><td>Baseline</td><td>Final visit</td></tr>
<tr><td>Debridement, N. (%)*
Autolytic
Mechanical
Enzymatic
Surgical
Anaesthesia</td><td>
51 (41.1%)
27 (21.8%)
22 (17.7%)
8 (6.5%)
3 (2.4%)</td><td>
34 (27.4%)
28 (22.6%)
21 (16.9%)
3 (2.4%)
1 (0.8%)</td></tr>
</table>
</td>
<td>Observational study multi-centre study.

Large range in wound duration.
Large range in wound size.
Mix of acute and chronic wounds.

Data expressed overall and not by wound type.</td>
</tr>
</table>

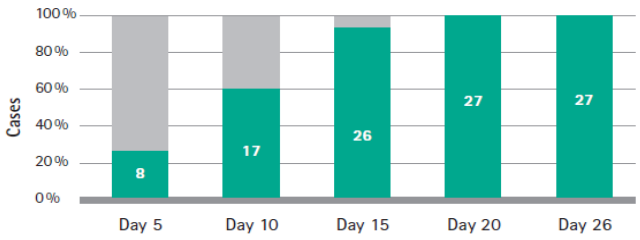
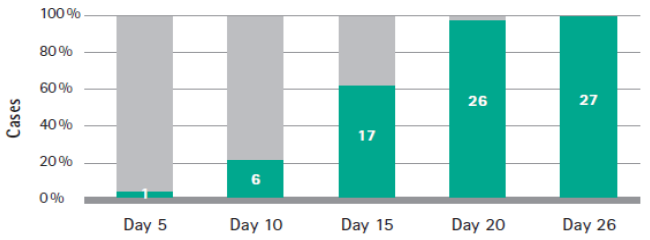
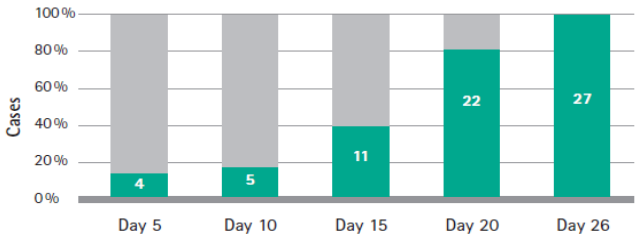
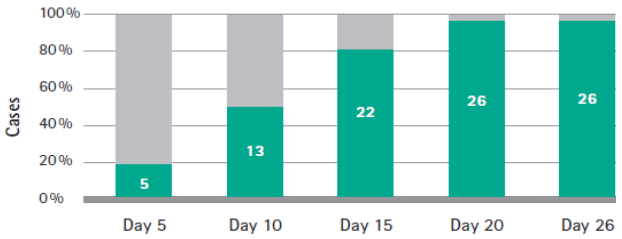
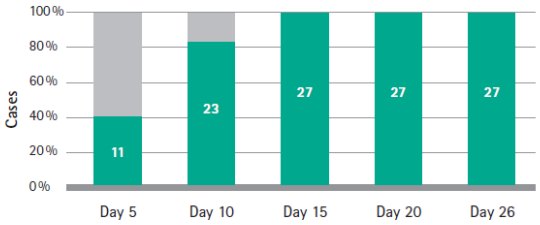
Wound bed, N. (%)*			
Fibrinous	73 (58.9%)	2 (1.6%)	
Partially necrotic	42 (33.9%)	3 (2.4%)	
With biofilm	29 (23.4%)	2 (1.6%)	
Clean	8 (6.5%)	55 (44.4%)	
Granulating	5 (4.0%)	59 (47.6%)	
Re-epithelialising	1 (0.8%)	33 (26.6%)	
Periwound skin, N. (%)*			
Erythematous	64 (51.6%)	13 (10.5%)	
Edematous	44 (35.5%)	3 (2.4%)	
Macerated	36 (29.0%)	1 (0.8%)	
Xerotic	24 (19.4%)	11 (8.9%)	
Undamaged	22 (17.7%)	94 (75.8%)	
Wound edges, N. (%)*			
Eroded	42 (33.9%)	4 (3.2%)	
Undamaged	35 (28.2%)	94 (75.8%)	
Planted	31 (25.0%)	2 (1.6%)	
Undermined	16 (12.9%)	2 (1.6%)	
Hyperkeratonic	10 (8.1%)	3 (2.4%)	
Slipping	2 (1.6%)	30 (24.2%)	
Exudate level, N. (%)			
Moderately exuding	68 (54.8%)	28 (22.6%)	
Exuding	25 (20.2%)	1 (0.8%)	
Non exuding	18 (14.5%)	83 (74.0%)	
Very exuding	12 (9.7%)	1 (0.8%)	
*A patient could have more than one type of debridement, wound bed, periwound skin and wound edge			

Harding *et al* (2012) Unpublished study NCT01153633, last update April 2014. (UK) Unpublished study – clinicaltrials.gov	Healing of target ulcer • PPS: Prontosan: 8 out of 17 healed (47%) Saline: 5 out of 15 healed (33%) p=0.4905 • ITT: Prontosan group;n=8/17 (47.1%) wounds healed. Saline group n=5/17 (29.4%) (P=0.4813),a treatment difference of -17.6 (95% CI -14.5-49.8). Number and percentage of wounds healed by week ITT • Prontosan group:2 week (n= 1; 6.3%), 4 weeks (n=2; 15.4%), 8 weeks (n=1; 9.1%),12 weeks (n=4; 44.4%). • In the Saline group:2 weeks (n=0; 0%), 4 weeks (n=2; 6.5%), 8 weeks (n=4; 28.6%), 12 weeks (n=0; 0%). Percentage change in wound size • PPS: Prontosan: -64.98 (SD=12.32), Saline: -42.78 (SD=13.13) p=0.2317 • ITT: Prontosan: -60.30% (SE±12.18) Saline: -45.48% (SE±12.18). Treatment difference calculated at -14.82 (95% CI -49.82-20.35), (p=0.3968), Infection rate • IIT Prontosan n=4/17 (23.5%), Saline n= 3/17 (17.6%) control group Number of different microorganisms post-treatment (mean) PPS • Prontosan: 0.8 (SD=0.9) Saline: 1.0 (SD=0.8) Change in pain (VAS score) (mean) PPS • PPS: Prontosan: -8.9 (SD=20.4) Saline: -12.8 (SD=26.0) • ITT: Prontosan: -9.5 (SD=19.5) Saline: -9.0 (SD=23.6) Condition of wound bed (mean percentage) • PPS Prontosan: 7.1 (SD=38.9) Saline: -1.5 (SD=52.0) Changes to granulation tissue by • ITT: Prontosan, 14.1% (SD 40.6) Saline -8.8% (SD 48.3)	P-values missing for three results, other three results are non-significant differences due to small study size as ruin as a pilot study.

Horrocks (2006) Published study	7/10 “dramatic improvements”, 1/10 not concordant with treatment regime and 2/10 “no significant outcome” in 3 weeks. Reported “reduced exudate”. Staff and patents reported “malodourous wounds no longer had odour”. 6/7 stopped silver dressings use. 6/7 stopped antibiotic use. 7/7 patient reported wound pain eliminated or reduced. Extra detail for n=3 patients. **Patient 1 – 2x pressure ulcers** 15 cm x 7 cm by 3 cm deep grade 4 pressure ulcer at baseline. • reduced to 12 cm x 4.5 cm x 1 cm deep after treatment. • Daily dressing change initially, reduced to alternate days after a “few weeks”. • No longer malodourous, exudate considerably reduced, regular bleeding stopped 1.5cm x 2cm pressure ulcer. • Dressing changed from daily to alternate days as soon as Prontosan used. • Bleeding and malodour eliminated. • Healed in 3 months. • Mood and morale of patient improved **Patient 2 – 2x large leg ulcers 5 year duration, mixed aetiology** • (1= full circumference, 1= semi circumference). • Both wounds contained >90% biofilm initially, by 1 week of daily solution and gel 50% of biofilm disappeared. • Initially high exudate with strike-through in 2-3 hours, reduced in 1 week, exudate no longer wetted dressing/slippers. • Patient reported Prontosan felt “soothing”. • Study ended Patient died from unrelated event, at study end. • All biofilm removed. • 60% wound reduction in ulcer and second ulcer “almost completely healed”. • Dressing change reduced from daily to alternate days.	Small case series. Descriptive with minimal details. Results per patient rather than per wound. Details only provided for n=3 patients.

	Patient 3 – 3x leg ulcers • Largest ulcer reduced in size and depth. • Ulcers 1 and 3 became pink and granulating – surrounding tissue no longer macerated and exudate reduced significantly. • Pain reduction immediately following dressing changes. • Patient reported he normally could not walk for 2 hours after dressing change due to pain. Upon commencing Prontosan patient was able to walk around house immediately after dressing change • Ongoing pain reduction. • Severe pain reported before treatment, patient nearly fainting, walking “unbearable” despite analgesia, slept poorly and would wake in pain. • Stopped takin opiate analgesia – required pain medication before he could get up at baseline, following treatment with Prontosan this was stopped. • Dressing change initially twice a week due to pain patient could not tolerate more frequent dressing changes, exudate would strike through and concern for effect of exudate on surrounding skin. • Prontosan dressing change initially twice a week and due to changes in wound and improvements with pain dressing changes able to commence every day. • Pain reduced allowing for compression bandage to be used. • Became independent again: driving, going to shops and socialising.	

Kiefer et al (2018)	• On postoperative day 5, complete graft take was seen in 14 patients (27.5%). • The median time to complete re-epithelialization was 7 days (mean 7.1 ± 0.2, 95% CI 5–9 days). • Only n=5 patients did not show complete graft take on postoperative day 7, and none on day 9. • The clinical assessment of re-epithelialization yielded a complete graft take after one, two, or three administrations of Prontosan Wound Gel X (PWX). There was one case of graft failure (PWX unlikely causal) • The changes from baseline were significant at all centres, but there were no differences between centres (log-rank test, *P* = .54). Time to complete re-epithelialization did not depend on the size of wound at baseline (tested as a covariate in the log-rank test, *P* = .92). • No wound infections were reported. • N=1 graft failure which was classified as a serious adverse event. (PWX unlikely to be causal, noted as due to patient severe comorbidities and insufficient compliance) • N=12 patients (23.5 %) experienced 1-4 adverse events resulting in 28 individually different events, 26 unlikely to be caused by PWX • N=2 Mild to moderate pruritus at skin graft sites, with a possible relationship to PWX. • N=1 itching in the donor area classed as a severe adverse event (PWX unlikely to have been causal as PWX was never applied to donor sites). **Table 2.** Overview of adverse events (*N* = 51) | Parameter | | *N* | (%) | E | |---|---|---|---|---| | | | 12 | (23.5) | 28 | | Serious | No | 11 | (21.6) | 27 | | | Yes | 1 | (2.0) | 1 | | Causal relationship | Unlikely | 10 | (19.6) | 26 | | | Possible | 2 | (3.9) | 2 | | Intensity | Mild | 7 | (13.7) | 23 | | | Moderate | 4 | (7.8) | 4 | | | Severe | 1 | (2.0) | 1 | | Outcome | Resolved, no sequelae | 10 | (19.6) | 26 | | | Resolved with sequelae | - | | - | | | Present at final visit | 2 | (3.9) | 2 | | | Death | - | | - | N = number of patients; % = percentage of patients; E = number of events. Twelve patients on 51 evaluable patients occurred 28 adverse events: one serious adverse event not related to the product and 27 adverse events have been reported as described in the table.	

Krylov (2012) Unpublished case series	EASY REMOVAL OF WOUND DRESSING  Dark green represents # of patients where an easy removal of wound dressing was reported and the day of treatment. GENTLE DRESSING CHANGE  Dark green represents # of patients where a gentle dressing change was reported and the day of treatment. NO EXUDATION  Dark green represents # of patients where no exudation was reported and the day of treatment. NO WOUND MACERATION  Dark green represents # of patients where no wound maceration was reporte and the day of treatment. NO ODOUR  Dark green represents # of patients where no wound odour was reported and the day of treatment. 9/9 Skin grafts taken. 1/1 complete wound re-epithelialisation. 10/10 microbiological count reduced (log 3 and log 5 n=2; log 4 n=3; log 2, log 7 and log 8 n=1).	B. Braun case series, potential risk of selection bias and reporting bias.

Möller, Nolte & Kaehn (2008) Published study	97% - good cleansing result with improved finding 80% wound closure. 391/953 (41%) initially infected in total - given antibiotics. 8% given prophylactic antibiotics. 66% of diabetic foot infected. Infection after treatment 3% overall. 620/953 (65%) complete reduction or improvement in odour. 276/953 (29%) slight improvement in odour. 1% patient reported slight burning sensation.	Non comparative. Retrospective.
Moore *et al* (2016) Published study	**Time to wound closure from baseline (days):** Burns (n=7) 44±17 Diabetic ulcer (n=6) 91±26 Pressure ulcer (n=5) 44±17 Surgical wound (n=19) 67±38 Trauma (n=17) 34 ±22 Venous ulcer (n=16) 38±24 Average venous wound close 29 days. Average diabetic wounds close 92 days. The percentage of patients requiring antimicrobial therapy was 10.2%, and this was limited to the surgical (n=3 wounds in 2 patients) and traumatic categories (n=3 wounds in 3 patients).	Retrospective Case Series. Epithelialised wounds included only.

Oropallo *et al* (Unpublished, NCT03369756)	[redacted]	

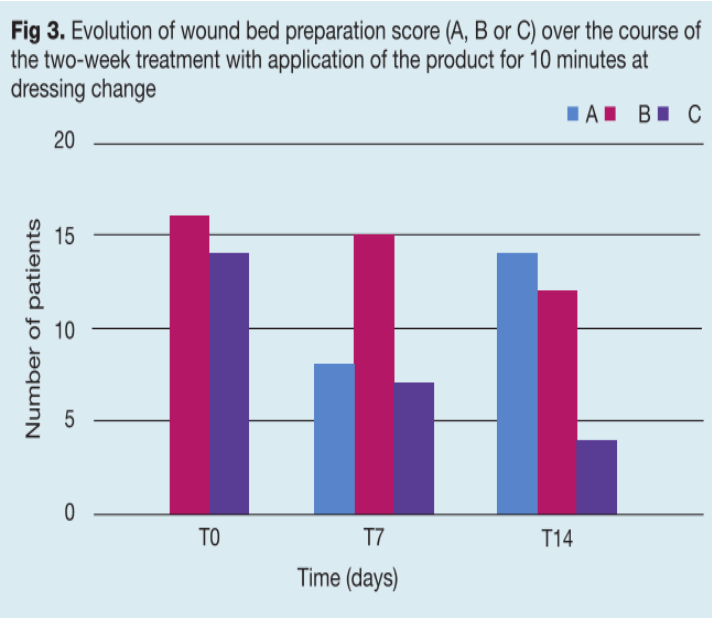
Ricci (2018) Published study	 **Fig 3.** Evolution of wound bed preparation score (A, B or C) over the course of the two-week treatment with application of the product for 10 minutes at dressing change 	N=16 class B. N=14 class C initially N=14 class A, 12 class B and 4 class C after 14 days Sum of exudate scores reduced over 2 weeks. Periwound skin improved in 29/30 (96.7%) cases, 1/30 (3.3%) worsened. N=26 average pain reduction of 47% 20/26 (76.9%) pain reduced, 5/26 (19.2%) no change, 1/26 (3.8%) pain increased. Cutting and Harding infection score initially, N=12 score 0, n=16 score 1 and n=4 score 2 initially. By 2 weeks: N=24 score 0. n=5 score 1. n=1 score 1.	Small sample size. Single application and 14 day treatment – for analysis group B will be included the treatment for 14 days as a single application is not clinically relevant. Short duration of treatment.

Fig 4. Change in the exudate level, according to the wound bed preparation score, over time

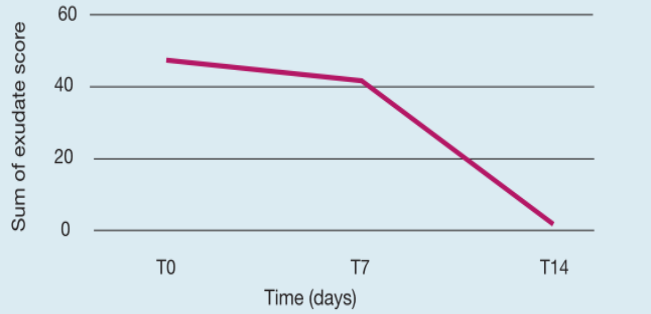


Fig 6. Change in visual analogue scale (VAS) during observational period

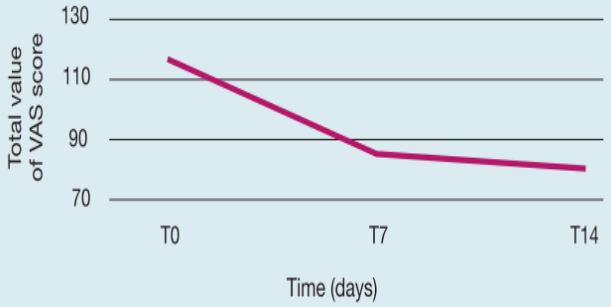


Fig 5. Change in the Cutting and Harding infection score (0, 1, 2 or 3) during the observational period

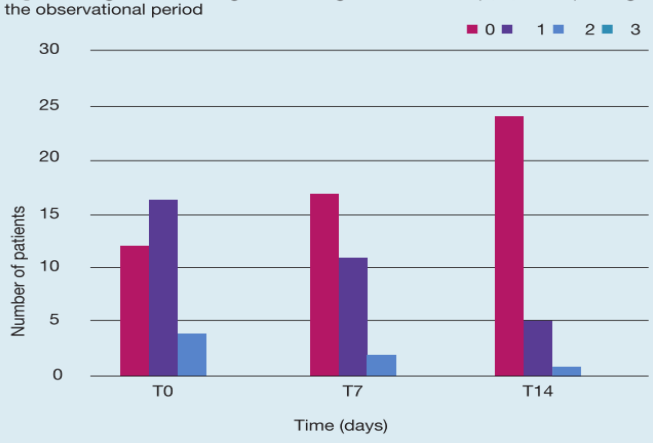
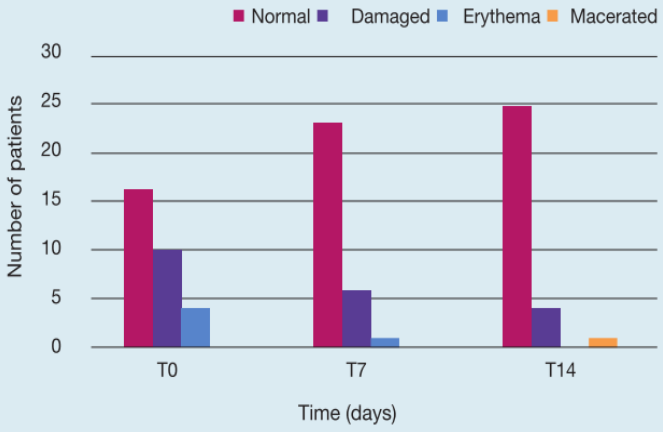
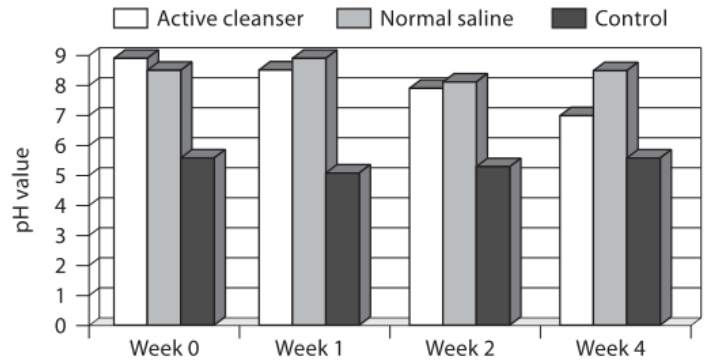
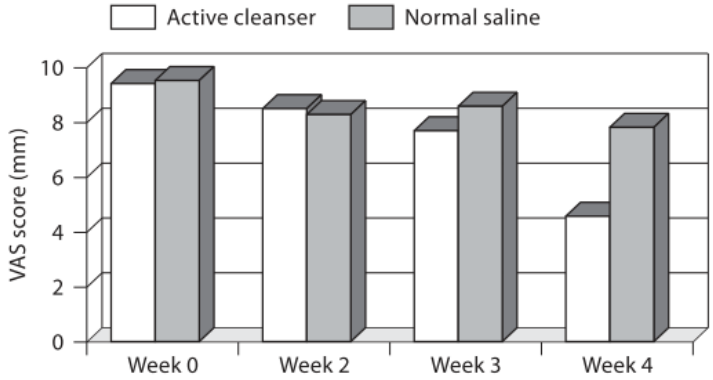


Fig 7. Change in periwound skin area during the observation period



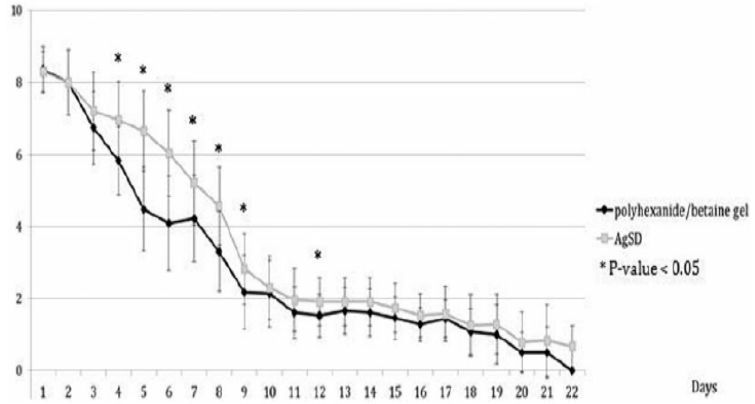
Romanelli *et al* (2010) Published study	**Wound surface pH:**  **Pain Score:**  	Baseline pH on the wound surface was initially 8.9 ± 0.6, and after 4 weeks of cleansing treatment pH was reduced and stable at 7.0 ± 0.3 in Prontosan group. At the end of the study, pH measurement was significantly lower ($p < 0.05$) in Prontosan group compared to normal saline. Significant reduction in pain for Prontosan group compared with normal saline after 4 weeks ($p < 0.05$). Patients were not affected by serious and/or unexpected adverse reactions. No significant change in wound size from base line in either group.	Single blinded, prospective controlled study. Text described median pH but mean and SD expressed.

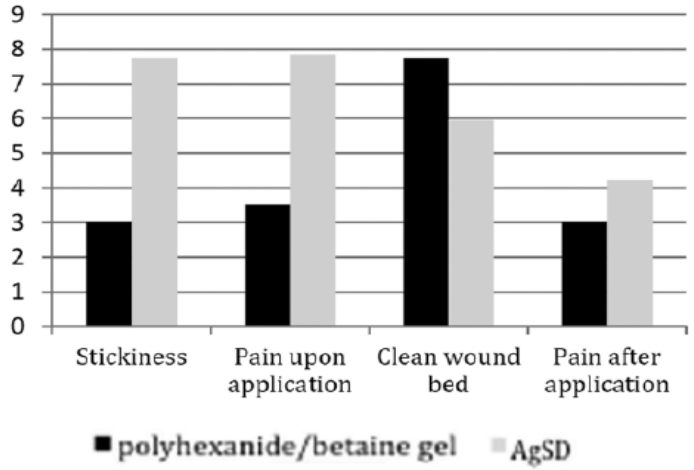
<table>
<tr>
<td>Valenzuela & Perucho (2008)

Published study</td>
<td>The mean absolute reduction in lesion size in the treatment groups was 19.71 cm² (CI 95%: 3.79-24.31cm²).
The mean absolute reduction in lesions for the Control group was 5.65 cm² (95% CI -0.17-11.47 cm^2).
There was a significant difference in the absolute reduction in wound size between two treatment groups p=0.013.
The mean reduction in wound size for Prontosan after 2 weeks was 46.64% (±34.91).
The mean reduction in wound size for the control group after 2 weeks was 17.3% (±35.07).
There was a significant difference in the percentage of wound size change between the two groups (p=0.000).

Microbial cultures: Significant different in effected between treatment group p=0.004.
<table>
<tr><th colspan="3">MICROBIOLOGICAL CONTROL VARIABLES</th></tr>
<tr><th>VARIABLES</th><th>CONTROL GROUP</th><th>EXPERIMENTAL GROUP</th></tr>
<tr><td>Initial evaluation
• Positive cultures
• Negative cultures
• Lost</td><td>
36
21
7</td><td>
52
20
6</td></tr>
<tr><td>Final evaluation
• Positive cultures
• Negative cultures
• Lost</td><td>
24
29
11</td><td>
25
48
5</td></tr>
</table>
</td>
<td>Multi centre RCT, non-blinded.
Short study duration of 2 weeks.
Prontosan Gel use only.</td>
</tr>
</table>

COMPARATIVE ANALYSIS OF VARIABLES DURING THE TWO WEEKS OF TREATMENT			
VARIABLES	CONTROL GROUP	EXPERIMENTAL GROUP	STATISTICAL SIGNIFICANCE
Reversal cultures Fa (%)	13 (9.2%)	32 (22.5%)	p=0.004
Stagnation cicatrisation process Fa (%) • Initial • Final	 50 (80.6%) 32 (57.1%)	 62 (81.6%) 19 (26%)	p=0.000
Surface of the lesion • Initial • Final	 39.394 cm^2 26.931 cm^2	 41.902 cm^2 21.602 cm^2	P=0.013
% Granulation tissue (CI 95%) • Initial • Final	 41.39 (32.83–49.95) 54.83 (45.73–63.93)	 49.52 (40.99–58.05) 74.34 (67.49–81.19)	P=0.001
% Slough (CI 95%) • Initial • Final	 49.13 (40.83–57.43) 40.12 (31.04–49.20)	 38.87 (31.76–45.98) 22.55 (16.38–28.72)	P=0.002
Presence of purulent exudate Fa (%) • Initial • Final	 17 (27.9) 11 (19.30)	 21 (19.3) 3 (4.100)	P=0.005
Pain Fa (%) • Initial • Final	 36 (57.1) 20 (35.7)	 50 (65.8) 15 (20.30)	P=0.049
Edema perilesional skin Fa (%) • Initial • Final	 24 (38.1) 23 (41.1)	 32 (42.7) 10 (13.5)	P=0.000
Erythema perilesional skin Fa (%) • Initial • Final	 39 (62.9) 29 (51.8)	 56 (71.8) 20 (27.0)	P=0.004
Smell Fa (%) • Initial • Final	 23 (37.1) 12 (21.4)	 24 (30.8) 6 (8.1)	P=0.029

Wattanaploy et al (2017)	All wounds completely epithelialised within 3 weeks. No patients had wound infection or required surgical treatment. The healing time in the polyhexanide/betaine gel treated group 17.8 ± 2.2 days and the silver sulfadiazine (SSD)treated group was 18.8 ± 2.1 days Kaplan-Meier analysis showed no significant difference in healing time between the groups (*P* = .13). Six patients (26.1%) in the polyhexanide/betaine gel treated group and 6 patients (26.1%) in the silver sulfadiazine treated group had positive surface swab culture, but there were no signs or symptoms of infection; and routine swab cultures in the next week were negative.  The treatment cost of both groups was not significantly different (*P* = .057). The pain score in the polyhexanide/betaine gel group was significantly less than that in the silver sulfadiazine group at 4 to 9 days and 12 days after treatment (5.8 ± 0.9 vs 7 ± 1.1, 4.5 ± 1.1 vs 6.7 ± 1.1, 4.1 ± 1.3 vs 6 ±1.2, 4.2 ± 1.2 vs 5.2 ± 1.2, 3.3 ± 1.1 vs 4.6 ± 1.1, 2.2 ± 1 vs 2.8 ± 1, and 1.5 ± 0.6 vs 1.9 ± 0.7, respectively),	RCT

		Staff consistently reported that polyhexanide/betaine gel was easier with regard to change dressing than silver sulfadiazine; and the wound surface with polyhexanide/betaine gel was easier to evaluate than the wound dressing with silver sulfadiazine due to the transparent nature of the gel allowing a visual assessment of the wound bed without removal of the dressing (SSD is opaque). The patients were also satisfied with polyhexanide/betaine gel when compared with silver sulfadiazine. polyhexanide/betaine gel was only assessed as average to very good, while satisfaction with silver sulfadiazine was assessed as very poor to average.	

Wilkins & Unverdorben (2013) Published study	**Articles gleaned from literature search classified as follows:** **Table 1.** **AACP GRADING RECOMMENDATIONS** (see table below) **Summary of findings:** **Table 2.** **SUMMARY OF CLEANSING AGENTS** (see table below) The authors noted that there are positive healing effects of polyhexanide/betaine and that toxicity is low.	Review – not systematic of different wound cleansing agents.

Grading	Description	Benefits vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low-quality or very-low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C	Weak recommendation, low-quality or very-low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Abbreviation: RCT, randomized controlled study.

Cleansing Product	Improves Wound Healing	Effective Antimicrobial Against Common Wound Contaminants In Vitro	Toxicity In Vitro
Acetic acid	Ineffective: 2C[6]	Effective: 1B[6]	Toxic: 1B[6,26]
Alcohol	Ineffective: 2C[6]	Effective: 1B[40]	Toxic: 1B[26]
Chlorhexidine	Ineffective: 2C[6,28,29]	Effective: 1B[40]	Toxic: 1B[6,26,39]
Hydrogen peroxide	Ineffective: 2C[6,28]	Effective: 1B[6]	Toxic: 1B[6,26,27]
Polyhexanide/betaine	Effective: 1B[6,11,12,47]	Effective: 1B[40,42,50]	Low Toxicity: 1B[40,42,44]
Povidone-iodine	Effective: 2C[5,28,34,34,37,40]	Effective: 1B[40]	Toxic: 2C[26]
Saline	Ineffective: 1A[19,20]		
Silver (ionized)	Effective: 2C[23,24,38]	Effective: 1B[6,24]	Toxic: 2C[26]
Sodium hypochlorite	Ineffective: 2C[6,19,28]	Effective: 1B[6,19]	Toxic: 1B[6,26,27]
Water	Ineffective: 1A[20]		

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Andriessen and Eberlein (2008), Assessment of a wound cleansing solution in the treatment of problem wounds	
How are the findings relevant to the decision problem?	This study compares use of Prontosan Solution directly with current standard wound cleansing care, with saline/Ringer's solution, in leg ulcers of at least 3 months previous duration, undergoing compression treatment.
Does this evidence support any of the claimed benefits for the technology? If so, which?	More rapid wound healing: mean wound healing time for leg ulcers of 4.42 months in Prontosan group compared with healing time of 3.31 months in the saline/Ringer's solution group (P<0.0001). High rate of wound healing: in leg ulcers, 97% treated with Prontosan were healed in 6 months compared with 89% treated with saline/Ringer's solution. Reduced infection rate/markers of infection: infection rate in Prontosan group n=2/59 (3%) and saline/Ringer's group n=7/53 (13%) P=0.056. More effective than saline: more leg ulcers healed following Prontosan treatment (97%) compared with saline/Ringer's solution (89%). In addition leg ulcers healed faster in the Prontosan Solution group (mean 3.31 months) compared with the saline/Ringer's solution group (mean 4.42 months) P<0.001. Also a reduction in infection rate was observed in the Prontosan group (3%) compared with saline/Ringer's solution group (13%) Freeing up nursing time and reducing costs due to rapid healing (above) and higher rates of wound healing in treatment group compared to standard current practice.
Will any information from this study be used in the economic model?	Yes in support case
What are the limitations of this evidence?	See critical appraisal Appendix C.
How was the study funded?	Not reported in the article.

Atkin et al (2020), Wound bed preparation: a case series using polyhexanide and betaine solution and gel-a UK perspective.	
How are the findings relevant to the decision problem?	A case series of various chronic, complex wounds of up to 20 year of presentation treated with Prontosan Solution and Gels; measuring impact on wound healing, and wound bed preparation in the real-world setting.
Does this evidence support any of the claimed benefits	More rapid wound healing: for mixed chronic wounds 26% healed in 2 months, 39.1% healed in 3 months, 47.8% healed in 6 months, 52.2% healed in 10 months.

Atkin et al (2020), Wound bed preparation: a case series using polyhexanide and betaine solution and gel-a UK perspective.	
for the technology? If so, which?	High rate of wound healing: for mixed chronic wounds treated for longer than 1 month n=12/23 (52%) healed within 10 months. Reduce nursing visits/dressing changes and associated costs: initial dressing change frequency of 4.68 times a week reduced to 2.25 times per week following use of Prontosan products- a 55% reduction. Pain reduction: in various chronic and complicated wounds, 86% reduced pain, 14% not followed up and (n=1) 5% increase pain. Reduced medication requirements e.g. analgesia and antibiotics: in patients with various chronic and complicated wounds, were on pain medication initially. Of these 4 (50%) reduced medication, 2 of which (25%) stopped pain medication altogether. Reduced wound odour: in various complicated chronic wounds, malodour improved in 83% of wounds and was fully resolved in 50%. Reduced exudate: in various complicated chronic wounds, exudate was reduced in all (100%) wounds and was fully resolved in 50%. Reduced slough: in various complicated chronic wounds, slough was fully resolved in all (100%) of wounds. General improvement to quality of life e.g. improved mobility and socialising: 20% commented on quality of life, all improved.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal below
How was the study funded?	DMC is employed by B. Braun and LA and JS received consulting fees from B. Braun Medical Ltd.

Bellingeri et al (2016), Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds	
How are the findings relevant to the decision problem?	An RCT reporting on improvements to wound bed condition of venous ulcers, category 2 or 3 pressure ulcers, ulcers of mixed aetiology and traumatic wounds in PU patients, following cleansing with saline or Prontosan.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Reduced wound odour: the total BWAT score for wound bed condition was significantly reduced by 12 points in the Prontosan group (P=0.02) compared with a reduction of only 4 points in the saline group.

Bellingeri et al (2016), Effect of a wound cleansing solution on wound bed preparation and inflammation in chronic wounds	
	Reduced exudate: the total BWAT score for wound bed condition was significantly reduced by 12 points in the Prontosan group (P=0.02) compared with a reduction of only 4 points in the saline group. Reduced slough: the total BWAT score for wound bed condition was significantly reduced by 12 points in the Prontosan group (P=0.02) compared with a reduction of only 4 points in the saline group. More effective than saline: Bates-Jensen Wound Assessment (BWAT) score, used to measure wound condition, with low score (13) the best and higher scores indicative of poor wound condition. Total BWAT was reduced significantly in the Prontosan group (reduced by 12 p=0.02) compared with the saline group (reduced by 4, non-significant). The inflammatory BWAT score was also reduced more with Prontosan (reduced by 7, p=0.03) compared with saline (reduced by 2, non-significant). Demonstrating greater improvement in wound condition following Prontosan treatment compared with saline.
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	See critical Appraisal Appendix C
How was the study funded?	The authors have no conflict of interest regarding this research. This is an investigator initiated trial. B. Braun Milano SpA kindly provided the material under investigation for both treatment groups, and paid the Ethics Committees' application fees in all participating centres.

Ciprandi et al (2018), A retrospective systematic data review on the use of a polihexanide containing product on burns in children	
How are the findings relevant to the decision problem?	Demonstrates safety profile for use of Prontosan in burns in children, also offers healing time information regarding burns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Reduced infection rate/markers of infection: in burns in children, low infection rate of 8% (16/198) reported. Rapid healing time: in burns in children, time to healing varied depend on total body surface area: 11.5 days for total body surface <5% and 15 days TBS 5-19%, as well as by depth of burns: 8.5 days for superficial burns, 10.9 days for superficial partial thickness burns, 13.5 days for deep partial thickness and 17.2 days full thickness
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal in Appendix C

Ciprandi et al (2018), A retrospective systematic data review on the use of a polihexanide containing product on burns in children	
How was the study funded?	Study grant by B. Braun Medical AG

Collier and Hofer (2017), Taking wound cleansing seriously to minimise risk	
How are the findings relevant to the decision problem?	Study reports on trust wide introduction of wound cleansing pathways, demonstrating impact of standard implementation in and acute trust for surgical sites, acute and chronic wounds.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Reduced infection rate/ markers of infection: prior to Prontosan implementation 544 reported HCAI/SSI's, after Prontosan implementation in hospital for surgical sites, acute and chronic wounds, 48 HCAI/SSI; a reduction of 92%.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal in Appendix C
How was the study funded?	Supported by B. Braun

Durante et al (2014), Evaluation of the effectiveness of a polyhexanide and propyl betaine-based gel in the treatment of chronic wounds	
How are the findings relevant to the decision problem?	Large study covering a variety of chronic and complex wounds, of varying durations demonstrating positive impact of Prontosan on a wide variety of complex wounds measuring improved wound bed preparation, pain, size and dressing change frequency.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Reduced exudate: wounds classed as "non-exuding" 14.5% increased to 74% "Very exuding" 9.7% decreased to 0.8%. "Moderately exuding" 54.8% reduced to 22.6% "Exuding" 20.2% reduced to 0.8% Reduced slough: multiple wound condition parameters improved following Prontosan treatment: "Fibrinous" 58.9% initially, reduced to 1.6% "Partially Necrotic" 33.9% initially, reduced to 2.4% "Wounds with biofilm" 23.4% initially, reduced to 1.6% "Clean" 6.5% initially, increased to 44.4% "Granulating" 4.0% initially, increased to 47.6% "Re-epithelialising" 0.8% initially, increased to 26.6% "Undamaged periwound skin" 17.7% initially, increased to 75.8% "Undamaged wound edges" 28.2% initially, increased to 75.8%

Durante et al (2014), Evaluation of the effectiveness of a polyhexanide and propyl betaine-based gel in the treatment of chronic wounds	
	Improved wound condition (other factors not mentioned above), promotes wound healing above and multiple wound condition parameters improved following Prontosan treatment: “Fibrinous” 58.9% initially, reduced to 1.6% “Partially Necrotic” 33.9% initially, reduced to 2.4% “Wounds with biofilm” 23.4% initially, reduced to 1.6% “Clean” 6.5% initially, increased to 44.4% “Granulating” 4.0% initially, increased to 47.6% “Re-epithelialising” 0.8% initially, increased to 26.6% “Undamaged periwound skin” 17.7% initially, increased to 75.8% “Undamaged wound edges” 28.2% initially, increased to 75.8% Freeing up nursing time to care through fewer dressing changes resulting in fewer nursing visits based on improving wound condition; with a reduction in exudate: dressing change frequency reduced to 1.4 times a week in various wounds and reduced wound exudate as above. Reduced pain: In 124 varying wounds, visual analogue scale reduced by -4.67 with Prontosan treatment.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal in Appendix C
How was the study funded?	The authors certify that there is no conflict of interest with any financial organisation regarding the material discussed in the manuscript.

Harding et al (2012), Pilot randomised, double blind, controlled clinical trial on the combined efficacy of Prontosan Wound Irrigation Solution and Prontosan Wound Gel in the reduction of size and change in bioburden of hard-to-heal venous leg ulcer	
How are the findings relevant to the decision problem?	RCT in the UK comparing use of Prontosan solution and Gel compared with saljne and hydrogel in venous leg ulcers
Does this evidence support any of the claimed benefits for the technology? If so, which?	Demonstrates faster wound healing 47% in Prontosan compared with 33% in saline group after 12 weeks. Larger reduction in wound size in Prontosan group (-60.3%) compared with saline group (-45.46%) after 12 weeks
Will any information from this study be used in the economic model?	Yes Base case
What are the limitations of this evidence?	See critical Appraisal Appendix C
How was the study funded?	Funded by B Braun Medical

Horrocks (2006), Prontosan wound irrigation and gel: management of chronic wounds	
How are the findings relevant to the decision problem?	Case series describing rapid improvements in wound bed condition and reduced use in silver dressings following 3 weeks treatment with Prontosan in chronic wounds of 2-5 year in duration prior to treatment.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Reduced nursing visits/ dressing change frequency: 1 wound changed from being dressed daily to alternate days and another wound changed from weekly to daily (due to patient being able to tolerate wound changes better) Reduce use of expensive dressings: n=6/7 (86%) stopped using silver dressings. Pain reduction: In 7 chronic wounds, pain reduced for all (100%) of patients. Reduced medication requirements e.g. analgesia and antibiotics: in patients with various chronic wounds, 7 were on antibiotics initially and 6/7 (86%) stopped taking antibiotics over the course of Prontosan treatment. Reduced exudate: exudate reported reduced within 3 weeks General improvement to quality of life e.g. improved mobility and socialising: 7/7 reported improved quality of life
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal in Appendix C
How was the study funded?	Product was provided by B. Braun, no other funding declared.

Kiefer et al (2018), Efficacy of a gel containing polihexanide and betaine in deep partial and full thickness burns requiring split thickness skin grafts: a non-comparative clinical study	
How are the findings relevant to the decision problem?	Burns study describing impact of Prontosan treatment in healing process of burns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Pain reduction: in burn patients having a skin graft, pain reduce significantly over 9 days postoperatively (P<0.02). Reduced infection rate/ markers of infection: in Burn patients following skin graft, 0/50 (0%) infection reported. Reduced medication requirements e.g. analgesia and antibiotics: in burns patients receiving skin graft, following prophylactic IV antibiotics during surgery no further antibiotics were given for all 50 patients.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal below
How was the study funded?	Sponsored by B. Braun

Möller, Nolte and Kaehn (2008), Experiences with the use of polyhexanide-containing wound products in the management of chronic wounds – results of a methodical and retrospective analysis of 953 patients	
How are the findings relevant to the decision problem?	Provide retrospective overview of impact of implementing Prontosan into standard clinical practice for chronic wounds on healing and dressing type used.
Does this evidence support any of the claimed benefits for the technology? If so, which?	High rate of wound healing: 80% of various chronic wounds healed. Reduced need for complex dressing e.g. silver: approximately 250/953 used silver dressings (26%) Reduced infection rate/ markers of infection: prior to implementation of Prontosan Solution and Gel infection rate was 41%, reduced to 3%.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal in Appendix C
How was the study funded?	Not discussed.

Oropallo et al (2020) [redacted]	
How are the findings relevant to the decision problem?	[redacted]
Does this evidence support any of the claimed benefits for the technology? If so, which?	[redacted]
Will any information from this study be used in the economic model?	[redacted]
What are the limitations of this evidence?	[redacted]
How was the study funded?	[redacted]

Moore, Dobson and Cetnarowski (2016), 0.1% Polyhexanide-Betaine Solution as an Adjuvant in a Case-Series of Chronic Wounds	
How are the findings relevant to the decision problem?	Study reports on healing time for a variety of wounds treated with Prontosan as standard clinical practice.
Does this evidence support any of the claimed benefits for the technology? If so, which?	More rapid wound healing: wound healing for various wounds measure by mean days to healing, Burns; 44 days, Diabetic ulcers, 91 days; pressure ulcer 44 days, surgical wound 67 days; trauma, 34 days and venous leg ulcer 38 days. Reduced infection rate/markers of infection/use of antibiotics: in various wounds, 10.2% required antibiotics, this was limited to the surgical and traumatic patients. Reduced wound odour: overall 896/953 (94%) reported “wound odour reduced”; 620/953 (65%) reported “very reduced odour” or “eliminated odour” and 276/953 (29%) slight reduction in odour
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal below
How was the study funded?	Study funded by B. Braun

Ricci (2018), Cleansing versus tailored deep debridement, a fresh approach to wound cleansing: an Italian experience	
How are the findings relevant to the decision problem?	In various ulcers of >6 week duration improved wound bed condition after 2 weeks treatment with Prontosan is described
Does this evidence support any of the claimed benefits for the technology? If so, which?	Pain reduction: on average pain reduced by 47%. Pain reduced for n=20/26 (76.9%) participants. Reduced infection rate/markers of infection: Cutting and Harding score for infection initially, n=12; scored 0, n=16; scored 1 and n=4; scored 2. Following two weeks of Prontosan the infection scores reduced, n=24; scored 0, n=5; scored 1 and n=1 scored 1. Promotes wound healing: Falanga's wound bed preparation score (class A=best wound, class C worst wound): At baseline: n=16 class B; and n= 14 class C. After 14 days Prontosan treatment: n=14 class A; n=12 class B; and n=4 class C. Following Prontosan treatment more wounds scored higher for wound bed condition. Sum of exudate scores reduced over 2 weeks. Periwound skin improved in 29/30 (96.7%) cases.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal in Appendix C
How was the study funded?	Not discussed

Romanelli et al (2010), Evaluation of the efficacy and tolerability of a solution containing propyl betaine and polihexanide for wound irrigation	
How are the findings relevant to the decision problem?	RCT in chronic leg ulcers of 2-24 month duration demonstrating improved wound pH, (pH linked to preferable wound healing conditions) after 4 weeks of treatment with Prontosan.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Pain significantly reduced in Prontosan group compared with saline group ($P<0.05$) Promotes wound healing: baseline pH on the wound surface was initially 8.9 ± 0.6, and after 4 weeks of cleansing treatment pH was reduced and stable at 7.0 8±0.3 following Prontosan treatment, indicating healthier wound bed. At the end of the study, pH measurement was significantly lower ($p < 0.05$) in Prontosan group compared to normal saline group. More effective than saline: in chronic leg ulcers, a significant reduction in pain was observed in the Prontosan group compared with saline ($P<0.05$). A significant reduction in wound pH was observed in the Prontosan group compared with the saline group ($P<0.05$), with wounds treated with Prontosan

Romanelli et al (2010), Evaluation of the efficacy and tolerability of a solution containing propyl betaine and polihexanide for wound irrigation	
	reduced from a pH of 8.9 ± 0.6 to a stable 7.08±0.3. Wounds with an alkaline pH have lower rates of healing and more acidic pH in wound bed is indicative of a restart of wound healing.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	See critical appraisal in Appendix C
How was the study funded?	Study funded by B. Braun Medical. MR received financial support for clinical consulting for B. Braun Medical.

Valenzuela and Perucho (2008), The effectiveness of a 0.1% polyhexanide gel	
How are the findings relevant to the decision problem?	RCT reporting impact of 2 weeks Prontosan treatment compared with saline on wound bed condition, infection rate and wound size reduction.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Pain reduction: pain significantly reduced in Prontosan group compared with saline group (P=0.049). Reduced infection rate/ markers of infection: baseline infection rate in Prontosan group 52/78 (67%) reduced to 25/78 (32%). Baseline infection rate in control group 36/64 (56%) reduced to (37.5%). Reduced wound odour: more significant reduction in odour in Prontosan group compared with control group (P=0.029). Odour: Control 37.1% reduced to 21.4%, Prontosan 30.8% reduced to 8.1%. Reduced exudate: more significant reduction in purulent exudate in Prontosan group compared with control group (P=0.005). Presence of purulent exudate: Control 27.9% reduced to 19.3%, Prontosan 19.3% reduced to 4.1 % Reduced slough: More significant reduction in slough Prontosan group compared with control group (P=0.002). Slough: Control group initially, 49.13% reduced to 40.12%, Prontosan group initially 38.87%, reduced to 22.55%. Promotes wound healing: in addition to above, more significant reduction in “wound stagnation” in Prontosan group compared with control group (P=0.00)). Stagnation Control 80.6% reduced to 57.1% Prontosan 81.65% reduced to 26%. More significant increase in granulation tissue in Prontosan group compared with control group (P=0.001). Granulation: Control 41.39% increased to 54.83% and Prontosan 49.52% increased to 74.34%.

Valenzuela and Perucho (2008), The effectiveness of a 0.1% polyhexanide gel	
	More significant reduction in oedema perilesional skin in Prontosan group compared with control group (P=0.002). Oedema perilesional skin: Control 38.1 % increased to 41.1%, Prontosan 42.7% reduced to 13.5%. More significant reduction in Erythema perilesional skin Prontosan group compared with control group (P=0.002). Erythema perilesional skin: Control 62.9% reduced to 51.8%, Prontosan 71.8% reduced to 27%. More effective than saline: All points above
Will any information from this study be used in the economic model?	Yes
What are the limitations of this evidence?	See critical appraisal below
How was the study funded?	Not discussed.

Wattanaploy et al (2017), Randomized Controlled Trial of Polyhexanide Gel Versus Silver Sulfadiazine for Partial Thickness Burn Treatment.	
How are the findings relevant to the decision problem?	Comparative study of Prontosan in burns demonstrating healing rate in burns.
Does this evidence support any of the claimed benefits for the technology? If so, which?	Pain reduction: In burns patients pain was significantly reduced in Prontosan group compared with Silver Sulfadazine group n day 4-9 (P<0.05) Reduced infection rate/ markers of infection: Same infection rate in burns as silver sulfadiazine (relevant as sulfadiazine is an antimicrobial/antiseptic treatment used prophylactically)
Will any information from this study be used in the economic model?	Yes Burns scenario
What are the limitations of this evidence?	See critical appraisal below
How was the study funded?	The author(s) received no financial support for the research, authorship, and/or publication of this article.

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

The MHRA 'Alerts and recalls for drugs and medical devices' were searched on 20th October, 2020 for any reports related to 'Prontosan' at any time and there were no reports listed.

A search undertaken in the FDA MAUDE database on 20th October, 2020 revealed 59 reports from a search of 'brand name': 'Prontosan' between 1st January, 2009 and 20th October, 2020. These were 59 entries relating to 40 separate incidents (19 of these were duplicate records). Of the 40 incidents, 3 were recorded as "Improper or Incorrect Procedure or Method"; these cases related to accidental injection of the product. 1 case was recorded as "Use of Device Problem" with the outcome of "No Consequences Or Impact To Patient". 14 incidents were recorded as "Adverse Event Without Identified Device or Use Problem". 4 incidents were recorded as having "Insufficient Information".

18 incidents were recorded as "Patient-Device Incompatibility". Samples and batch number were only available for n= 2 and 3 cases respectively and were analysed: in all cases no deviations were found.

- 1 case was reported to the FDA by a party who had discovered a report of anaphylaxis during a routine literature search.

Symptoms experienced by these 18 patients were:

- Skin reactions (Itching/tingling n=6, Skin rash/erythema n=7, Skin flushing n=2, Urticaria/wheals n=4, Swelling/oedema n=3, Blisters n=1)
- Symptoms related to the circulatory system (reduced blood pressure n=2, Palpitations/tachycardia n=3, Cardiac/cardiorespiratory arrest n=2, Hypertension n=1)
- Symptoms related to the respiratory system (Shortness of breath n=5, Peripheral cyanosis n=1, Bronchospasm n=1; "may also have occurred due to applicated anaesthetics", Decreased oxygen saturation n=1; "may also have occurred due to applicated anaesthetics")
- Further symptoms (Unresponsiveness/unconsciousness n=5, Dizziness n=2, Nausea n=2, Claminess n=1, Cramping n=1, Trembling n=1)

[redacted]

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

29 journal articles report on the presence or absence of adverse events covering details from 1023 patient treated with Prontosan. Overall in the literature 68/2013 (3.3%) adverse events of any type were reported. Of these 29 pieces of literature measuring adverse events, 13 covering 664 patients, reported that there were no treatment-related adverse events in patients treated with Prontosan. For the remaining 16 in which adverse events were present, 4 were single patient case studies reporting on anaphylaxis, 5 reported pain/burning, 4 reported itching/paraesthesia, 1 reported periwound inflammation, 1 reported skin maceration, 1 reported a rash, 2 reported hypergranulation, 1 reported periwound pustules, 2 reported infection. 1 report, in which the brand of PHMB product was not specified, reported frothing coming from the wound. Finally, one literature review by Block & Wu (2019) reported that skin sensitisation to PHMB was found to be around 0.5% even when the tested concentrations were higher than those used in wound applications.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

Due to the diverse nature of studies identified in this submission we were unable to perform a meta-analysis of the data.

Report all relevant results, including diagrams if appropriate.

N/A – qualitative review provided.

Explain the main findings and conclusions drawn from the evidence synthesis.

N/A – qualitative review provided.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

In total, 14 full published studies 3 poster abstracts and 3 unpublished studies were relevant for inclusion for review and contained primary results regarding the use of Prontosan in wounds appropriate to the scope. The results from the systematic reviews into wound cleansing agents in general shall not be included due to broad nature of systematic searches and low specificity towards Prontosan use. However these systematic reviews were used to source extra material; no extra source material was found which differed from the search included here. One study looked at implementation of Prontosan in a UK Trust and its impact on hospital acquired infections (Collier and Hofer 2017) and therefore shall be discussed separately. The poster abstracts provide minimal details and shall not be further discussed. The remaining 13 full studies and 3 unpublished studies are included for discussion, covering 2232 patients; 1909 wounds treated with Prontosan (Prontosan Solution alone and/or with Gel/Gel X) and 323 wounds treated with control (n=300 saline/Ringer's, n=23 silver sulfadiazine in burns). Included in the full studies are 5 comparator studies comprising: 4 RCTs (Valenzuela and Perucho 2008; Bellingeri 2016; Wattanaploy et al. 2017; Romanelli et al. 2010) and 1 observational study (Andriessen and Eberlein 2008) additionally, one pilot RCT is included (Harding et al 2012). Of the overall 6 comparative studies, 2 cover mixed wounds (both RCTs), 3 leg ulcer studies (2 being RCTs), and 1 RCT in burns.

The studies cover a range of combinations of the Prontosan treatment options: 4 studies with Prontosan Solution alone (2 used on wound of various aetiologies, including an RCT; 2 leg ulcer studies, including an RCT), 3 studies with Prontosan Gel used (1 standard Gel on wounds of various aetiologies and 2 Gel X on burns; 1 of which is an RCT) and 9 studies used both Prontosan Solution and Gel: 6 in wounds of various aetiologies (1 being an RCT), 1 RCT in leg ulcers and 2 studies in burns, one using Gel X.

Of the 16 studies, 3 covered leg ulcers (n=186 wounds, 2 studies were exclusively venous leg ulcers), 4 were burns studies (n=322 wounds). The majority of the studies covered wounds of various aetiologies (n=1739 wounds). These included: 436 leg ulcers (25.1%), 617 diabetic ulcers (35.5%), 7 burns (0.4%), 176 pressure ulcers (10.1%), 177 post surgery wounds (10.2%), 25 trauma (1.24), 1 calciphylaxis (0.1%), 2 buttock wounds (0.1%), 6 auto-immune disease wounds (0.3%), 19 stomal/peristomal wounds (1.1%), 38 radiotherapy reactions (2.2%) and 232 described as "other" (13.3%). Overall the included studies covered 1420 (64%) chronic wounds, 595 (27%) acute wounds and 232 (10%) "other" wounds, representative of the complexity and heterogeneity of wounds requiring treatment within the healthcare system.

Wound bed condition; slough, malodour, exudate etc.

Wound bed condition is reported as a primary measure in 2 RCTS (n=431 wounds) (Bellingeri 2016; Valenzuela and Perucho 2008) and as a secondary measurement in 7 other studies (n=1688 wounds in total) (Harding 2012; Durante et al. 2014; Möller 2008; Ricci 2018; Atkin et al. 2020; Horrocks 2006; Oropallo et al. 2020).The two published RCTs are the most robust pieces of evidence regarding wound bed condition, due to study size and design. These studies demonstrated significant improved wound bed condition following Prontosan treatment compared with control. The largest RCT, Bellingeri et al (2016) (n=289 mixed wounds), reported wound bed condition as its primary outcome using the validated Bates-Jensen wound assessment tool (BWAT). BWAT score contains 13 items that assess wound condition scored on a Likert scale, with the total score ranging from a minimum of 13 to a maximum score of 65 (Harris et al. 2010). Bellingeri et al (2016) reported, in n=289 wounds of various aetiologies, a significant reduction in the BWAT score, from 26 initially to a healthy wound bed score of 14, after 28 days of treatment with Prontosan Solution (P=0.0248). Whereas saline treatment did not significantly impact the BWAT score, reducing score from 26 initially to 22 after 28 days. In another large RCT; Valenzuela and Perucho (2008) (n=142 wounds of various aetiologies), using Prontosan Gel, a significant improvement in wound bed condition was reported after 2 weeks, compared with control regarding: stagnation (P=0.004), increased granulation (P=0.013), slough reduced (P=0.002), presence of purulent exudate reduced (P=0.002), malodour reduced (P=0.004), oedema of perilesional skin reduced (P=0.000) and erythema of perilesional skin reduced (P=0.004) (Valenzuela and Perucho 2008). More specifically, Valenzuela and Perucho (2008) reported the percentage of granulation tissue in the control group increased from 41.39% (95% CI 32.83-49.95%) to 54.83% (95% CI 45.73-63.93%), whereas in the treatment group granulation tissue increased from 49.52% (95% CI 40.99-58.05%) to 74.34% (95% CI 67.49-81.19), a significant improvement in the Prontosan group compared with the control (P=0.001). Significantly greater reduction in slough following Prontosan treatment was reported (P=0.002); control group reduced slough from 49.13% of the wound surface (95% CI 40.83-57.43) to 40.12% (95% CI31.04-49.20), compared with the Prontosan group where slough reduced from 38.87% of the wound surface (95% CI 31.76-45.98) to 22.55% (95% CI 16.68-28.72%). The pilot RCT (Harding et al 2012) (n=34 leg ulcers), looked at wound bed condition as a secondary measure following treatment with Prontosan Solution and Gel compared with saline and inert gel over 12 weeks. Here control group reported an 8.8% (SD 48.3) reduction in granulation tissue whereas Prontosan increased granulation by 14.1% (SD 40.6). This was a feasibility pilot RCT and the numbers are not powered to provide significance.

The non-comparative studies also indicate that moving from standard care (irrigation with saline) to treatment with Prontosan improved wound bed condition. Durante et al (2014), a prospective single arm cohort of n=124 wounds of various aetiologies, reported on wound bed status initially and after 60 days of Prontosan Gel use: 58.9% of wounds were initially fibrinous, this reduced to 1.6%, also necrotic material was initially present in 33.9% of wounds, this was reduced to 2.4% at the final visit following

Prontosan treatment. In addition, wounds described as “clean” increased from 6.5% to 44.4%, “granulating”, increased from 4.0% to 47.6% and “re-epithelising” increased from 0.8% to 26.6% following up to 60 days treatment with Prontosan Gel. Ricci et al (2018) reported on wound bed condition using a wound bed appearance score (Falanga 2000), with “A” being the best and “D” the worst wound condition. Here, treatment of n=30 leg and foot ulcers with Prontosan Solution for 2 weeks resulted in 97% of periwound skin improved. There was an increase in number wounds with the highest scores ”A” (from n=0 initially to n=14) and a reduction in wounds scoring “C” (from n=14 initially to n=4) after 2 weeks treatment with Prontosan. Möller et al (2008), a large retrospective study over 2 years (n=953 wounds of various aetiologies), reported 97% of wounds with a “good cleansing result and improved wound”, 94% of wounds had reduced or resolved malodour. The UK case series by Atkin et al (2020) reported the following: resolution of slough within all wounds reporting presence of slough initially (n=16), exudate reduced in half and resolved in half of wounds initially reporting exudate (n=20), malodour (n=16) resolved or reduced in 83% of wounds and was not followed up in the remaining 17%.
Together these studies support the rapid improvement of wound bed condition following a move to treatment with Prontosan and support the RCT evidence. Importantly improvements in wound condition is a prerequisite for wound healing, wounds with a poor wound bed condition will be unable to progress to healing (Halim et al. 2012).

Wound Healing indicators

This is a summary of the three outcomes listed in the scope: rates of partial and complete wound closure, mean time to partial or complete wound closure and mean time to healing. Any measurement regarding wound healing is covered in 8 clinical studies; 2 RCTs, 1 retrospective study and 5 single arm studies (n=1516).

Wound healing rate:

The pilot RCT (Harding et al, 2012), in n=34 venous leg ulcers compared treatment with Prontosan Solution and Gel with a control group; saline and an inert hydrogel, over 12 weeks. This was a feasibility study and not powered for significance. Here, in the ITT: n=8/17 (47.1%) wounds healed in the Prontosan group compared with n=5/17 (29.4%) in the control group (P=0.4813). The retrospective comparative study by Andriessen and Eberlein (2008) reported in n=142 venous leg ulcers, that 97% of wounds were successfully closed within 6 months in the Prontosan Solution group compared with 89% in the saline control group (P<0.0001). Möller et al (2008) reported on impact of implementing Prontosan Solution and Gel in an outpatient setting for n=953 chronic wounds over 15 months. Here, wounds of various aetiologies were included and 80% of wounds were reported as closed over the 15 months. The UK case series by Atkin et al (2020) reported retrospectively in wounds of mixed aetiology and of up to

20 years in duration that 52.2% of wounds healed within 1-10 months The retrospective studies echo those from other more robust studies.

Time to wound healing:

A significant reduction in mean time to complete healing was reported by Andriessen and Eberlein (2008) with a mean healing time of 3.31 months (SE 0.17) was reported in VLUs treated with Prontosan Solution and Gel compared with 4.42 months (SE 0.19) in the control group (P<0.001). The same data was also reported in another study (Kaehn and Eberlein 2008). Moore et al (2016) report on mean time to wound healing for different wound types following treatment with Prontosan Solution and Gel: burns (n=7) 44±17, diabetic ulcer (n=6) 91±26, pressure ulcer (n=5) 44±17, surgical wound (n=19) 67±38, trauma (n=17) 34 ±22, venous ulcer (n=16) 38±24. Harding et al (2012) reported on time to healing at 2 weeks then 4 weekly intervals, with number and percentage of wounds healed in ITT in the Prontosan group: n=1 (6.3%) wounds at 2 weeks post Prontosan treatment, with additional wounds healed after 4 weeks (n=2; 15.4%), 8 weeks (n=1; 9.1%) and 12 weeks (n=4; 44.4%). In the control group: after 2 weeks (n=0; 0%) after 4 weeks (n=2; 6.5% ITT) with further wounds healed after 8 weeks (n=4; 28.6%) and 12 weeks (n=0; 0%). The UK case series by Atkin et al (2020) reported retrospectively out of 4 wounds treated with Prontosan Solution: n=1 (25%) healed at 3 months, n=1 (25%) healed at 6 months. In the 19 wounds treated with Prontosan Solution and Gel: n=6 (31.6%) healed at 2 months, n= 2 (10.5%) healed at 3 months, n=1 (5.2%) wound healed at 6 months and n=1 (5.2%) wound healed at 10 months.

Changes to wound size:

Changes to wound size, an indicative measure of wound healing, was reported in several studies. The RCT by Valenzuela and Perucho (2008) reported significant reduction in wound size, following 2 weeks treatment with Prontosan Gel compared with saline in n=142 wounds of varied aetiology. Prontosan treatment resulted in a larger wound size reduction (-19.71 cm^2; CI 95%: 3.79-24.31cm^2) compared with the saline control (-5.65 cm^2; 95% CI -0.17-11.47 cm^2), P=0.013. Wound size change as a percentage of the initial wounds was also significantly greater in the Prontosan group compared with control (-46.64% [±34.91] treatment, versus -17.3% [±35.07] control), p<0.001. The pilot study by Harding report a 45.58% reduction in wound size in the control group and a 60.3% wound size reduction in the Prontosan group. These author report on wounds size for those wounds which had not healed within the study time period. The single arm study by Durante et al (2014) report significant changes were observed in wound length (-17.5±21.4 cm), wound width (-15.5±21.1 cm) and wound area (-8.1±16.7 cm^2) (P=0.001) in n=124 wounds of various aetiologies treated with Prontosan Gel for up to 60 days. The UK case series by Atkin et al (2020) reported retrospectively on wounds which were chronic and then moved onto Prontosan treatments. Here, in wounds of various aetiologies, a wound size reduction of >90% was report on

average, ranging from 7-100% in wounds of 2weeks to over 1 year in previous duration. Wound size ranged from 15cm^2 to 300cm^2 initially and reduced to 0cms -157cm^2 after treatment of between 6 days and 6 months.

Healing in burns:

Two full studies reported on burns in adults: 1 RCT and 1 observational study. The RCT by Wattanaploy et al (2017) compared treatment of n=46 partial thickness burns with Prontosan Gel X compared with standard treatment for burns: silver sulfadiazine, a antimicrobial-antibiotic compound. Healing rate in the two groups was similar. Time to complete healing in the Prontosan Gel X treated group was 17.8 ± 2.2 days and the silver sulfadiazine–treated group was 18.8 ± 2.1 days. The prospective single arm cohort study by Kiefer et al (2018) reported use of Prontosan Gel X in n=50 burns requiring split thickness skin grafts in wounds between 10cm^2 and 1000 cm^2 in size initially. The median time to complete re-epithelialisation was 7 days (mean 7.1 ± 0.2, 95% CI 5–9 days). Re-epithelialisation yielded a complete graft take after one, two, or three administrations of Prontosan Gel X. Time to complete re-epithelialization did not depend on the size of wound at baseline (tested as a covariate in the log-rank test, P = 0.92). Separately, a large observational study in burns in children (n=198), estimated healing by last dressing change and reported healing time by total body surface area (TBSA):11.5 days for a wound (TBSA) of less than 5%, 15 days for 5–19% TBSA. Healing time ranged from 8.5 days for superficial burns, 10.9 days for superficial partial thickness burns, 13.5 days for deep partial thickness burns to 17.2 days for full thickness burns (Ciprandi et al. 2018).

Infection rate / markers of infection

The pilot RCT in venous leg ulcers by Harding et al reports in the ITT a similar infection rate between both groups (Prontosan Solution and Gel compared with saline and inert gel): n=3/17 (17.6%) were reported in the control group and n=4/17 (23.5%) in the treatment group over 12 weeks. Another venous leg ulcer study; Andriessen and Eberlein (2008), report reduced infection rate following Prontosan Solution treatment (n=2/59, 3%) compared with saline treatment (n=7/53, 13%) over a 6 month period. Both groups in Andriessen and Eberlein (2008) reported fewer infections than those reported by Harding et al (2012) this may be a reflection of the small sample number in Harding or the retrospective reporting nature of Andriessen and Eberlein (2008).

Several single arm studies also report on infection rates. A retrospective cohort analysis by Moore et al (2016) reported on wounds of various aetiologies(n=70), here Prontosan Solution and Gel replaced saline as a standard wound treatment, only 10% of wounds required antibiotics, an indicator of presence

of wound infection. Use of antibiotics was reported to be limited to surgical and traumatic wounds only and none of the chronic wounds required antibiotics while on Prontosan treatment.

Two studies indicate reduction in infection markers following Prontosan treatment. The RCT by Valenzuela and Perucho (2008) reported resolution of positive bacterial cultures in 33% of the saline treated wounds group compared with 52% in the Prontosan Gel treated groups after a period of 2 weeks. In addition Ricci et al (2018) reported infection rate on n=30 wounds of various aetiologies using the Cutting and Harding score, where 0 indicates no signs of infection (Cutting and Harding 1994). Initially, n=12 scored 0, n=16 scored 1 and n=4 scored 2. Following two weeks of Prontosan Solution the infection scores reduced: n=24 scored 0, n=5 scored 1 and n=1 scored 1, demonstrating wounds moving to a less infected state. The case series by Horrocks (2006) reports in wounds of various aetiologies aged 1-5 years in duration in the UK, following 3 weeks of treatment with Prontosan Solution and Gel, 7/10 (70%) patients no longer required use of antibiotics and 6/10 (60%) no longer required silver products, indicating improved infection status of the wounds.

Collier and Hofer (2017) report on before and after implementation of Prontosan pathway implementation in a secondary care setting. They describe how the Prontosan products are used for different contact times depending on the wounds' condition. Health Care Associated Infections and Surgical Site Infections are reported on before the change in practice to Prontosan: n=544 in August 2012-November 2013, compared with data following the implementation of the Prontosan products: n=49 in June 2015-September 2016, indicating a 92% reduction in the number of infections in the year following the introduction of Prontosan products.

There is a trend towards lower level of infections within Prontosan treatment groups across the published evidence in chronic wounds.

The RCT by Wattanapoly et al (2017) in burns comparing Prontosan Gel X with silver sulfadiazine reported the same level of bacterial colonisation in both treatment groups: 6/23 (26.1%), with no clinical signs of infection reported in either group and the second swab in the following week was negative for all. The observational study by Kiefer et al (2018); using Gel X, did not report any infections in n=50 burns, although impact of treatment is unclear as all patients received prophylactic antibiotics immediately following surgery. Ciprandi et al (2018) report on a systematic retrospective data review of use of Prontosan Solution and Gel on burns in children; n=5/198 wounds were diagnosed as infected upon treatment commencement and n=11/193 wounds developed an infection (5.7%).

Nationally, UK infection rates estimated between 40-89% across chronic wounds (Guest et al. 2018c; Guest et al. 2018d; Guest et al. 2018b) and estimated by wound type as: 53% for pressure ulcers, up to

30% of venous leg ulcers at time of presentation and 45% of diabetic foot ulcers at time of presentation (Guest et al. 2020; Guest et al. 2018b, c; Guest et al. 2018d). Infected wounds have prolonged healing times, with only 18% - 45% of infected VLUs healed within 12 months vs 75% of non-infected VLUs (Guest et al. 2018c). Nationally presence of definite or suspected infection reduces healing rate of chronic wounds from 59% (without infection) to 45% healing rate with infection (Guest et al. 2020).

The studies here reported the infection rates with Prontosan products ranging from 3-23.5% in VLUs (Harding 2012; Andriessen and Eberlein 2008), 0-5.7% in burns (Kiefer et al. 2018; Wattanaploy et al. 2017; Ciprandi et al. 2018) and 10% in a study covering wounds of various aetiologies (Moore et al. 2016). This pooling of data, while it offers insight into infection rate overall with a variety of wounds treated with Prontosan, when in the context of the UK the infection rate reported following treatment with Prontosan is consistently lower than those reported in national studies in wound types relevant to the scope (Guest et al. 2018c; Guest et al. 2018d; Guest et al. 2018b).

Patient Reported Outcomes

This section covers any patient reported measure such as pain, malodour and quality of life.

Pain:

The leg ulcer RCT Romanelli et al (2010) reports significantly reduced pain in the Prontosan Solution group compared with the saline group after 4 weeks of treatment, with pain reducing from 9.5 (out of a maximum of 10) initially in both arms to 4 in the Prontosan group, while only reducing to 7.5 in the control (p=0.05). The two week RCT by Valenzuela and Perucho (2008) reported that in the control group, n=36 wounds were described as “painful” at baseline, which reduced to n=20 (pain resolved in 44% of painful wounds) after two weeks. In the Prontosan Gel group: n=50 wounds were described as “painful” at baseline, which reduced to n=15 (pain resolved in 70% of painful wounds) after two weeks. This difference in pain reduction was significant between the control and Prontosan group (P=0.049). The pilot RCT in VLUs, by Harding (2012), reported changes from baseline between the two groups, using a 100-point Likert scale. Interestingly, low levels of pain was reported in both groups initial (maximum pain recorded 23.5/100 and 32.1/100 for control and treatment respectively). Similar reductions in pain was reported in both groups over the 12 weeks (reporting -9.0 ;± 23.6 and -9.5 ;±19.5 for control and treatment respectively). The RCT by Bellingeri et al (2016); in wounds of various aetiologies, also reported low levels of pain in both treatment and control groups initially (average score 3 out of a maximum of 10) and this pain score did not change in either group over the 28 day study period. Initial low level of pain recorded in both groups may indicate no difference when wounds are not very painful.

The observational single arm studies also report pain reduction. The case series by Atkin et al (2020), reported pain in 21 wounds at the start of their treatment; pain was reduced at the end of the study following Prontosan treatment in 18/21 (86%). The authors also report details of two patients who had previously been unable to tolerate compression (for their VLU) were able to initiate compression after treatment with Prontosan. The authors report that pain medication was taken by eight patients before commencing Prontosan treatment, including: paracetamol, co-codamol, morphine, co-dydramol, ibuprofen, fentanyl lozenges, diclofenac and oxycodone. On follow-up, four patients had reduced their pain medication, two of which had stopped taking any pain medication during the case study. The retrospective study by Durante et al (2014), in n=124 wounds of various aetiologies treated with Prontosan Gel, reported 80% reduction in average VAS/FLACC score from baseline to the final visit (up to 60 days). In addition, Ricci (2018) reported pain reduced by 47% on average following 2 weeks' treatment with Prontosan Solution, with pain reducing in 76.9% of participants. Horrocks (2006) reports pain reducing for 70% of wounds in a small mixed-aetiology case series in the UK. The retrospective studies offer useful insight into the effects of Prontosan treatment on pain as the wounds will have previously been on standard care of utilising saline irrigation for wound cleansing.

In burns, the RCT by Wattanaploy et al (2017), reported on significantly reduced pain reported during dressing changes in the Prontosan Gel X group on days 4, 5, 6, 7, 8, and 12 ($P<0.05$). In addition, the prospective observational study in burns by Kiefer et al (2018) reported a significant reduction in pain over 9 days post-surgery at the graft site with treatment with Prontosan Gel X ($P<0.02$).

Malodour:

Valenzuela et al (2008), an RCT in n=142 wounds of various aetiologies, reported malodour was resolved significantly more frequently in the Prontosan Gel group compared with the saline group ($P=0.029$) within 2 weeks. The single arm observational studies also reported on malodour. Moore et al (2014) reported wound odour reduced in n=896/953 (94%) wounds of various aetiologies; n=620/953 (65%) reported "very reduced" or "eliminated odour" and n=276/953 (29%) reported "slight reduction" in odour. Atkin et al (2020) reported in a UK case series of various complicated chronic wounds that malodour improved in 83% of wounds and was fully resolved in 50% following treatment with Prontosan. Another UK case series by Horrocks (2006) reported malodourous wounds no longer have odour within three weeks of treatment of Prontosan Solution and Gel.

Quality of Life measures:

The unpublished study by Oropallo (2020)

The case series by Atkin et al (2020) reported patients descriptive changes to QoL, specific details reported were "one patient starting swimming again and another was mobile enough to attend clinic for appointments rather than home visits". Psychological improvements were also noted for patients, with recorded comments including: 'morale improved'; 'able to attend first social occasion in five years'; 'the ability to resume normal social activities'; 'able to go on holiday abroad' and 'able to engage in family life'. The wounds included ranged up to 20 years in previous duration, highlighting the impact chronic wounds have on patient QoL and the impact of this wound cleansing routine. Similar descriptive patient reported outcomes are reported by Horrocks (2006) including: "mood and morale of patient and wife improved", "no longer had wet dressing or slippers", "pain was less, especially on dressing change", "pain levels were reduced immediately", "since commencing Prontosan Mr R has not taken any opiate for break through pain and his complexion changed from pale to pink.

Resource use

Impact on resources is more anecdotally reported, however lack of reporting is not indicative of lack of effect. Durante et al (2014) report dressing change frequency reducing to 1.4±2.3 times per week. In addition, the UK case series by Atkin et al (2020) reported dressing changes initially occurred 4.68 ± 2.14 times per week reducing by 33-86% to 2.25 ± 0.88 times per week. Both of these studies are retrospective and cover mixed wound aetiologies. In addition Horrocks (2006) reported in a UK case series that dressing changes reduced from alternate days to twice weekly.

One study, the UK case series by Atkin et al (2020), report on reduced pain medication use following introduction of Prontosan products. 8 patients reported being on pain medication, of which, 2 (25%) had reduced pain medication, another 2 (25%) stopped taking any pain medication and the remaining 4 (50%) patients were not followed up.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

Healing of chronic wounds is a complicated process, involving many patient risk factors and co-morbidities all of which influence the probability of whether a wound will heal or not. These include, but are not limited to: chronic venous disease, obesity, diabetes and nutritional status (Guest et al. 2017; Atkin 2019). Despite the difficulties in reporting on wound improvements, the evidence supports the expectation that Prontosan will improve wound bed condition leading to improved healing, reduction in infection, and improved patient experience over standard care of saline, Ringer's or potable water.

Chronic wounds occur when the orderly cascade of wound healing is interrupted; often delayed in the inflammatory phase of wound healing, during which slough and exudate are produced in response to inflammatory factors present in the wound bed (Parnham and Bousfield 2018; Newton et al. 2017). The presence of slough and exudate in turn further exacerbate the host immune response, creating a recurring cycle of inflammation and consequently more slough and exudate. In order for wounds to progress to healing, the wound must move out of the inflammatory stage of healing (Milne 2015). Biofilms are well acknowledged to impede wound healing, there is increasing knowledge around biofilms contributing to and being harboured by slough (Percival and Suleman 2015; Murphy et al. 2020; UK 2017; Bjarnsholt 2017). Wound bed preparation and anti-biofilm strategies which favour early intervention are recommended (Murphy et al. 2020; (IWII) 2016).

By addressing these factors within the wound bed, Prontosan enables wounds to progress to healing, reducing time to healing, fewer resources used such as dressings and nursing time. The main clinical benefits are summarised by category below overall for chronic wounds and separately by wound type. For this summary burns are discussed separately.

Wound Bed Condition; chronic wounds

A 'good' wound bed condition is defined by decreased presence of slough and excessive exudate along with increased presence of granulation tissue (Halim et al. 2012). Evidence supporting the role of Prontosan in rapid improvements in wound bed condition, compared with saline, is reported in 9 studies (n=1688 wounds). Considering the multifactorial wound healing process this evidence is robust, supported by two RCTs in wounds of various aetiologies. Both studies reported significant improvements in wound bed condition following short treatment periods with Prontosan compared with controls. Bellingeri et al (2016) reported significant improvements following 4 weeks treatment with Prontosan Solution and Valenzuela and Perucho (2008) reported significant improvements following two weeks of

treatment with Prontosan Gel. The 'real world' single arm studies support the findings in the RCTs with improvements from baseline reported for: slough, exudate, necrosis and odour, amongst others. These single arm studies reported improved wound condition when wounds were moved from a standard treatment (irrigation with saline/water) to treatment with Prontosan. While single arm retrospective studies can be judged as a lower grade of evidence, considering the limitations of evidence gathering in wound care and the heterogeneous nature of wounds, these studies offer clinically relevant insights into the impact of implementing Prontosan. The single arm studies support and provide a larger pool of clinically relevant evidence supporting RCT evidence demonstrating improved wound bed condition following Prontosan treatment.

The presence of slough, exudate and biofilm all contribute to an adverse wound environment and deterioration of wound bed condition. This makes proliferation and migration of cells required during the remodelling phase of wound healing difficult to achieve, delaying wound healing progress (Halim et al. 2012). Slough and exudate prolong a host immune response which can in turn damage tissue and result in devitalised tissue, prolonging the chronicity of the wound (Parnham and Bousfield 2018). Slough is a contributor to biofilm, providing a surface for biofilm to attach to and reside within. Resolving slough, exudate and improving wound bed condition promotes an environment conducive to re-epithelisation and healing (Percival and Suleman 2015; Bjarnsholt 2017; Martin and Nunan 2015). Wound bed condition and biofilms are intricately linked; biofilms delay wound healing due to inflammatory factors and can be a source of acute infection. Biofilms also contribute to deterioration of wound bed condition including: increasing slough, malodour and exudate presence within a wound due to a prolonged host immune response (Percival et al. 2017; Phillips PL 2010; Atkin et al. 2019; Wolcott et al. 2010; Mahmoudi et al. 2019; Vestby et al. 2020).

The evidence for Prontosan demonstrates rapid improvement in wound bed condition: de-sloughing, reduction in exudate and odour, leading to increased granulation tissue signalling the wound is entering the proliferation phase, which positively impacts wound healing. The improved wound bed condition is consistent with a disruptive effect on biofilm. Wounds with poor or deteriorating wound bed condition will not heal in a timely manner, the condition of a poor wound bed needs to be improved in order allow proliferative and re-epithelisation of the wound bed to progress (Halim et al. 2012) furthermore the maintenance of a wound bed to prevent deterioration and an early intervention strategy can prevent unnecessary delay to healing (Murphy et al. 2020).

Wound condition, particularly high levels of exudate, also has a direct impact on resource use with HCPs reported excess exudate and evidence of leakage through the dressing increased the frequency of dressing changes (Tickle 2016) and reductions in dressing change frequency from baseline was reported in three of the single arm studies. The improvement in wound bed condition following Prontosan

treatment allows for wounds to move into the proliferative phase and increase wound healing, discussed in detail below. According to clinical experts (Supplement 3), improved wound bed condition will directly impact on patient quality of life, excessive exudate can cause frequent strike through of wounds, also wound condition is associated with malodour and pain all of these factors can impact patient mental well-being. Patient quality of life is discussed in more detail below. Wound condition will directly impact resource use, clinical experts confirmed that wounds with high levels of exudate require more frequently dressing changes and nursing visits to prevent strike through of the dressing, a potential risk for infection. High levels of slough were also described by experts as needing more resource with time spent debriding and more frequent dressing changes.

Wound Healing; chronic wounds

Evidence supporting the role of Prontosan products in healing in chronic wounds comes from 8 clinical studies covering n=1516 wounds reporting on: healing rate compared to control, time to complete healing and wound size reduction as an indicator of healing rate. Two comparative studies indicated higher rates of healing following Prontosan treatment compared with the control treatment in VLUs. The rate of healing differed between the two studies, ranging from 47.1% (12 weeks) to 97% (6 months) for the Prontosan group, compared with healing rates in the control group ranging from 29.4% (12 weeks) to 89% (6 months) (Harding 2012; Andriessen and Eberlein 2008). Both studies indicated increased rates of complete wound healing in the Prontosan group, the pilot RCT was performed as a double blind study in the UK, so is likely to be the most informative regarding the NHS, particularly with regards to VLUs. While this pilot RCT was not powered to generate statistically significantly results, it may offer clinically significant insights into the impact of Prontosan on wound healing, in conjunction with the supporting evidence from other studies. The non-comparative single arm studies reported healing rates between 52.4% in 10 months (Atkin et al. 2020) and 80% in 15 months (Möller 2008) in chronic wounds of various aetiologies when the wounds were moved onto Prontosan treatment. Wounds in the single arm studies generally included wounds of 6 weeks up to 20 years in duration, making them representative of the wide range of chronic wounds which occur in the healthcare setting. Burns will be discussed separately.

Andriessen and Eberlein (2008) also reported a significantly faster mean time to healing in the Prontosan Solution group (3.31 months) compared to a saline/Ringer's control (4.42 months) in Venous Leg Ulcers, a reduction of 1.22 months in mean time to healing ($P<0.001$). The VLUs in this study had all been present for at least 3 months, representative of chronic VLUs found in the UK.

Wound size reduction can be used as an indicator of wound healing. The RCT by Valenzuela and Perucho (2008) report a significant reduction in wound size in the Prontosan Gel group compared with control group (46.64% and 17.3% respectively $P<0.001$) in wounds of various aetiologies. The significant difference in wound size, observed after 2 weeks, supports the notion of reduced time to healing following treatment with Prontosan.

Data supports the trend towards Prontosan having a positive impact on: reducing wound size, the rate of wound healing and reducing the time to wound closure compared with saline, likely linked to the positive improved wound bed condition discussed above. Clinically reducing time of healing in chronic wounds would have benefits to patients' quality of life, reducing the duration of enduring a chronic wound and all of the associated QOL parameters discussed below and the impact of repeated health care visits and appointments required to treat the wound. There are also economic benefits to the healthcare system by reducing time to healing the resource use (clinician time and product usage) would be minimised. Chronic wounds are estimated to account for 48% of all wounds in the UK, of which only 43% are estimated to heal within 12 months (Guest and Vowden 2017). In the UK, 53% of VLUs are estimated to heal within 12 months, presence of infection is pertinent to healing with 75% of VLUs without an infection healing within 12 month compared with 18-45% of VLUs with an infection. Importantly, the burden of chronic wounds is growing, with the annual prevalence rate estimated to increase by 12%, technologies supporting faster wound healing are therefore of increasing clinical and economic importance.

Infection rate / markers of infection; chronic wounds

In the majority of studies the indication is that treatment with Prontosan results in low levels of infection. The pilot RCT reported no significant difference in infection rates after 12 weeks of using Prontosan Solution and Gel in VLUs compared with control. However, a larger comparative study reported large differences in infection rate (3% Prontosan versus 13% saline control) following 6 months' treatment with Prontosan Solution and Gel in VLUs (Andriessen and Eberlein 2008). Overall studies indicate that infection rates in wounds treated with Prontosan products ranged from 3-23.5% in VLUs (Harding 2012; Andriessen and Eberlein 2008), 0-26.1% in burns (Kiefer et al. 2018; Wattanaploy et al. 2017; Ciprandi et al. 2018) and 10% in a study covering wounds with various aetiologies (Moore et al. 2016). Taking a 'real world' example – the introduction of a Prontosan wound cleansing pathway in a UK NHS Trust, was reported to reduce Health Care Associated Infections and Surgical Site Infections by 92% compared with the previous reporting period (Collier and Hofer 2017). Combined, all these results indicate a trend for reduced infection rates with the use of Prontosan products in a real world setting compared with use of saline. Supporting resolution of infection: Valenzuela and Perucho (2008) reported resolution of positive bacterial cultures in 33% of the saline treated wounds group compared with 52% in the Prontosan Gel treated groups after a period of 2 weeks.

Slough and devitalised tissue are acknowledged as increasing infection risk with biofilm a potential source of acute infection, Prontosan's effect on improving wound bed condition is likely to result in lower reported wound infection rates ((WUWHS) 2016).

Within the context of the UK, the reported infection rates following treatment with Prontosan are consistently lower than infection rates reported in national studies for chronic wounds. UK infection rates are estimated between 40-89% (Guest et al. 2018c; Guest et al. 2018d; Guest et al. 2018b). Nationally pressure ulcers wound infection rates are estimated as 53% over 12 months, with up to 30% of venous leg ulcers at time of presentation and 45% of diabetic foot ulcers at time of presentation (Guest et al. 2020; Guest et al. 2018b, c; Guest et al. 2018d). Infected wounds had prolonged healing times, only 18% - 45% of infected VLUs healed within 12 months vs 75% of non-infected (Guest et al. 2018c)

Reducing the risk of infection in chronic wounds will have a positive clinical impact on the patient in terms of the need for antibiotics and impact on pain and other quality of life parameters including time to healing. A UK case series by Horrocks (2006) who reported that in wounds of various aetiologies in the UK aged 1-5 years in duration, 70% of patients no longer required use of antibiotics and 60% did not require silver products after the introduction of Prontosan.

Patient reported outcomes; chronic wounds

Chronic wounds are frequently associated with papain, clinical experts (Supplement 3) report that patients often request additional visits to manage pain in chronic wounds. Prontosan is reported to have positive effects on resolving high levels of pain. The RCT by Valenzuela and Perucho (2008) reported wound pain in a binary fashion with a significant reduction in number of patients reporting pain in the Prontosan Gel group compared with the control after 2 weeks. In two RCTs, where pain was reported as a secondary measure, pain levels were initially reported as low by the patients (3/10 and 30/100) and neither study reported any significant changes in pain in either control or Prontosan groups (Harding 2012; Bellingeri 2016). It is worth noting that this finding may well reflect there being little scope available for further reductions in patient pain. In addition, in the UK, Atkin et al (2020) reported reduced pain in 86% of patients initially reporting pain and a reduction use of analgesics. Pain in burns will be discussed separately below.

Malodour associated with a wound is a commonly reported complaint by patients, one which negatively impacts on social interactions. Numerous studies here report on significant reduction in odour in 65-94%in wounds treated with Prontosan (Moore et al. 2016; Atkin et al. 2020). Furthermore, a significant rapid reduction in wound odour was reported in 2 weeks following treatment with Prontosan Gel compared with saline (Valenzuela and Perucho 2008). Such improvements will have a directly positive impact on patient quality of life. Clinical experts (Supplement 3) also agreed that malodour was a limiting factor for patient socialisation and often a reason patients or their family would request additional nursing visits.

One study, Oropaello 2020, [redacted]. In addition, case series in the UK (Atkin et al. 2020; Horrocks 2006) provide more detailed and descriptive patient feedback supporting the notion that chronic wounds of up to 20 years in duration, once treated with Prontosan, improve in such a manner as to improve patient well-being. Many of the descriptive feedback comments refer to improvements in line with reduction in smell, excessive exudate and pain, resulting in improved social interactions (Atkin et al. 2020; Horrocks 2006). Specific details reported by the authors were "one patient starting swimming again and another was mobile enough to attend clinic for appointments rather than home visits". Psychological improvements were also noted for patients, with recorded comments including: 'morale improved'; 'able to attend first social occasion in five years'; 'the ability to resume normal social activities'; 'able to go on holiday abroad' and 'able to engage in family life'. The wounds included ranged up to 20 years in previous duration, highlighting the impact chronic wounds have on patient QoL and the impact of this wound cleansing routine. Similar descriptive patient reported outcomes are reported by Horrocks (2006) including: "mood and morale of patient and wife improved", "no longer had wet dressing or slippers", "pain was less, especially on dressing change", "pain levels were reduced immediately", "since commencing Prontosan Mr R has not taken any opiate for break through pain and his complexion changed from pale to pink.

A recent review demonstrated that chronic VLUs impact negatively across all areas of daily living. Pain, exudate, odour and the impact on mobility were daily challenges. The ability to engage with everyday functioning was restricted either due to the ulcer, the dressing or due to a self-imposed isolation in response to the impact of symptoms, with depression and low mood were common (Green et al. 2014). Improvements in wound bed condition: slough, exudate, odour and pain (discussed above) are likely the driving parameters to improved QoL as strike through of dressing and odour were common descriptive issues reported by patient as improved following Prontosan treatment, reduction in infection and inflammation may play a role in reduction of pain (Mudge. E. and H. 2010). Significant and rapid improvements in wound bed echo and support the improved QoL reported by patients and are inherently linked.

Resource Use:

Resource use was not reported as a primary outcome in any of the RCTs. Impact on resources is more anecdotally reported, with dressing change frequency reported as reduced by 33-86%; reducing from 4.68 ± 2.14 times per week to 2.25 ± 0.88 times per week (Atkin et al. 2020) and elsewhere reducing to 1.4±2.3 times per week (Durante et al. 2014), in wounds of various aetiologies. Considering the RCTs above report rapid improvements in wound bed condition following Prontosan treatment, specifically rapid reduction in levels of excessive exudate, a reduction in the need to change dressing would be

expected. Indeed a UK survey revealed that HCPs reported wounds having excess exudate, evidence of leakage through the dressing had increased the frequency of dressing changes (Tickle 2016). Economic benefits from reduced dressing change frequency and shorter times to healing have far reaching economic benefits and are major drivers for reduced wound care costs (Guest et al. 2015).

In line with reports above for reduced pain, an additional positive consequence is a reduced need for pain medication. One study, the UK case series by Atkin et al (2020), reports on reduced pain medication use following the introduction of Prontosan products. Specifically, 8 patients reported being on pain medication, of which 2 (25%) had reduced pain medication, another 2 (25%) stopped taking any pain medication and the remaining 4 (50%) patients were not followed up.

Clinical experts (Supplement 3) advised that poor wound condition is associated with increased resource use, specifically increased slough and exudate as discussed earlier with more frequent and complex dressing required to manage these conditions. Experts also report that pain and infection are also associated with increased resource by prescribing analgesics, antibiotics and more complex dressing to manage these conditions. Experts consulted agreed the largest investment in chronic wound management was the nursing visits which ca vary from 20-30 minute for a chronic unilateral leg ulcer up to 45-60 minute when bilateral wounds are involved. Guest 2020 utilise £45 per community nurse visit which is in line with at least 30 minutes per visit (Guest et al. 2020)

In accordance with the scope, the results shall be summarised by wound type.

Leg Ulcers:

Leg ulcers are exclusively investigated in: 2 RCTS (1 exclusively VLUs), 1 comparative study (VLUs) and 1 single arm study (VLUs) (Harding 2012; Romanelli et al. 2010; Andriessen and Eberlein 2008). In the studies with various wound aetiologies, on average 44.43% (range 10-70%) of the wounds were leg ulcers (Atkin et al. 2020; Bellingeri 2016; Durante et al. 2014; Horrocks 2006; Möller 2008; Moore and Gray 2007; Ricci 2018).

Studies covering rate of wound healing were performed in Venous Leg Ulcers, providing the strongest evidence for this subgroup regarding improved wound healing. The complete healing ranged from 47.1% (12 weeks) to 97% (6 months) for the Prontosan group, compared with control group where healing ranged from 29.4% (12 weeks) to 89% (6 months) (Harding 2012; Andriessen and Eberlein 2008). In addition, mean healing rate was reported to be reduced in the Prontosan Solution group compared with saline, (mean 3.31 versus 4.42 months) (Andriessen and Eberlein 2008).The pilot RCT was performed as a double blind study in the UK, so likely to be the most informative regarding the NHS, particularly with

regards to VLUs. While this pilot RCT was not powered to generate statistically significantly results, it may offer clinically and economically significant impact to wound healing in VLUs.

Clinically reducing time of healing in VLUs would have benefits to both patients and healthcare system as VLUs were estimated to account for 278,000 (13%) of chronic wounds in the UK in 2012-2013. Furthermore and all leg ulcers account for 731,000 (34%) of all chronic wounds (Guest et al. 2015).

In 1 of the RCTs reporting on wound bed condition as a primary measure, 67.12% of these wounds were leg ulcers (48.44% VLUs and 18.69% mixed ulcers) (Bellingeri 2016). Here significant improvements in wound bed condition were observed following treatment with Prontosan solution following 4 weeks treatment. Due to the high number of leg ulcers included in this study this data could be applicable for use with this subgroup population. In addition,

[redacted]

Diabetic Foot Ulcers:

No single study focussed on diabetic foot ulcers alone. In the large retrospective study by Möller et al (2008), 62% of the 953 wounds included, presented as diabetic foot wounds. The majority of the wounds here improved their condition and 80% healed over a 15 month period, indicating potential benefits for this patient subgroup. This a higher rate of healing than that reported nationally; 35% of DFUs heal within 12 months (Guest et al. 2018b). Möller et al (2008), reported that only 26% of wounds required silver dressings. This is lower than nationally reported data where 31-36% of DFUs are prescribed and antimicrobial dressing (Guest et al. 2018b). Reduced need for antimicrobial dressing is indicative of fewer infections and better wound condition, required for wound healing. Improved healing of DFU would reduce risk further down-stream of complications and costs associated with DFUs including amputation.

Acute wounds; Burns

The RCT (Wattanaploy et al, 2017) reported that Prontosan Gel X and silver sulfadiazine resulted in similar clinical outcomes for wound healing, bacterial colonisation and infection rate, with periods of significantly less pain reported in the Prontosan Gel X group and positive clinical responses regarding ease of use. Clinically this is interesting as silver sulfadiazine, as an antimicrobial-antibiotic compound, is indicated for the treatment of infected wounds and used prophylactically in burns to prevent infection, this result suggests that a preventative effect can be achieved with a cleansing product. Positive clinical outcomes, with healing and low infection rates were reported in the single arm observational studies supporting the RCT evidence (Kiefer et al. 2018). Separately, a large observational study in burns in

children (n=198), reported high rates of healing with time to healing varying depending on total body surface area and thickness of burn, ranging from 8.5 days to 17.2 days when treated with Prontosan Solution and Gel/Gel X (Ciprandi et al. 2018). Ciprandi et al (2008) reported low rates on infection in the Prontosan treated children (5.7%) and the authors discuss how these infection rates were far lower than those reported previously (23.5 – 67.8%) (Schneider et al. 2015; Rosanova et al. 2013). Standard care of burns differs from that of chronic wounds, treatment objectives are focused on prevention of infection. In the UK over 60% of burns are estimated to be infected experiencing significantly prolonged healing times compared with wounds without an infection (Guest et al. 2020). Prontosan Gel in burns demonstrates high healing and low infection rates and appears to be as clinically effective as primary infection prevention treatments.

Pain has been reported to be reduced in burn patients treated with Prontosan Gel X. The RCT by Wattanaploy et al (2017), reported on significantly reduced pain reported during dressing changes in the Prontosan Gel X group on days 4, 5, 6, 7, 8, and 12 ($P<0.05$). In addition, the prospective observational study in burns by Kiefer et al (2018) reported a significant reduction in pain over 9 days post-surgery at the graft site with treatment with Prontosan Gel X ($P<0.02$).

Adverse events:
Adverse events reported in the literature are in line with those expected according to the instructions for use.

Finally, the effects of Prontosan on improving and maintaining good wound bed condition lead to improved clinical and patient outcomes of reduced time to healing, reduction in infection and prevention of infection, and associated reduced resource use.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

Fourteen published and two unpublished studies provide evidence directly related to the scope, Four are in the UK (Harding 2012; Collier and Hofer 2017; Atkin et al. 2020; Atkin 2019). These studies provide evidence for effectiveness of Prontosan.

The studies cover uses across the Prontosan product range. Prontosan Solution alone is reported in: 2 RCTS, 1 comparative study and 2 single arm studies. Prontosan Solution and Gel combination is reported in: 1 RCT, 1 comparative study and 7 comparative studies. Prontosan Gel/Gel X alone was reported in 2 RCTs and 3 single arm studies. The wound sub group discussed in the studies were mainly: leg ulcers (n=5 studies), burns (n=4 studies) and wounds of various aetiologies (n=8 studies), all in line with the scope. Time line of treatment effects were 2 weeks to 6 months. Studies exploring short term treatment durations indicate the rate of impact to wound condition and offer some insight into wound size reduction. The longer 3-6 months RCTs allow for more long term insight into healing. In line with the scope the studies report on: overall healing rate (n=8 studies), time to healing (n=8 studies) and wound size reduction (n=8 studies), improvements in wound bed (n=7 studies) condition, infection rate/markers of infection (n= 8 studies) as well as patient reported outcome such as pain and analgesics use and quality of life measure and comments (n=3 studies).

The RCTs were critically appraised using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials (Higgins et al. 2011). These appraisals are reported in full in Appendix C and summarised below.

The pilot RCT by Harding (2012) is deemed to have a low risk of bias, due to the assessors, patients and carers being blinded. Data in the full report is provided on intention to treat. No patients were lost to follow up in either group. However no samples size calculation was offered for this pilot as it was described as a feasibility to run a larger study, this is some cause for concern regarding results. As a study performed in the UK this is a strength in this study, specifically for the treatment of VLUs with Prontosan solution and Gel regarding: wound healing rate, time to partial wound healing

The RCT on wound bed condition in wounds of various aetiologies by Bellingeri et al (2016) is also considered at low risk of bias, as the wound assessment was performed by personnel blinded to the treatment group and had no involvement in the treatment. Groups were comparable for wound type and co-morbidities and a power analysis was provided. A slightly higher number of patients in the baseline group were lost to follow up in the saline group, this difference was not sufficient to impact the results and data was reported as intention to treat. This study provides low risk of bias data reporting on wound bed condition following 4 week treatment with Prontosan Solution.

The multi centre RCT on wound bed condition by Valenzuela and Perucho (2010) was a non-masked RCT as patients either received the gel or did not. Some concerns exists regarding the collection of results as wound bed condition is subjective, however photographic follow up was carried out, although details on use of photos for judgement of the wound condition was not clear. Sample size calculation informed study population size and no patients were lost to follow up adding strength to the data. This study has some methodological concerns and provides information on use of Prontosan Gel alone for 2 weeks on wounds bed condition (slough, exudate, oedema, erythema and odour), reduced positive bacterial cultures and wound size.

The RCT in burns by Wattanaploy et al (2017) was scored overall as having some concerns towards bias due to lack of blinding. There were no wounds lost to follow up and all wounds were reported on. This study provides information on use of Prontosan Gel X alone on burns reporting on: mean time to healing, healing rate, infection rate and pain.

The RCT by Romanelli et al 2010, was scored overall as with some concerns. However the main outcome measure, pH, is not defined in the scope and information on in-scope outcomes measures such as pain and wound size is limited. Data from this study offers limited information, other than to support the accumulative notion.

Two comparative studies were reviewed by CASP (Chowdhry & Wilhelmi 2019) and the full analysis can be found in Appendix C. The comparative study by Andriessen and Eberlein (2008) compared VLUs treated with Prontosan Solution with those treated with Ringer's or saline. This study was found to be of low quality, due to the retrospective nature of data collection, lack of patient demographic information and lack on details defining how the patients were selected, however further details for inclusion were presented in another study (Kaehn and Eberlein 2008). However, the retrospective studies offer more insight into the longer term impacts of using Prontosan products and when used in conjunction with the RCTs provide wider insight into real world outcomes. This study reports on use of Prontosan Solution in VLUs reporting on: healing rate, mean time to healing and infection rate (Andriessen and Eberlein 2008).

The comparative study by Collier and Hofer (2017) reported on the impact of implementing the range of Prontosan products as a pathway in an NHS trust. In addition, the implementation process was described and explored the impact to bacterial cultures. Ultimately this study was found to be of low quality, due to its retrospective nature. However, it offers real world insight into the impact of implementing a wound cleansing pathway as standard for all wounds in a NHS trust.

The remaining single arm studies offer "before" and "after" effect data, as standard care will have existed prior to the implementation of Prontosan products to the treatment pathways: as such were reviewed

using CASP. These studies were all found to be of low quality due to their retrospective single arm nature. The single arm studies covered treatment of burns with Prontosan Gel/Gel X, reporting on overall healing rate and infection rates. The majority of studies reported on the real world use of Prontosan products in wounds of various aetiologies and various treatments options. As such they provide insights into real clinical practice and real world understanding. Two of the case series were in the UK (Atkin et al. 2020; Atkin 2019).

Study	Risk of bias						
	Random allocation sequence	Allocation concealment	Blinding of outcome assessment personnel	Missing data	Measurement of outcome	Selective reporting	Overall
(Bellingeri 2016)	✓	✓	✓	✓	✓	✓	✓
(Harding 2012)	✓	✓	✓	✓	✓	✓	✓
(Romanelli et al. 2010)	✓	∅	∅	✓	✓	∅	∅
(Valenzuela and Perucho 2008)	✓	✓	✘	✓	∅	✓	∅
(Wattanaploy et al. 2017)	✓	∅	∅	✓	∅	∅	∅
Key: Low risk of bias: ✓ some concerns: ∅ high risk of bias: ✘							

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The clinical evidence spans across different European centres, including 5 studies in the UK. The outcomes observed are all relevant to NHS practice as wound care within Europe has comparable treatment pathways and objectives. The pilot RCT by Harding (2012) offers directly relevant UK data on healing rates and times in VLU.(Harding 2012). In addition, retrospective data was provided from other sources. This included the impact of implementing a Prontosan wound cleansing pathway into a UK NHS trust (Collier and Hofer 2017). This study focused on the role of Prontosan in the prevention of infections across a whole care pathway; with the use of Prontosan products dependant on wound condition. Furthermore, 2 of the case series offered clinical insights into Prontosan across an array of wound care treatment settings in the UK.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

All wounds (chronic and acute) can benefit from Prontosan, due to improving wound bed condition and preventing deterioration in wound condition and minimising complications. Prontosan has been demonstrated to reduce: slough, excessive exudate, devitalised tissue and biofilm; creating the ideal environment for wound healing and preventing complications which can delay healing.

Patients with wounds requiring cleansing.

This includes, but is not limited to:

- Chronic infected and non-infected wounds
- Acute and Surgical infected and non-infected wounds
- Leg Ulcers e.g. venous and mixed aetiology
- Diabetic foot ulcers
- Pressure Ulcers
- Surgical sites
- Dehisced wounds
- Burns
- Fistulae and abscesses

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

There is a wide breadth of evidence for Prontosan products and this continues to develop. The evidence covers heterogeneous wounds and treatment options due to nature of chronic wound care and various product formulations available to align with wound condition.

The best quality evidence for wound healing are in two wound group areas: VLUs and burns. Overall, 1 pilot RCT and 1 comparative study report on Prontosan and healing rate in VLUs (Harding 2012; Andriessen and Eberlein 2008) and 1 RCT and 2 single arm studies report on healing and infection rate in burns in adults and children (Wattanaploy et al. 2017; Ciprandi et al. 2018; Kiefer et al. 2018).

High quality evidence for rapid improvements in wound bed condition exist in wounds of various aetiologies treated with either Prontosan Solution or Gel (Bellingeri 2016; Valenzuela and Perucho 2008). Furthermore, 1 pilot RCT (Harding 2012) and 6 observational studies (Durante et al. 2014; Ricci 2018; Möller 2008; Oropallo et al. 2020; Horrocks 2006; Atkin et al. 2020) show a consistent improvement in wound bed condition with the move from standard of care to a Prontosan wound cleansing pathway.

Four of the available studies were in the UK (Harding 2012; Collier and Hofer 2017; Atkin et al. 2020; Horrocks 2006).

Not all results are statistically significant at the conventional 5% level and were not powered to be so, but observed effects could be clinically and economically meaningful.

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	17.09.2020
Date span of search:	01.01.2005 – 17.10.2020

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Set	Search	EBSCO – CINHAHL Complete, Medline Complete, Biomedical Reference collection and STM		Cochrane		PubMed	
		Search type	Outcome	Search type	Outcome	Search type	Outcome
S1	Wound healing	Subject term	149,849	MeSH (EAT)	5,795	MeSH	126,952
S2	Wound	Subject term	907,099	MeSH (EAT)	23,133	MeSH	907,672
S3	"Wounds and injuries"	Subject term	530,730	MeSH (EAT)	23,133	MeSH	907,672
S4	Chronic wounds	Subject term	67,238	All text	2,255	MeSH	46,539
S5	Non healing wounds	Text word	279,053	All text	1,898	MeSH	9,967
S6	Hard to heal wounds	Text word	18,042	All text	96	MeSH	305
S7	Burn*	Subject term	136,814	MeSH (EAT)	1,682	MeSH	71,467
S8	Leg ulcer*	Subject term	17,574	MeSH (EAT)	1,973	MeSH	22,599
S9	VLU	Text word	2,773	All text	119	Text word	236
S10	Diabetic foot ulcer	Subject term	5,044	MeSH (EAT)	974	MeSH	9,319
S11	Foot ulcer	Subject term	9,206	MeSH (EAT)	1,060	MeSH	10,327
S12	DFU	Text word	6,585	All text	269	Text word	1,027
S13	Pressure ulcer	Subject term	34,065	MeSH (EAT)	739	MeSH	12,339
S14	PU	Text word	368,834	All text	2,446	Text word	7,698
S15	Biofilm	Subject term	65,282	MeSH (EAT)	739	MeSH	33,432

S16	**S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15**	**Text word**	**1,674,766**	**All text**	**44,325**	**All fields**	**1,072,062**
S17	PHMB	Text word	3,101	All text	76	Text word	494
S18	Polyhexanide	Text word	1,264	All text	71	Text word	158
S19	Polihexanide	Text word	968	All text	29	Text word	465
S20	Polihexanid	Text word	203	All text	71	Text word	544
S21	Prontosan	Text word	511	All text	17	Text word	31
S22	"Polyhexamethylene biguanide"	Text word	2,620	All text	76	Text word	396
S23	Polyhexamethylenebiguanide	Text word	111	All text	7	Text word	18
S24	**S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23**	**Text word**	**5,635**	**All text**	**196**	**All fields**	**926**
S25	**S16 AND S24**	**Text word**	**2,607**	**All text**	**102**	**All fields**	**173**
S26	Gingivitis	Text word	51,385	MeSH (EAT)	1377	MeSH	11,405
S27	Ophthalm*	Text word	1,248,486	All text	26539	MeSH	168,766
S28	Dent*	Text word	3,408,924	MeSH (EAT)	17242	MeSH	572,161
S29	**S26 OR S27 OR S28**	**Text word**	**4,575,004**	**All text**	**72,732**	**All fields**	**743,387**
S30	**(S17 AND S24) NOT S29**	**Text word**	**2,215**	**All text**	**99**	**All fields**	**172**

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Additional publications were sought from the product manufacturer (B. Braun Medical)

Inclusion and exclusion criteria:

Inclusion criteria

Population	Wounds of any aetiology
Comparator	Tap water or saline or Ringer's solution
Interventions	Use of Prontosan irrigation solution and/or gel Polyhexanide 0.1% with betaine
Outcomes	Measurements of wound improvement: • Wound size reduction • Pain reduction (self-reported/reduced analgesics) • Biofilm reduction • Exudate reduction • Slough reduction • Reduced malodour • Patient quality of life • Reduction in bioburden
Study design	Systematic reviews, randomised, non-randomised, cohort, case studies, observational and qualitative studies. Studies with a total sample size of 10 or more patients.
Language restrictions	No language restrictions
Search dates	01.01.2005-17/09.2020
Exclusion criteria	
Population	Surgical procedures, non-wounds (oral, ocular)
Interventions	Any intervention that did not incorporate PHMB solution or gel. Dressings with PHMB incorporated within the dressing. Negative pressure wound therapy. Polyhexanide alone without betaine
Outcomes	Outcomes related to surgical site infections
Study design	Testimonials, non-systematic reviews containing no primary data, editorials, reports describing product news. In vitro studies and animal biofilm studies. Studies with a total sample size of fewer than 10 patients.
Language restrictions	No English translation available
Search dates	Before 01.01.2005

Data abstraction strategy:

Data were extracted from included studies by one reviewer and reviewed by a second reviewer.

Excluded studies

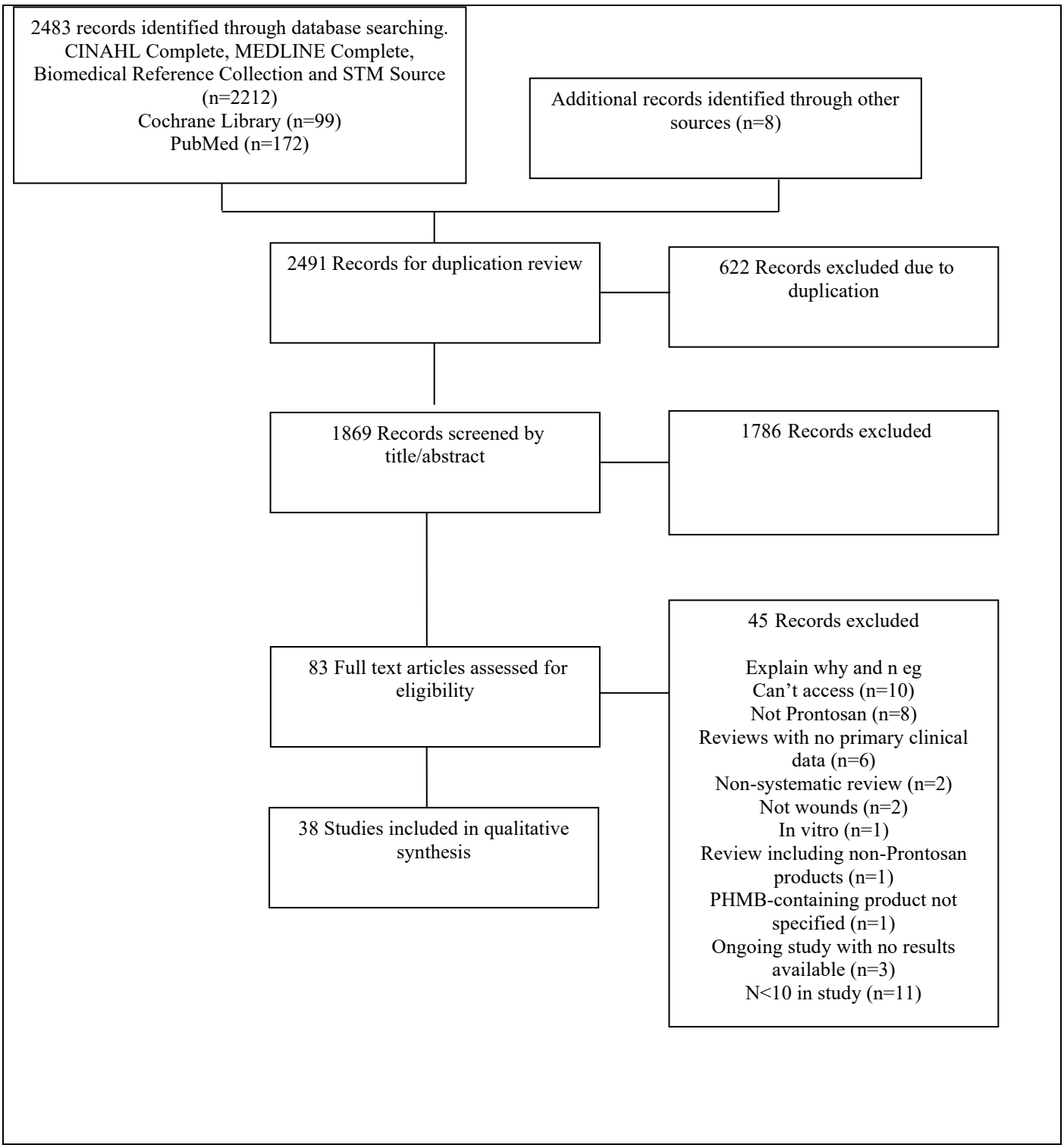
List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Arzt et al (2012)	Systematic review of literature of treatment of pressure ulcers searched in English and French	Poor quality systematic literatures search	Lack of detailed discussion of individual papers. Bibliography checked and any addition papers included in literature search
Assadian *et al* (2018)	Prospective cohort study with 12 study arms. Total N=260 patients and 299 wounds; Prontosan n=33 patients and 36 wounds. Single 20-minute wet-to-moist cleanse with Prontosan irrigation solution.	Use outside of instructions for use.	This was a single application of the irrigation solution; the instructions for use state that Prontosan should be applied frequently in order to achieve and maintain a visually clean wound. A sinlge applitaion is not indicative of clinical practice or clinical impact
Borges *et al* (2018), Brazil	Double blinded randomised control trial. 44 adult patients with venous ulcers. Single one-minute treatment with Prontosan 0.1% Propylbetaine polyhexanide solution with no follow up.	Use outside of instruction for use	The inclusion criteria for the RCT included wounds with at least 8 weeks' duration and an area greater than 6 cm^2. Patients who had absence of bacteria in the first wound tissue fragment biopsied were eliminated from the study. These parameters indicate that the wounds included were large, chronic and had a biofilm present (i.e. they were not acute or small) and as such would be recommended for an exposure time of 15 minutes with a Prontosan-soaked gauze. Within the RCT, Prontosan was used for only one application of rinsing for only 1 minute; according to the product instructions for use "application should be conducted frequently in order to achieve and maintain a visually clean wound."
Chiarella *et al* (2014)	Single-patient case study. Use of Prontosan (Gel/Irrigation Solution not specified) for a diabetic foot ulcer.	Combination treatment with Askina and Iruxol Mono.	Lack of detailed discussion of application methods, contact time, etc. Combination treatment with two other products makes it impossible to ascertain whether the adverse reactions were to Prontosan specifically.

Kaehn & Eberlein (2008)		Publication duplication	Same study as Andriessen and Eberlein (2008) For the purposes of this piece of work data from Andriessen and Eberlein (2008) in data Poster/abstraction and analysis
Naude 2018	Case series	Use of Prontosan alongside use of Calgitrol get in wound.	Unable to ascertain impact of Prontosan alone
Norman *et al* (2016)	Systematic review of wound care containing PHMB	All relevant articles contained within the review have already been included.	Largely comprises a comparison between polyhexanide dressings with polyhexanide swabs. Lack of detailed discussion of individual articles.
Nunes *et al* (2019)	Randomised control trial.	Combination therapy with either papain or hydrogel.	All patients' wounds were treated with Prontosan; they were then randomised to receive either papain or hydrogel. Therefore, there is no comparative investigation of Prontosan and the focus of study is on other treatments.
Smith (2013)	Text	Lacking primary data	Lack of qualitative or quantitative data within the study of a single case study.
Schwarzer *et al* (2020)	Systematic review of topical agents used in wound care.	Review of PHMB-based products generally,	Lack of detailed discussion of individual articles. Does not separate Prontosan from these. All relevant articles contained within the review have already been included.
Tabari *et al* (2018), Brazil	Descriptive "before and after" case study. 5 inpatients with grade 4 pressure ulcers of the spinal cord. Polyhexanide 0.1% solution and gel use once daily for unspecified time frame "until surgery"	Use outside of instruction for use	The researchers treated the wounds with "the spray of the product vial or 20ml syringe". The instructions for use of Prontosan describe such irrigation for acute or uncomplicated wounds and soak times of up to 15 minutes for more complex or chronic wounds. Stage 4 pressure ulcers are considered neither acute nor uncomplicated and therefore in this case irrigating such wounds is not following the instruction for use.
To et al (2016)	Systematic review of wound care containing PHMB	Not the review product	Study is investigating gauze impregnated with Polyhexanide rather than use of polyhexanide and betaine solution or gel. No presence of the surfactant betaine

Vallejo et al (2018)	Case series	Prontosan used in conjunction with low-frequency ultrasonic debridement	LDUD is not standard practice and effects observed would be unable to ascertain to Prontosan use.
Unpublished study NCT01333670 (Bellingeri *et al*)	RCT in chronic ulcers	Actually published as Bellingeri et al 2016	Published data included already
Unpublished study NCT02253069 (Saleh *et al*)	RCT skin cancer surgeries	Surgical a papers excluded for published studies	Outside inclusion exclusion criteria, no data available
Unpublished Study NCT01554644 (Ennis & Mulder)	RCT in diabetic patients with leg ulcers	Study withdrawn	No patients recruited – study withdrawn
Unpublished study WHO; ACTRN12617001291370 (Wallis & Vallejo)	Randomised control trial in patients with chronic wounds	Prontosan used in conjunction with low-frequency ultrasonic debridement	LDUD is not standard practice and effects observed would be unable to ascertain to Prontosan use.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished studies

[redacted]

Appendix B: Search strategy for adverse events

Date search conducted:	17.09.2020
Date span of search:	01.01.2005-17.09.2020

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

A search of four electronic bibliographic databases (CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM) was performed upon the EBSCO platform. Separate searches were conducted on PubMed, and Cochrane Library.

Set	Search	EBSCO – CINHAHL Complete, Medline Complete, Biomedical Reference collection and STM		Cochrane		PubMed	
		Search type	Outcome	Search type	Outcome	Search type	Outcome
S1	Wound healing	Subject term	149,849	MeSH (EAT)	5,795	MeSH	126,952
S2	Wound	Subject term	907,099	MeSH (EAT)	23,133	MeSH	907,672
S3	"Wounds and injuries"	Subject term	530,730	MeSH (EAT)	23,133	MeSH	907,672
S4	Chronic wounds	Subject term	67,238	All text	2,255	MeSH	46,539
S5	Non healing wounds	Text word	279,053	All text	1,898	MeSH	9,967
S6	Hard to heal wounds	Text word	18,042	All text	96	MeSH	305
S7	Burn*	Subject term	136,814	MeSH (EAT)	1,682	MeSH	71,467
S8	Leg ulcer*	Subject term	17,574	MeSH (EAT)	1,973	MeSH	22,599
S9	VLU	Text word	2,773	All text	119	Text word	236
S10	Diabetic foot ulcer	Subject term	5,044	MeSH (EAT)	974	MeSH	9,319
S11	Foot ulcer	Subject term	9,206	MeSH (EAT)	1,060	MeSH	10,327
S12	DFU	Text word	6,585	All text	269	Text word	1,027
S13	Pressure ulcer	Subject term	34,065	MeSH (EAT)	739	MeSH	12,339
S14	PU	Text word	368,834	All text	2,446	Text word	7,698
S15	Biofilm	Subject term	65,282	MeSH (EAT)	739	MeSH	33,432
S16	**S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15**	**Text word**	**1,674,766**	**All text**	**44,325**	**All fields**	**1,072,062**
S17	PHMB	Text word	3,101	All text	76	Text word	494

S18	Polyhexanide	Text word	1,264	All text	71	Text word	158
S19	Polihexanide	Text word	968	All text	29	Text word	465
S20	Polihexanid	Text word	203	All text	71	Text word	544
S21	Prontosan	Text word	511	All text	17	Text word	31
S22	"Polyhexamethylene biguanide"	Text word	2,620	All text	76	Text word	396
S23	Polyhexamethylenebiguanide	Text word	111	All text	7	Text word	18
S24	**S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23**	**Text word**	**5,635**	**All text**	**196**	**All fields**	**926**
S25	**S16 AND S24**	**Text word**	**2,607**	**All text**	**102**	**All fields**	**173**
S26	Gingivitis	Text word	51,385	MeSH (EAT)	1377	MeSH	11,405
S27	Ophthalm*	Text word	1,248,486	All text	26539	MeSH	168,766
S28	Dent*	Text word	3,408,924	MeSH (EAT)	17242	MeSH	572,161
S29	**S26 OR S27 OR S28**	**Text word**	**4,575,004**	**All text**	**72,732**	**All fields**	**743,387**
S30	**(S17 AND S24) NOT S29**	**Text word**	**2,215**	**All text**	**99**	**All fields**	**172**

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

None

Inclusion and exclusion criteria:

Inclusion criteria	
Population	Chronic wounds of any aetiology. Normal intact skin.
Comparator	N/A
Interventions	Use of Prontosan irrigation solution and/or Gel/Gel X. Polyhexanide with betaine.
Outcome	Report of: • Adverse event/ response/effect • Side effect • Patient discomfort
Study design	Primary data: randomised, non-randomised, cohort, case studies, observational and qualitative studies.
Language	No language restrictions
Search dates	Before 01.01.2005

Exclusion criteria	
Population	Burn-skin graft Surgical sites Non wounds (oral, ocular)
Comparator	No exclusions.
Interventions	Any intervention that did not incorporate PHMB solution or gel. Dressings with PHMB incorporated within the dressing. Negative pressure wound therapy. Polyhexanide with substances other than betaine.
Outcome	No exclusions.
Study design	Testimonials, all reviews, no primary data, editorials, reports describing product news. In vitro or animal studies.
Language	No English translation available
Search dates	Before 17.09.2020

Data abstraction strategy:

Data were extracted from included studies by one reviewer and reviewed by a second reviewer.

Papers including any report on adverse events – presence or absence were included for detailed analysis.

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

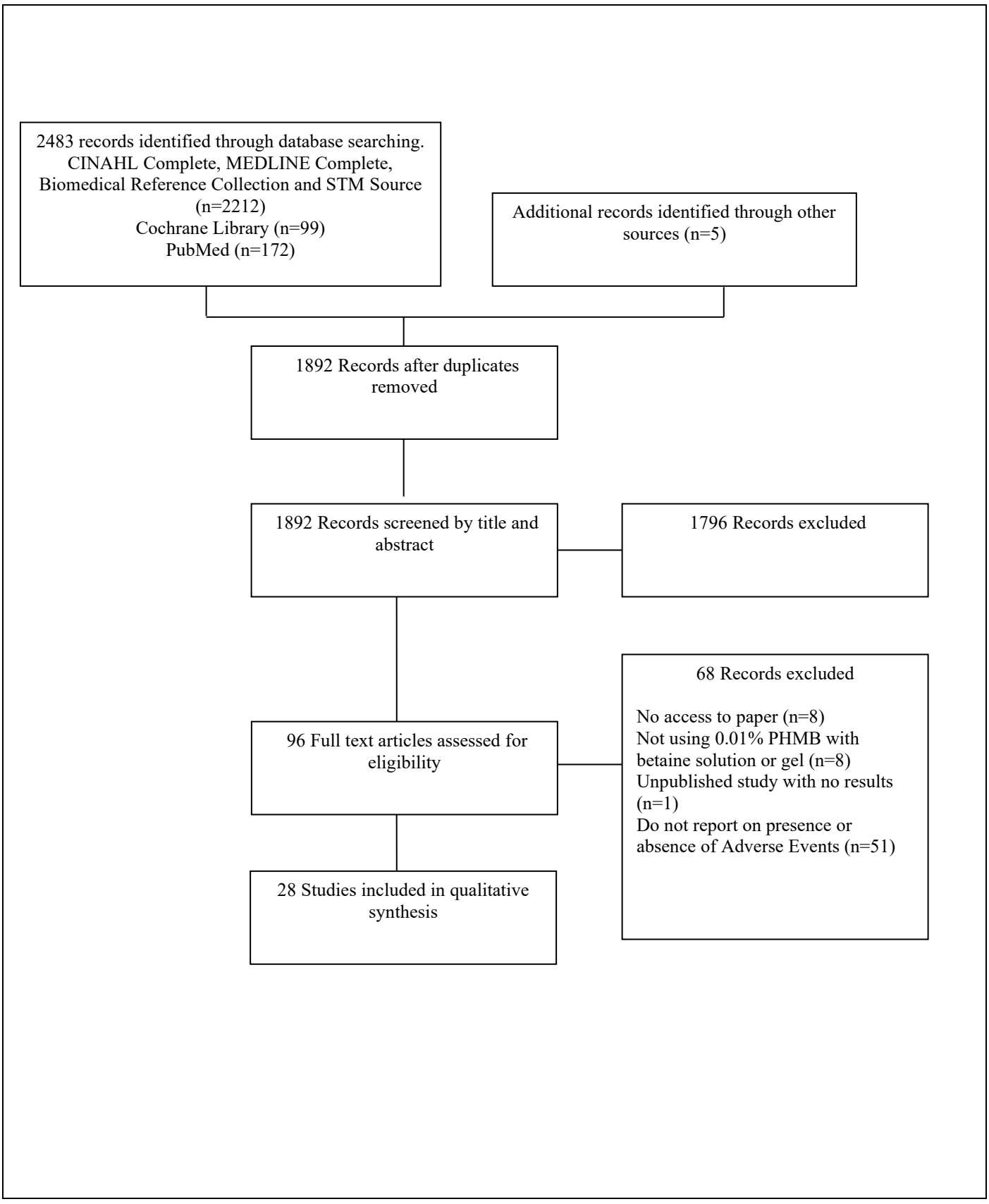
Only 31 papers of the total 79 report on presence or absence of adverse events. The table below provides narrative comments upon the occurrence or absence of adverse events.

Published studies		
Paper	N	Comments
Bellingeri *et al* (2016)	Total (n=289) Prontosan (n=143) Control (n=146)	There were no adverse events (n=0/143)
Block & Wu (2019)	N/A (non-systematic review)	Skin sensitisation to PHMB was found to be approximately 0.5% even when the tested of concentrations of 2.5% and 5% were five to ten times the concentration normally used in wound applications.
Borges *et al* (2018)	Total N=280 Prontosan N=141	There were no adverse events (n=0/280)
Carolino & Cernadas (2017)	Total (n=1) Prontosan and petrolatum (n=1)	Anaphylactic shock case study
Chiarella *et al* (2014)	Total (n=1) Prontosan, Askina & Iruxol Mono	Anaphylactic shock: -
Ciprandi *et al* (2018)	Total N=198 Prontosan N=198	Adverse events were reported in n=5/198 itching (n=3), rash (n=1) and hypergranulating tissue (n=1). No event was severe
Collier & Hofer (2017)	Sample size unknown	No adverse events were reported over the course of the RCT.
Durante *et al* (2014)	Total (n=124) Prontosan (n=124)	No systemic or local side effects reported (n=0/124)
Fjeld & Lingaas (2016)	Total articles N=27	“None of the articles contained report adverse reactions.
Kiefer *et al* (2018)	Total N=51 Prontosan N=51	N=13/51Mild to moderate pruritus at skin graft sites, with a possible relationship to Prontosan, occurred in only two patients. I
Kramer & Hübner (2010)	N/A (non-systematic review)	None of the articles report adverse reactions.

Lachapelle (2014)	N/A (non-systematic review)	None of the articles contained t adverse reactions.
Möller, Nolte and Kaehn (2008)	Total (n=953) Prontosan (n=953)	1 % of the treated patients reported a slight burning sensation
Moore *et al* (2014)	Total (n=49) Prontosan (n=49)	n=2/49 had adverse events. n=1/49 had periwound inflammation N=1/49 had periwound itchiness
Norman *et al* (2016)	Review of total N=12 trials with n=576 participants Polyhexanide N=1 trial with 30 participants	None reported for polyhexanide.
Nunes *et al* (2019)	Total N=33 Prontosan N=33	N=3 lost to follow-up due to adverse reaction – worsening of clinical signs of infection and allergy to the Unna boot and to the crepe bandage
Ricci (2018)	Total (n=70) Prontosan x 1 application (n=40) Prontosan 14 day (n=30)	No relevant allergy phenomena or side effects were seen in either group (n=0/70)
Romanelli *et al* (2010)	Total (n=40) Prontosan (n=20) Saline (n=20)	During treatment, patients were not adverse reactions (n=0/20)
Sams-Dodd & Sams-Dodd (2020)	Total N=1 PHMB-based gel (brand unspecified) N=1	After 6 days, PHMB gel was observed to cause tissue degeneration, disruption of the structure of the exposed bone, and the appearance of froth coming through the hip bone. A pain syndrome developed.
Schunter *et al* (2017)	Total (n=1) Prontosan (n=1)	Anaphylaxis case study
Schrøder 2014	Total (n=1) Prontosan (n=1)	Anaphylaxis case study
To *et al* (2016)	Review of total N=6 articles	None of the studies reported adverse events in the groups treated with PHMB agents.
Vallejo *et al* (2018)	Total (n=4) Prontosan & LFUD (n=4)	The treatment was accepted, with no reports of discomfort during the LFUD procedure or application of antiseptic. Participant No.1 initially reported pain in the evening, following treatment, which was managed well with an oral opioid

Unpublished studies		
Paper	N	Comments
Bell & Traynor (2010)	Total (n=1) Prontosan (n=1)	Pustules began to develop around the periwound skin. These were treated successfully, however it is unclear whether Prontosan treatment was resumed.
Cairns *et al* (2012)	Total (n=15) Prontosan (n=15)	One patient (n=1/15) reported increase in pain and treatment was discontinued
Harding *et al* (2012) (unpublished, NCT01153633)	Total (n=34) Prontosan (n=17)	**Serious adverse events** Prontosan: 0/17 (0%) Infected skin ulcer (n=8) Skin maceration (n=1) Excessive granulation tissue (n=1)
Krylov (2012)	Total (n=27) Prontosan (n=27)	No allergies reported.
Oropallo *et al* (unpublished, NCT03369756)	Total (n=43) Prontosan (n=43)	[redacted]

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Appendix C: Critical Appraisal and Risk of Bias Analysis for included Clinical Studies

Bellingeri et al 2016

Reference	Bellingeri et al 2016	**Aim**	Adhering to intervention (the 'per-protocol' effect)
Experimental	Prontosan Solution	**The effect of adhering to intervention….**	Failures in implementing the intervention that could have affected the outcome
Comparator	Saline	**Source**	Journal article
Outcome	Wound improvement BWAT score		
Results	P=0.0248		
Domain	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**		Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
	Risk-of-bias judgement		Low

Risk of bias due to deviations from the intended interventions (effect of	**Signalling questions**	**Comments**	**Response options**
	2.1. Were participants aware of their assigned intervention during the trial?	Both arms patients were treated with solution irrigating using need and syringe	PN

assignment to intervention)	**2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?**	Staff providing wound care were different from those carrying out wound assessments, those performing assessments were blind to the solution being used	N
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	BWAT is a validated score for wound bed condition and investigators received training in how to use BWAT.	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
	Risk-of-bias judgement		Low

	Signalling questions	Comments	Response options
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	**2.1. Were participants aware of their assigned intervention during the trial?**	Both arms patients were treated with solution irrigating using need and syringe. Staff providing wound care were different from those carrying out wound assessments, those performing assessments were blind to the solution being used	N
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NA
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		PN
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?	N=2/143 lost to follow up intervention and n=7/146 lost to follow up or deceased in control group.	PN
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NI
	Risk-of-bias judgement		Low

	Signalling questions	Comments	Response options
Domain 3: Missing outcome data	**3.1 Were data for this outcome available for all, or nearly all, participants randomized?**	N=2/143 lost to follow up intervention and n=7/146 lost to follow up or deceased in control group.	Y
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA

	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 4: Risk of bias in measurement of the outcome	**4.1 Was the method of measuring the outcome inappropriate?**	BWAT is a validated score for wound bed condition and investigators received training in how to use BWAT.	N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Staff providing wound care were different from those carrying out wound assessments, those performing assessments were blind to the solution being used	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		N
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		N
	Risk-of-bias judgement		Low

Domain 5: Risk of bias in selection of the reported result	**Signalling questions** **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**Comments**	**Response options** Y
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
	5.3 ... multiple eligible analyses of the data?		N
	Risk-of-bias judgement		Low

Overall risk of bias	**Risk-of-bias judgement**		Low

Harding et al (2012) NCT01153633

Reference	Harding unpublished Study NCT01153633	**Aim**	Adhering to intervention (the'per-protocol' effect)
Experimental	Prontosan and Gel	**The effect of adhering to intervention….**	Failures in implementing the intervention that could have affected the outcome
Comparator	Saline and inactive gel	**Source**	Clinicaltrials.gov and study report
Outcome	Wound healing and Percent change of wound size		
Results	P=0.4905 and P=0.2317		
Domain	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**		Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		PY
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	More females in Intervention group and mean wound age shorter in intervention group – small sample size possibly contributing	Y
	Risk-of-bias judgement		Some concerns

Risk of bias due to deviations from the intended interventions (effect of	**Signalling questions**	**Comments**	**Response options**
	2.1. Were participants aware of their assigned intervention during the trial?		N
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N

assignment to intervention)	**2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?**		NA
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PPS reported in results in clinical; trails.gov. However IITT reported in unpublished study report	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	**2.1. Were participants aware of their assigned intervention during the trial?**		N
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		N
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		N

	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		N
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 3: Missing outcome data	**3.1 Were data for this outcome available for all, or nearly all, participants randomized?**	ITT reported in study report	Y
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 4: Risk of bias in measurement of the outcome	**4.1 Was the method of measuring the outcome inappropriate?**		N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
	Risk-of-bias judgement		Low

Domain 5: Risk of bias in selection of the reported result	**Signalling questions** **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**Comments**	**Response options** NI
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
	5.3 ... multiple eligible analyses of the data?		N
	Risk-of-bias judgement		Some concerns

Overall risk of bias	**Risk-of-bias judgement**		Some concerns

Romanelli et al 2010

Reference	**Romanelli et al 2010**	**Aim**	Adhering to intervention (the'per-protocvol' effect)
Experimental	Prontosan	**The effect of adhering to intervention….**	Failures in implementing the intervention that could have affected the outcome
Comparator	**Saline**	**Source**	Journal article
Outcome	**pH**		
Results	**Baseline pH on the wound surface (median range) 8.9 ± 0.6, and after 4 weeks of cleansing treatment was reduced and stable at7.0 ± 0.3 and was significantly lower (p <0.05) compared with saline control**		
Domain	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**	Electronic randomisation reported	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
	Risk-of-bias judgement		Low

Risk of bias due to deviations from the intended interventions (effect of	**Signalling questions**	**Comments**	**Response options**
	2.1. Were participants aware of their assigned intervention during the trial?	Single blinded unclear who is blinded	N
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

assignment to intervention)	**2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?**		N
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		NI
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NI
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	**2.1. Were participants aware of their assigned intervention during the trial?**	Described as a single blinded study, probably patient not aware and possibly carer were aware although not enough detail	PN
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		PY
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NI
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NI
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NI

	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NI
	Risk-of-bias judgement		High

	Signalling questions	**Comments**	**Response options**
Domain 3: Missing outcome data	**3.1 Were data for this outcome available for all, or nearly all, participants randomized?**		N
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Small deviation around data provided, additional extra results unlikely to effect results	PY
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 4: Risk of bias in measurement of the outcome	**4.1 Was the method of measuring the outcome inappropriate?**		N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Single blined study – but lack in details who was blinded	PY

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Digital reading of pH – not influenced by assessor	N
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
	Risk-of-bias judgement		Low

Domain 5: Risk of bias in selection of the reported result	**Signalling questions** **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?**	**Comments**	**Response options** NI
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
	5.3 ... multiple eligible analyses of the data?		N
	Risk-of-bias judgement		Some concerns

Overall risk of bias	**Risk-of-bias judgement**		Some concerns

Valenzuela et al 2008

Reference	**Valenzuela et al 2008**	**Aim**	Adhering to intervention (the 'per-protocol' effect)
Experimental	Saline wash followed by Prontosan gel	**The effect of adhering to intervention….**	Failures in implementing the intervention that could have affected the outcome
Comparator	Saline wash only	**Source**	Journal article
Outcome	Wound condition		
Results	P<0.05		
Domain	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**	Number table used	Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Central administrator assigned groups using number table	Y
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Both groups were comparable	N
	Risk-of-bias judgement		Low

Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	**Signalling questions**	**Comments**	**Response options**
	2.1. Were participants aware of their assigned intervention during the trial?	Hydrogels were only used in control arm if autolytic debridement was required. Prontosan gel was always applied to intervention group.	PY
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y

	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		N
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All participants completed treatment and were included	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	**2.1. Were participants aware of their assigned intervention during the trial?**	Hydrogels were only used in control arm if autolytic debridement was required. Prontosan gel was always applied to intervention group.	PY
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		NI
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		NA

	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 3: Missing outcome data	**3.1 Were data for this outcome available for all, or nearly all, participants randomized?**		Y
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 4: Risk of bias in measurement of the outcome	**4.1 Was the method of measuring the outcome inappropriate?**		N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		PY

	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		PY
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		PN
	Risk-of-bias judgement		Some concerns

Domain 5: Risk of bias in selection of the reported result	**Signalling questions**	**Comments**	**Response options**
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		PY
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
	5.3 ... multiple eligible analyses of the data?		N
	Risk-of-bias judgement		Low

Overall risk of bias	**Risk-of-bias judgement**		Some concerns

Wattanoploy et al 2017

Reference	Wattanoploy et al 2017	**Aim**	Adhering to intervention (the 'per-protocol' effect)
Experimental	Prontosan solution	**The effect of adhering to intervention….**	Failures in implementing the intervention that could have affected the outcome
Comparator	Silver sulfadiazine	**Source**	Journal
Outcome	Wound healing		
Results	P=0.13		
Domain	**Signalling questions**	**Comments**	**Response options**
Bias arising from randomisation process	**1.1 Was the allocation sequence random?**		Y
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
	Risk-of-bias judgement		low

Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	**Signalling questions**	**Comments**	**Response options**
	2.1. Were participants aware of their assigned intervention during the trial?		PN
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		N

	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	All Participants included and completed study	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
	Risk-of-bias judgement		low

	Signalling questions	**Comments**	**Response options**
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	**2.1. Were participants aware of their assigned intervention during the trial?**		PN
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		Y
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?		Y
	2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?		N
	2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants' outcomes?		NA

	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 3: Missing outcome data	**3.1 Were data for this outcome available for all, or nearly all, participants randomized?**	No drop outs	Y
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
	Risk-of-bias judgement		Low

	Signalling questions	**Comments**	**Response options**
Domain 4: Risk of bias in measurement of the outcome	**4.1 Was the method of measuring the outcome inappropriate?**		N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		PN
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		Y
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		PY

	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		PN
	Risk-of-bias judgement		Some concerns

Domain 5: Risk of bias in selection of the reported result	**Signalling questions**	**Comments**	**Response options**
	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		NI
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		N
	5.3 ... multiple eligible analyses of the data?		N
	Risk-of-bias judgement		Some concerns

Overall risk of bias	**Risk-of-bias judgement**		Some concerns

Paper reference: Andriessen & Eberlein (2008)		
Did the study address a clearly focussed question?	**Yes**	Retrospective data review on the effectiveness of Prontosan vs. either Ringer's or saline as a control, namely in relation to time to wound closure.
Was the cohort recruited in an acceptable way?	**Unclear**	States inclusion and exclusion criteria and the recruitment source, – criteria not specified in this publication although was specified in Kaehn and Eberlein (2008) (where the same data is presented) but does not state whether all patients meeting criteria were recruited. No power analysis performed for sample size goal. Limited demographics described in each group were comparable, although no test was performed to determine statistically significant difference.
Was the exposure accurately measured to minimise bias?	**Unclear**	15 minute wet-to-dry cleansing. All patients on same care pathway. Doesn't state how many treatments each patient had. Treatment intervals and number not reported
Was the outcome accurately measured to minimise bias?	**Yes**	Signs of infection defined as "the presence of typical clinical signs of infection" (e.g., redness, swelling). The patients were followed until ulcer closure, or up to 6 months.
Have the authors identified all important confounding factors?	**No.**	Confounding factors not discussed
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	Confounding factors not discussed
Was the follow-up of patients complete?	**Yes**	All patients were follow-up for up to 6 months or wound closure if earlier. Length of study was long enough to determine wound healing.
What are the results?		Prontosan: n=57/59 (97%) healed Control: n=47/53 (89%) healed Infection rate Prontosan 13% and Control 3%
How precise (for example, in terms of confidence interval and p values) are the results?		P<0.0001 for time to healing, no CI given. P and CI not given for % of wounds in each group which healed
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Collier & Hofer (2017)		
Did the study address a clearly focussed question?	**No**	Rates of surgical site infection. Focused question lacking, no primary data or methodology. Prontosan was only one element of the new pathway and the whole pathway was being discussed.
Was the cohort recruited in an acceptable way?	**N/A**	Trust wide implementation of pathway, data reported from hospital standard practice or recording HCAIs and SSIs.
Was the exposure accurately measured to minimise bias?	**Unclear**	How wounds are to be treated depending on stage descried I pathway. Trust wide implementation of pathway, provide real word evidence and exposure records are limited in retrospective analysis.
Was the outcome accurately measured to minimise bias?	**Yes**	Swabbing technique clearly defined.
Have the authors identified all important confounding factors?	**No**	Confounding factors not discussed.
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	Confounding factors not discussed.
Was the follow-up of patients complete?	**Unclear**	Retrospective study, follow up as clinically required.
What are the results?		Percentage reduction in SSI from T1 to T2 Enterococcus -17% MRSA -26% E. coli/vulneris -88% Pseudomonas -97% Anaerobic organisms -98% MSSA -97% Enterobacter -96% Streptococcus -95% Yeast -100% Other -100% TOTAL -92%
How precise (for example, in terms of confidence interval and p values) are the results?		No p or CI given. Although authors state “significant”
Hofer is an employee of B. Braun		
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Möller, Nolte & Kaehn (2008)		
Did the study address a clearly focussed question?	**Unclear**	Addresses clinical outcome of chronic and poorly healing wounds after implementation of Prontosan products in outpatient setting as retrospective single arm review.
Was the cohort recruited in an acceptable way?	**Yes**	• All patients with complete records who received treatment between qualifying dates – reduces selection bias. • Patients only excluded in the case of incomplete records.
Was the exposure accurately measured to minimise bias?	**No.**	Due to retrospective nature of this observational study clinical practice will be determined as per the needs of the wound and clinical decision. A pathway was introduced with some wounds on Prontosan solution alone and other required the addition of gel.
Was the outcome accurately measured to minimise bias?	**No.**	• Wounds were descriptively classifies into: healing, a wound was classified as healed if the original defect was stably and completely closed (formation of epithelium); improvement: a wound was classified as improved if the wound size decreased by at least 25 % in relation to the original size and no improvement: The wound did not meet either of the above criteria. • Duration of treatment to outcome reported was not defined • Wound infection was clinically described and it was not standard practice to swab all wounds. • Many results descriptive in nature – a limitation of using retrospective data • Study is too high level to ascertain how bias was minimised
Have the authors identified all important confounding factors?	**Unclear**	• Comorbidities were not reported • Use of prophyltactive systematic antibiotics reported • Aetiology of wounds does not feature in the analysis of wound outcomes.
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	• No adjustments to statistics or experimental design were reported. • Authors state that 2/3 DFUs were already infected but do not take this into account in later analysis
Was the follow-up of patients complete?	**Yes**	Retrospective study, patient followed up as per clinical need. Only patients with complete records were included
What are the results?		17% improved without wound closure 80% improved with wound closure 3% either deteriorated or did not change Time frame for these improvements was not provided.
How precise (for example, in terms of	No mean, SD, P or CI provided	No p values or Cis. Graphs do not include error bars.

confidence interval and p values) are the results?		
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Ciprandi et al (2018)		
Did the study address a clearly focussed question?	**Yes**	To obtain information on the safety profile of the Prontosan range of products in children in routine clinical practice.
Was the cohort recruited in an acceptable way?	**Yes**	Large sample, multi-centre, clearly appropriate to the study question. However power analysis on required N was not carried out/described.
Was the exposure accurately measured to minimise bias?	**No.**	Retrospective so cannot guarantee that exposure was standardised. Prontosan products were used as per usual standard of treatment practice in each centre – variation likely, although offer real world information. Author report that not all children were necessarily treated with a Prontosan product for the entire healing period.
Was the outcome accurately measured to minimise bias?	**Yes – primary measure**	Safety outcomes, primary focus were accurately measured. However outcomes were entered in free-text fields in CRF
Have the authors identified all important confounding factors?	**Yes**	"Prontosan products were combined, if needed, with skin substitutes and skin grafts." – unfortunately this can't be avoided given the types of wounds but nonetheless remains a confounding factor. Information on previous treatment of wounds and other medication used was collected in the CRFs as was total body surface area (TBSA) , a known compounding factor in healing.
Have the authors taken account of the confounding factors in the design and/or analysis?	**Yes**	Healing reported determined by TBSAMedical history reported not to impact healing, although not factored statistically adjusted. Subgroup analysis performed on hands in terms of function and appearance.
Was the follow-up of patients complete?	**Yes**	Followed up until complete healing or re-epithelialisation.
What are the results?		• 5 AEs reported (MILD itching n=3; MILD rash n=1; MODERATE WITH TREATMENT WITHDRAWAL hypergranulation n=1) • N=16 clinical signs of infection. In n=5/16 the infection was already present. In remaining n=8 (where the infection developed during treatment) antibiotics were used. • "Healing time was not directly reported in the questionnaire for this data review. Therefore, [healing time] results are based on the last day of dressing change and when wound was healed or re-epithelialised. • Healing rate by TBSA
How precise (for example, in terms of confidence interval and p values) are the results?	SD, P and CI not reported	

Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)

Paper reference: Durante et al (2014)		
Did the study address a clearly focussed question?	**Yes**	To evaluate the therapeutic effects of Prontosan gel in patients of all ages with chronic wounds. Single arm prospective study.
Was the cohort recruited in an acceptable way?	**Yes**	Detailed inclusion and exclusion criteria provided. Multi-centre study; 6 centres. Range of wounds, size and duration included.
Was the exposure accurately measured to minimise bias?	**Unclear**	The duration of treatment and the frequency of dressing changes were defined by the investigator. Clinical practice can vary by centre, this is a limit with real world evidence.
Was the outcome accurately measured to minimise bias?	**Yes**	The size of the wounds was measured by metric scale and/or two-dimensional photographic images. VAS and FLACC for measuring pain in adults and infants respectively are both validated scores, plus type of pain and frequency of pain was measured. 2 weeks between visits: day 7, 15, 30, 45 and 60 but not later than the eventual complete healing
Have the authors identified all important confounding factors?	**Yes**	Confounding factors of diabetes, obesity, use of vasoconstrictor drugs, malnutrition and smoking status all identified. Have identified that clinical practice will vary by the choice of the clinician. Data collected on type of debridement, condition of wound bed, condition of periwound skin, level of exudate, presence of bacteria, type of dressing, frequency of treatment, tolerability of the treatment. Variability in dressing change frequency and duration of treatment reported.
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	No adjustment to results for confounding factors
Was the follow-up of patients complete?	**Unclear**	Follow up until 60 days or complete wound healing if sooner. Completeness of follow up and patient loss not discussed.
What are the results?		Improved wound condition (exudate) Improved periwound condition Reduced wound size Reduced dressing change frequency Reduced pain
How precise (for example, in terms of confidence interval and p values) are the results?	**P values reported**	P<0.05 taken as significant, CIs 95% P<0.0001 for length and width of wounds (CI not reported) P=0.0001 for area of wounds (CI not reported) P<0.0001 for VAS (CI -5.36 to -3.98) P<0.00005 for FLACC (CI -12.4 to -7.75)

Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)

Paper reference: Oropallo et al (unpublished, NCT03369756)		
Did the study address a clearly focussed question?	**Yes**	[redacted]
Was the cohort recruited in an acceptable way?	**Yes**	[redacted]
Was the exposure accurately measured to minimise bias?	**No**	[redacted]
Was the outcome accurately measured to minimise bias?	**Unclear**	[redacted]
Have the authors identified all important confounding factors?	**No**	[redacted]
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	[redacted]
Was the follow-up of patients complete?	**Yes**	[redacted]
What are the results?		[redacted]
How precise (for example, in terms of confidence interval and p	[redacted]	[redacted]

values) are the results?		
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Atkin, Stephenson & Cooper (2020)		
Did the study address a clearly focussed question?	**Yes**	To evaluate outcomes of the effectiveness of Prontosan in hard-to-heal wounds.
Was the cohort recruited in an acceptable way?	**No**	Existing case studies were selected (some of them unpublished and therefore provided by one of the authors) – possible selection bias. "Hard-to-heal" was defined as chronic/complex, >6 weeks' duration and/or had signs of complications. Scope for selection bias. All comprised case studies were UK-based
Was the exposure accurately measured to minimise bias?	**No**	"Soak times varied according to wound condition, with the majority stating 5-10 minutes." "Duration of case studies ranged from nine days to 10 months." Some patients were treated with solution alone, some with solution and gel. Lack of detail on treatment methods in general
Was the outcome accurately measured to minimise bias?	**No**	Due to being a collection of case studies by different authors, there was variation in the outcomes which were measured. Not specified whether photography was used to document wound development. "Treatment was followed to complete wound healing for 12 (23%) wounds; for all other case studies (77%) the reason for ending observation was not documented." This gives an incomplete picture of healing with Prontosan.
Have the authors identified all important confounding factors?	**No**	The authors identified variable soak times as a confounding factor, however did not identify comorbidities, wounds of various aetiologies and previous duration, and treatment in different settings,
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	Any wound with "a treatment duration of <1 month was determined to be unlikely to result in complete healing; case studies with treatment <1 month were excluded from analysis for complete healing." Case series format limits the ability to adjust for confounding variables in the analysis. No statistical design alteration was noted to account for these confounding factors.
Was the follow-up of patients complete?	**Unclear**	Follow-up after treatment not discussed.

		"Treatment was followed to complete wound healing for 12 (23%) wounds; for all other case studies (77%) the reason for ending observation was not documented."
What are the results?		Of 23 wounds with >1 month's treatment, 52% completely healed. Mean wound size reduction of 75.6% Pain reduction for 86% Reduction of exudate Reduction of slough Reduction of dressing change frequency
How precise (for example, in terms of confidence interval and p values) are the results?	Not precise	P values and CI not provided SD given for dressing change frequency only
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Kiefer et al (2018)		
Did the study address a clearly focussed question?	**Yes**	Assessing the safety and efficacy of Prontosan for moistening and cleansing in deep tissue burn wounds requiring STSG.
Was the cohort recruited in an acceptable way?	**Yes**	Single arm, detailed inclusion and exclusion criteria reported. Prospective recruitment.
Was the exposure accurately measured to minimise bias?	**Yes**	Three separate sites so may be some variability in application. Sufficient detail provided for duration schedule of Prontosan Gel X administration – repeated every post-op day until healing. Wounds assessed every post-op day before treatment.
Was the outcome accurately measured to minimise bias?	**Yes**	Photographic documentation. Photo-planimetric analysis software for re-epithelialisation. However this was done "by digitally assessing a representative 10 cm2 rectangular section (5 x 5 cm) of the wound." Representative according to whom? Why not analyse the whole wound – limitation of the software? "…photo-planimetric evaluation is dependent on the manual placement of the meshed skin grafts which can lead to high baseline values on day 0"
Have the authors identified all important confounding factors?	**Unclear**	Authors identify a number of limitations to the study, however do not acknowledge the use of opioid analgesics at one of the three sites.
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	Statistical analysis has not accounted for variation in analgesics, despite the fact that the stronger opioids give statistically significant favourable pain outcomes.
Was the follow-up of patients complete?	**Yes**	Patients observed from postoperative day 5 until complete graft take / reepithelialisation.
What are the results?		All patients achieved re-epithelialisation except one Median time for graft take was 7 days No wound infection or erythema Pain reduced
How precise (for example, in terms of confidence interval and p values) are the results?	Means and SD	P<0.05 regarded as significant SD and CI were included in all appropriate data sets.
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Moore, Dobson & Cetnarowski (2014)		
Did the study address a clearly focussed question?	**Yes**	To retrospectively quantify the days to wound closure.
Was the cohort recruited in an acceptable way?	**Yes**	In line with the research question -limited to wounds which healed. However the scope of the study and this limitation has cause for some concern.
Was the exposure accurately measured to minimise bias?	**Unclear**	Retrospective so exact treatment technique and soak time only as accurately as reported in the patient notes. Indicative of rea world use.
Was the outcome accurately measured to minimise bias?	**Yes**	Healing rate quantified by days to complete epithelialisation.
Have the authors identified all important confounding factors?	**Yes**	Antimicrobial therapy in 5 patients Mean BMI was high (30) but range encompasses both "normal" and "morbidly obese" ranges. Various concomitant therapies Various aetiologies of wounds Large range of size at baseline
Have the authors taken account of the confounding factors in the design and/or analysis?	**Unclear**	"Significant comorbid and concomitant medications were present in all groups and did not appear associated with closure rates." Different wound aetiologies were analysed separately. Baseline size discussed. However, did not account for the impact of antimicrobial treatment on outcomes. Also recorded BMI but did not account for this in the analysis – this may have impacted wound healing but it's unclear.
Was the follow-up of patients complete?	**Unclear**	Retrospective analysis of wounds who healed, all patents followed up as until wound healing. "Patients were followed up as needed."
What are the results?		Low percentage of patients requiring systemic antibiotics relative to other studies Reduction in wound size
How precise (for example, in terms of confidence interval and p values) are the results?	Mean +/- SD and range given P values and CI not provided	
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Ricci (2018)		
Did the study address a clearly focussed question?	**Yes**	Evaluating whether cleansing with Prontosan can aid effective wound bed preparation.
Was the cohort recruited in an acceptable way?	**Unclear**	Date range and recruitment centre are not stated. Clear inclusion and exclusion criteria.
Was the exposure accurately measured to minimise bias?	**Yes**	Set soak time (10 minutes) and dressing change frequency (daily) for group B.
Was the outcome accurately measured to minimise bias?	**Yes**	WBP (Flanaga) score and Cutting & Harding score used to measure outcomes; these are validated measures. Photographs taken of all wounds on days 0, 7 and 14.VAS score for pain although expressed as total of all patients' VAS rather than their mean scores.
Have the authors identified all important confounding factors?	**No**	Confounding factors not discussed.
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	Confounding factors not discussed
Was the follow-up of patients complete?	**Unclear**	Patients observed up to 14 days, unclear if all patient are included
What are the results?		Group B Increased number of patients with C&H score of 0, decreased number with score of 1, 2 or 3 Reduction in VAS Increased number of patients with normal periwound skin condition, decreased number of patients with damaged, erythematous or macerated periwound skin
How precise (for example, in terms of confidence interval and p values) are the results?	SD, P and CI not reported	
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Krylov (2012)		
Did the study address a clearly focussed question?	**No**	General observations, does not state a clear aim
Was the cohort recruited in an acceptable way?	**No**	Does not state how the individual cases were selected for inclusion in the case series, may be subject to bias particularly as the author is an employee of B. Braun.
Was the exposure accurately measured to minimise bias?	**Unclear**	Details not provided on the soak time or dressing change frequency. Scant detail provided on other additional ongoing treatment.
Was the outcome accurately measured to minimise bias?	**Unclear**	No detail provided on how microbial log count was performed. Criteria for determining skin graft take not discussed.
Have the authors identified all important confounding factors?	**No**	Confounding factors not discussed
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	Confounding factors not discussed.
Was the follow-up of patients complete?	**No**	Follow up not discussed.
What are the results?		Over time, increase in the number of patients describing the dressing change removal as “easy” and “painless” Increase in the number of patients with no exudation, no maceration and no odour Skin graft take in n=9/10 of the photographed cases and complete epithelialisation in the other n=1/10. Microbial count reductions of between 2 and 8 log in all n=10.
How precise (for example, in terms of confidence interval and p values) are the results?	Not precise	SD, P, mean, error bars and CI not provided.
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Atkin, Barker & Shirlow		
Did the study address a clearly focussed question?	**No**	To review improvements to QoL and wound healing rates. QoL improvements not discussed
Was the cohort recruited in an acceptable way?	**Unclear**	Recruitment details not provided
Was the exposure accurately measured to minimise bias?	**Unclear**	Soak time not provided Dressing change frequency not provided All patients from the same clinic so same care pathway used
Was the outcome accurately measured to minimise bias?	**Unclear**	Details of wound size measurement and the time scale for reduction not provided Extent of slough reduction and time scale for reduction not provided Other outcomes not discussed
Have the authors identified all important confounding factors?	**No**	Confounding factors not discussed.
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	Confounding factors not discussed
Was the follow-up of patients complete?	**Unclear**	Follow up not discussed
What are the results?	Remind endpoints?	N=9/12 reduction in wound size N=8/12 reduction in slough
How precise (for example, in terms of confidence interval and p values) are the results?	No mean, SD, P or CI provided	Actual measurements of wound size only provided for n=1/12
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Paper reference: Horrocks (2006)		
Did the study address a clearly focussed question?	**No**	To evaluate return to normal wound bed, reduction in wound size, use of antibiotic/silver prior to and during use of Prontosan, patient comfort, ease of application, and adverse reactions.
Was the cohort recruited in an acceptable way?	**Unclear**	No recruitment details provided
Was the exposure accurately measured to minimise bias?	**No**	Soak time only provided for n=2/10 and may have varied in the remaining patients Dressing change frequency only provided for n=2/10 and may have varied in the remaining patients
Was the outcome accurately measured to minimise bias?	**No**	The types of treatment outcomes measured varied between patients, e.g. size reported in n=1/3 case study, biofilm reduction reporting in n=1/3 case study,
Have the authors identified all important confounding factors?	**No**	Confounding factors not discussed.
Have the authors taken account of the confounding factors in the design and/or analysis?	**No**	Confounding factors not discussed.
Was the follow-up of patients complete?	**Unclear**	Follow up not discussed
What are the results?		Cessation of silver products in n=6/10 All patients had reduced or eliminated pain Improvements to QoL
How precise (for example, in terms of confidence interval and p values) are the results?	No mean, SD, P or CI provided	No numeric outcomes given except wound size reduction in n=1/10
Adapted from Critical Appraisal Skills Programme (CASP): (Chowdhry and Wilhelmi 2019)		

Appendix D: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
9, 10, 45, 62, 78, 86, 93, 102, 109, 113, 122, 128, 156	☐ Commercial in confidence ☒ Academic in confidence	Oropallo et al (2020). Full results not yet published.	[redacted]
9, 46, 56, 75, 85-92, 97-99, 101, 104, 107, 108, 109, 112, 128, 135	☐ Commercial in confidence ☒ Academic in confidence	Harding et al (2012). Results not yet published.	Time frame unclear.

15, 113	☐ Commercial in confidence ☒ Academic in confidence	Salisbury et al (2020). Results not yet published.	[redacted]
82	☒ Commercial in confidence	Commercially sensitive sales volumes	[redacted]

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*:

** Must be Medical Director or equivalent*

Date: 06.01.2021

Print: Dr Tarik Yalaoui

Role / organisation: Chief Medical Officer

Contact email:

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

GID- MT551 Prontosan for acute and chronic wounds

Company evidence submission

Part 2: Economic evidence

Company name	B Braun
Submission date	18th February 2021
Contains confidential information	Yes

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		4
Number of studies identified as being relevant to the decision problem.		0
Of the relevant studies identified:	Number of published studies.	0
	Number of abstracts.	0
	Number of ongoing studies.	0

List of relevant studies

No relevant economic studies for Prontosan were identified, only *de novo* models were found and excluded for no providing any economic data for Prontosan

2 Details of relevant studies

No relevant economic studies for Prontosan were identified, only *de novo* models were found and excluded for no providing any economic data for Prontosan

3 Economic model

Description

Based on the literature submitted in part 1, Prontosan use has been observed predominantly in two ways: following chronic wounds until wound closure and following chronic wounds until improvement in wound condition (wound bed preparation). This aligns with wounds following a continuum of healing, and that improved wound condition leads to improved healing rates – both observed uses of Prontosan shall be explored in the economic model.

This economic submission is separated into two parts to represent both the ways Prontosan has been observed. The first section covers use on chronic wounds continuously (Venous Leg Ulcers (VLUs)), until wound closure, where Prontosan Solution and Prontosan Gel X would be used at every dressing change until the wound has closed. This is presented as the “wound closure model” and is the model recommended by the company for best clinical outcome with use of Prontosan.

The second section covers Prontosan use to achieve improvements in wound condition. Wounds in need of improvement could include wounds with the presence of any of the following: slough, excess exudate, markers of infection such as inflammation, malodour, necrosis or pain. In this model Prontosan Solution and Prontosan Gel X are used at every dressing change until the wound condition is improved i.e. issues such as slough, excess exudate, markers of infection such as inflammation, malodour and/or pain are resolved and the wound condition improves to a “good”, healthy, progressive wound. This is presented as the “wound bed condition model”. The wound condition model does not cover impact on wounds deteriorating after treatment with Prontosan has stopped. If wounds deteriorate they would re-enter the model again as another incident of needing to improve the wound bed condition.

Wound Closure Model

This section shall deal with the model data, results and sensitivity analysis for wound closure use of Prontosan until wound closure, in the patient group: VLU

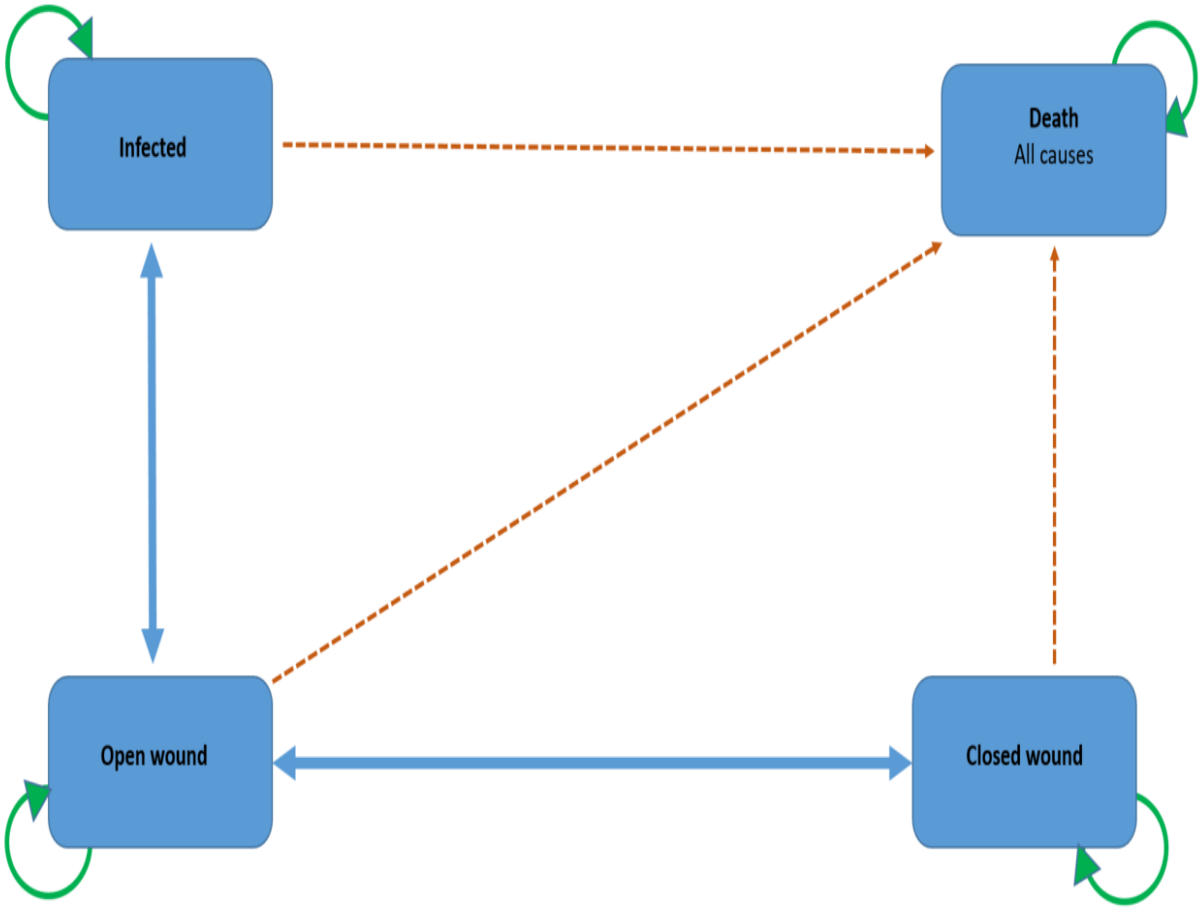
Patients - wound closure model

The wound closure model could be suitable for all chronic wounds. The literature demonstrating the impact of Prontosan on wound closure is reported as two comparative studies in Venous Leg Ulcers (VLUs) (Andriessen and Eberlein 2008; Harding 2012); as such this model is utilising VLUs only. The Markov models have been populated separately, using transition probabilities from the above two studies. Data from the two Markov models are presented as “Harding” and “Andriessen”.

Model structure - wound closure model

The economic model for wound closure is a Markov model with 4 wound states: open, closed, infected and death of the patient by any cause; these cover the principle of wound healing as a continuum in which wounds can improve and regress over time and may reoccur (Figure 1). Amputation has been reported previously by NICE as more commonly associated with diabetic foot ulcers - accounting for 80% of amputations (NG 19: Diabetic foot problems: prevention and management). Amputation was not included in this model as this is not a common occurrence for VLUs; this is a conservative assumption from the perspective of treatment on impact to healing. The model starts with 70% of VLUs in the open state and 30% in the infected state, this is based on UK data for VLUs (Guest, Fuller, and Vowden 2018). The open wound can become infected. Infected wounds can resolve and return to the open state. An open wound can heal and become closed. A closed wound can reoccur and become open again. An infected wound cannot close until the infection has resolved and must move to the open state first before closing. In all health states patients have a risk of death by any cause. In this model different resource use is assigned to the different wound conditions, with an infected wound incurring more resource than an open wound, which in turn incurs more resource than a closed wound. As taken from the perspective of healthcare resource; death is assumed to be not cost incurring. The wound closure model compares use of Prontosan Solution and Gel X compared with saline (or tap water in the sensitivity analysis).

Figure 1 Wound closure Markov model



Assumptions in Wound closure model

Table 1 Assumptions in Wound closure model

Assumption	Justification	Source
All patients start in one of the two open wound states (open or infected)	In line with how VLU wounds first present to health care professional.	(Guest, Fuller, and Vowden 2018)
30% of wounds start as infected	At initial presentation, 18% of VLUs reported as infected and a further 12% of VLUs prescribed an anti-infective.	(Guest, Fuller, and Vowden 2018)
Death is not cost incurring		
Mean VLU is 52.3 cm^2	Based on average wound sizes for VLU as reported from UK data.	(Guest, Fuller, and Vowden 2018)
One sachet of saline (25ml or 20ml) used as standard per dressing change for a 52.3cm^2 VLU	Clinicians provided opinion that 1 sachet would be used for an average sized wound.	Clinical expert opinion Dec 2020
Intervention group utilised Prontosan Solution and Gel X	Addition of both for every wound is more cost incurring and stresses robustness of model.	Clinical expert opinion December 2020
40ml Prontosan Solution per dressing change for a 52.3cm^2 VLU	Smallest volume able to be purchased and volume suitable to soak gauze for the average VLU size.	Drug Tariff December 2020, Clinical experts
2mm thick Prontosan Gel X used per application for a 52.3cm^2 VLU	2mm taken as an average for flat wounds such as VLUs.	Clinical expert opinion December 2020 and company advice
Practice nurse appointment 15 minutes	Nationally reported standard appointment time.	(Phillips et al. 2015)
Community nurse appointment 20 minutes	Clinical experts reported 20-30 average appointment time. The shorter time makes the model more conservative.	Clinical expert opinion December 2020 PSSRU 2008

Clinical parameters wound closure model

Two clinical studies compare the use of Prontosan with saline and measure wound closure, both of the studies were completed in VLUs and are suitable for use in this model. The first is an unpublished, double blind, pilot RCT, not powered for significance (n=37), undertaken in the UK, reporting on healing and infection rate (Harding 2012). The results from this study are referred to as "Harding" The second is a larger comparative study (n=119), which ran for 6 months, reporting on healing rate and infection rate (Andriessen and Eberlein 2008). The results from this study are referred to as "Andriessen". In the UK a mixture of either saline and/or tap water can be used for

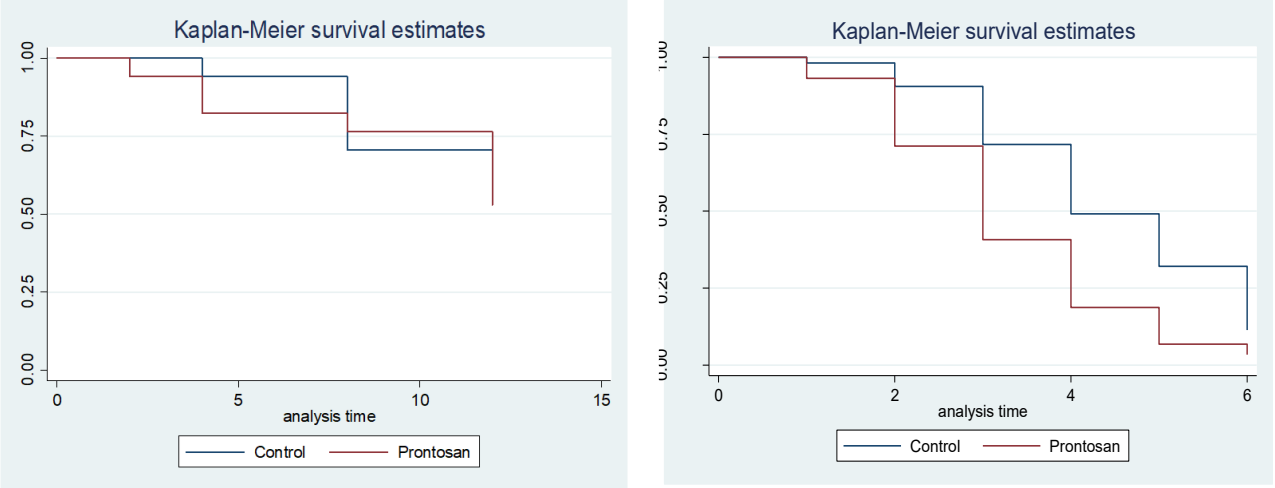
wound irrigation; a Cochrane report concluded that tap water and saline had the same impact and were equivalent (Fernandez and Griffiths 2012). These models are transferable for clinicians using tap water for irrigation and tap water use is covered in the sensitivity analysis by applying cost of £0.00 to the comparator.

Healing rate

As is common in wound care modelling and where the study time frames do not match model time frames, parametric survival models have been used to estimate the underlying 'hazard' of healing and the incremental impact treatment has over time. Figure 2 shows the associated Kaplan-Meier graphs for Harding (2012) and Andriessen and Eberlein (2008). Please note that in Harding the time dimension is measured in weeks whereas in Andriessen it is months.

Figure 2 Kaplan Meier survival estimates

Harding (2012) **Andriessen and Eberlein (2008**



For each study, a parametric survival model was estimated using Stata 14.1 and assuming an exponential hazard from treating unhealed wounds as censored observations. Results indicate an estimated hazard ratio equal to 1.655 and 1.455 for Prontosan for Harding (2012) and Andriessen and Eberlein (2008) respectively (table 2), relative to saline treatment. The 95%CI for the Harding (2012) study is not indicative of a significant difference, which is unsurprising due to the study size. Whereas the 95%CI for the Andriessen and Eberlein (2008) just overlaps 1 when expressed to three decimal places and is very close to indicating a significant difference in treatment effects between Prontosan and saline (and would be significant at a 10% level of significance).
This available evidence provides a point estimate of wounds healing at 1.46 - 1.66 times faster, using Prontosan relative to treatment with the saline control. Note that the constant terms differ across models mainly due to the difference in the metric of time (weeks or months).

Table 2 Hazard ratio for wound healing

		Haz. Ratio	Std. Err.	z	P>z	L95% CI	U95% CI
Harding (2012)	Prontosan	1.655	0.944	0.880	0.377	0.541	5.059
	Constant	0.028	0.012	-8.010	0.000	0.012	0.067
Andriessen and Eberlein (2008)	Prontosan	1.455	0.287	1.900	0.057	0.989	2.141
	Constant	0.201	0.029	-11.000	0.000	0.151	0.267

To calculate monthly probabilities, the natural log of data in table 2 were generated (table 3), the resulting Beta, standard error and confidence intervals were used to calculate: constant hazard ratio (h) and the cumulative survival (non-healed) function over time (in weeks) as S.

Calculation 1

$$h(t|x_j) = \exp(\beta_0 + x_j\beta_x)$$
$$S(t|x_j) = \exp\{-1\exp(\beta_0 + x_j\beta_x)\,t\}$$

Next the probability of healing between time t and time t+1 was calculated as:

Calculation 2

$$p = \left(1 - \frac{S(t+1)}{S(t)}\right)$$

Table 3 Log relative hazard data

In log relative Hazard form							
Study	RCT Survival Reg (exponential PH)	Beta	Std. Err.	z	P>z	L95% CI	U95% CI
Harding (2012)	Prontosan (β1)	0.504	0.570	0.880	0.377	-0.613	1.621
	Constant (β0)	-3.584	0.447	-8.010	0.000	-4.460	-2.707
Andriessen and Eberlein (2008)	Prontosan (β1)	0.375	0.197	1.90	0.057	-0.011	0.761
	Constant (β0)	-1.605	0.146	-11.00	0.000	-1.891	-1.319

The estimation results from Harding (2012), suggest monthly healing probabilities of 10.5% and 16.8% for saline and Prontosan respectively, with a mean healing time of 21.75 weeks if treated with Prontosan and 36 weeks if treated with saline. The estimated results from the Andriessen and Eberlein (2008) study suggest a monthly healing probability of 18.2% and 25.4% for saline and Prontosan respectively with a mean healing time is 4.98 months (20 weeks) for control and 3.42 months (13.5 weeks) for Prontosan.

Other clinical parameters

The study by Valenzuela and Perucho (2008) reported infection resolution occurred in 33.33% and 51.92% of wounds treated with saline and Prontosan respectively for two weeks. This data was converted to rate of infection resolution per week and then to probability per month as per the calculation 3.

In the UK it is reported that 3% of patients with a chronic wound die within the year (Guest et al. 2017), this annual data was converted into a monthly probability as below.

VLUs can reoccur; in the UK a large study (n=1324) reports 17% reoccurrence of a VLU within the year (Gohel et al. 2005). This annual data was converted into a monthly probability (calculation 3).

For infection, infection resolution, death and recurrence the overall results were provided over time; this data was transformed into a rate then expressed as a probability per calendar month as described in calculation 3.

Calculation 3

Probability to rate

$$\text{Rate} = \frac{-\ln(1-p)}{t}$$

p=probability
t = time
r = rate

Rate to probability

$$\text{Probability} = 1 - exp^{(-rt)}$$

Table 4 Transition probabilities Harding wound closure model

Harding wound closure model						
		Open	Healed Wound	Infected	Death (by any causes)	Sum of Probability
Prontosan	Open	0.73713	0.16800	0.09233	0.00254	1.00000
	Healed Wound	0.01553	0.98193	0.00000	0.00254	1.00000
	Infected	0.79542	0.00000	0.20204	0.00254	1.00000
	Death	0.00000	0.00000	0.00000	1.00000	1.00000
Saline	Open	0.82475	0.10500	0.06771	0.00254	1.00000
	Healed Wound	0.01553	0.98193	0.00000	0.00254	1.00000
	Infected	0.58460	0.00000	0.41286	0.00254	1.00000
	Death	0.00000	0.00000	0.00000	1.00000	1.00000

Table 5 Transition probabilities Andriessen wound closure model

Andriessen and Eberlein wound closure model						
		Open	Healed Wound	Infected	Death (by any causes)	Sum of Probability
Prontosan	Open	0.73827	0.25346	0.00573	0.00254	1.00000
	Healed Wound	0.01553	0.98193	0.00000	0.00254	1.00000
	Infected	0.79542	0.00000	0.20204	0.00254	1.00000
	Death	0.00000	0.00000	0.00000	1.00000	1.00000
Saline	Open	0.79216	0.18197	0.02333	0.00254	1.00000
	Healed Wound	0.01553	0.98193	0.00000	0.00254	1.00000
	Infected	0.58460	0.00000	0.41286	0.00254	1.00000
	Death	0.00000	0.00000	0.00000	1.00000	1.00000

Resource Identification measurement and valuation

Resource use

Chronic wounds are primarily treated in the community and as such do not have any ICD or OPCS codes related to wound care. A literature search was performed to look for resource use regarding wound care in the UK. Search information is in Appendix B, 19 studies relevant to the scope were identified. These studies estimate the resource costs for treating wounds in the UK.

Two UK papers with resource use specific to VLUs were identified (Phillips et al. 2020; Guest, Fuller, and Vowden 2018) and a more recent paper reporting wound burden with information on VLUs was also identified (Guest, Fuller, and Vowden 2020). While these papers report the burden of VLUs, they did not differentiate between ‘wound states’ or report on parameters related to the continuum of wound healing, rather, grouped data was presented. Many assumptions would need to be made to utilise these grouped data. Another UK paper was identified, which reported weekly cost per “leg ulcer” defined by wound status: healed, progressing, static, deteriorating or infected

(Harding, Posnett, and Vowden 2013). Due to this well-defined data on resource use by wound condition, the paper by Harding, Posnett and Vowden (2013) has been used to inform the monthly cost in the model. Data was validated against the other papers (Phillips et al. 2020; Guest, Fuller, and Vowden 2018; Guest, Fuller, and Vowden 2020); validation is discussed later in this section.

Weekly leg ulcer costs were reported by Harding, Posnett and Vowden (2013) at 2008/2009 costs for each of the wound conditions. Cost of healthcare professional (HCP) visits were reported per week, split by each wound condition. From this, number of visits per week were calculated (table 6) by dividing the weekly HCP cost presented by Harding, Posnett and Vowden (2013) by the healthcare cost per visit reported in 2008/2009 (Curtis 2008). Healthcare professional costs were increased to 2018/2019 (table 7) by multiplying the calculated weekly HCP visit number by the visit cost as reported using PSSRU 2018/2019. As recent UK resources papers (Guest 2020) reported minimal hospital admission for VLUs, the cost of hospital admissions were removed from this model; this mostly impacted the infected wound cost by reducing it. The remaining resource use costs (excluding HCP and hospital admission) were inflated using the HCHS (2008-2015) and NHSCII Prices (2015-2019) inflation index (Curtis 2018). Weekly data was converted to monthly data by multiplying weekly data by 52 then dividing by 12. Monthly cost used in the model can be found in table 6 and data is separated into HCP cost and other (non-hospital admission cost) in table 7. 95%CI were calculated on 2008 resource data and used to calculate 95%CI for the inflated data (table 6). In the model, healed and infected costs (“severe”) were used directly. For the “open” wound state, a weighted mean was calculated from “progressing, static and deteriorating” (table 6 and 7).

Table 6 resource use by wound state

	Weekly cost (95%CI) Harding, Posnett and Vowden (2013)	**Inflated monthly** cost to 2018/2019 prices (95%CI)	**Monthly** number of HCP visits
Healed	£6.04 (£5.73-£6.35)	£42.87 (£40.65-£45.10)	0.343
Progressing	£87.55 (£86.41-88.69)	£566.10 (£558.50-£573.24)	9.891
Static	£100.30 (£98.59-£102-00)	£655.55 (£644.59-£666.86)	10.993
Deteriorating	£159.43 (£157.28-£161.58)	£796.71 (£785.85-£807.36)	13.571
Severe	£637.13 (£402.03-£872.23)	£2,034.15 (£1,283.52-£2,784.64)	14.177

Technology use

An average cost per dressing change for Prontosan Solution was calculated based on 40ml per application as the smallest volume available to purchase and clinical expert opinion. The Drug Tariff January 2021 cost of Prontosan Solution is £5.03 for a 350ml bottle and available in 40ml ampoules (24 x 40ml £14.93, £0.62 per 40ml ampoule).

[redacted]. The more viscous Prontosan Gel X is the most appropriate of the gel products to use on large flat wounds such as VLUs. The amount of Prontosan Gel X used per dressing change is estimated using a 2mm thickness of Gel X and an average VLU size of 52.3cm^2 (Guest, Fuller, and Vowden 2018). Saline is purchased in single use sachets of typically 20-25ml. Clinical experts reported that a single sachet would be used to irrigate wounds at each dressing change. According to NHS drug tariff, saline is available as follows: Irripod; 25 x 20ml £5.90 cost per 20ml sachet £0.24, Steripod; 25 x 20ml £5.07 cost per 20ml sachet £0.20 and Normasol; 25 x 25ml £6.62 cost per 25ml sachets £0.26, the average of these costs have been applied at £0.23. Number of HCP visits per month, determined by wound state, were calculated above (table 6) and each visit was assumed to result in a dressing change and used to calculate cost of the technology (Prontosan or comparators) per month based on wound condition (table 7). As tap water is reported as being used to irrigate wounds in the UK, the impact of a cost of £0.00 is included in the sensitivity analysis.

Table 7 Monthly resource and treatment cost by wound state

	Resource TOTAL cost	Treatment	Treatment cost	Total cost
Healed	**£42.87**	Prontosan	£0.00	**£42.87**
		Saline	£0.00	**£42.87**
Open	**£635.76**	Prontosan	£29.54	**£665.3**
		Saline	£2.69	**£638.45**
Infected	**£2,034.15**	Prontosan	£31.59	**£2,065.74**
		Saline	£3.32	**£2,037.47**

Adverse event costs

Costs of infections as a complication are included as described in table 7. Conservative infection cost as hospital costs estimated at inflated costs of £1,281.28 per month was excluded due to discrepancies in resource data and hospital admission for VLU described above.

Table 8 Other parameters in the model

Parameter	Description	Justification	Source
Time horizon	1yr provided	UK papers report over a 12 month period	(Guest, Fuller, and Vowden 2020)
Discount rate	N/A	Time horizon less than 1 year	NICE
Cycle length	1 month	National Wound Care Strategy Lower Limb recommendations are for assessment at 4 weeks.	Clinical expert opinion (NWCSP 2020)

Results – wound closure model

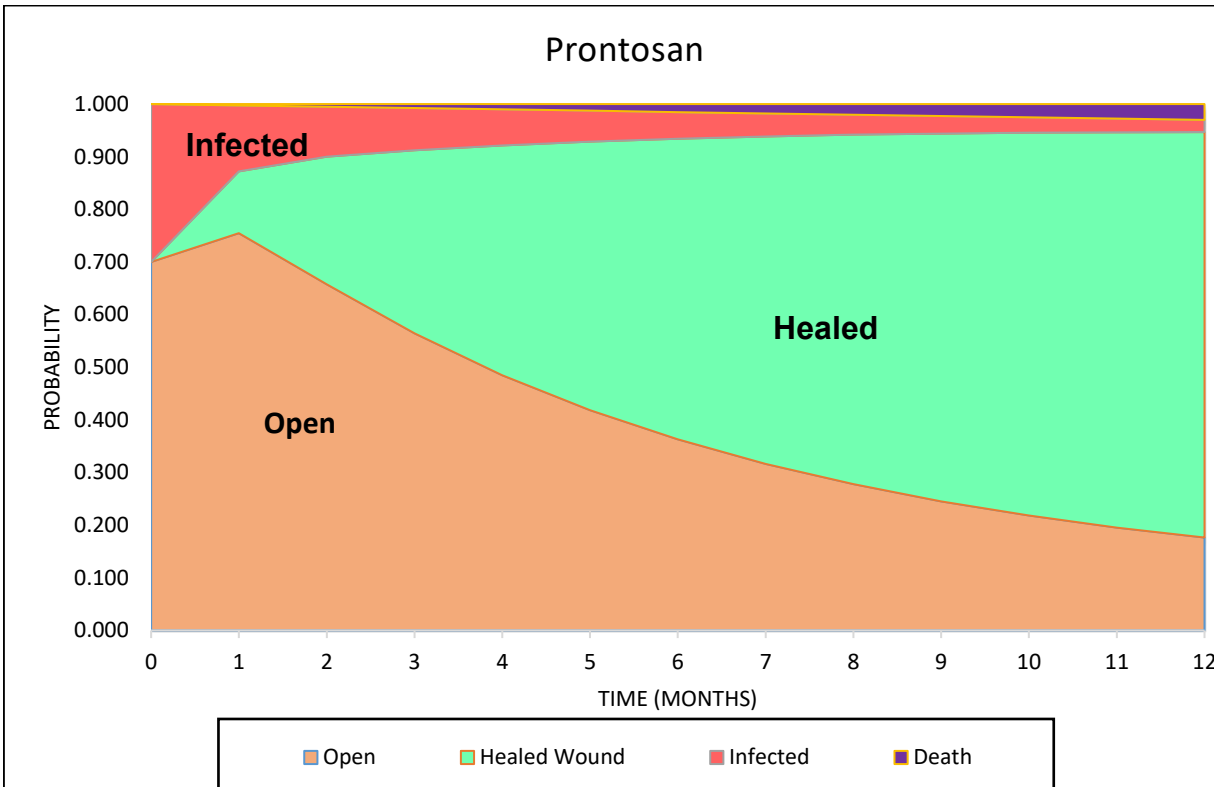
Results are presented for the wound closure model based on VLUs. Markov traces for both data sets are provided in figures 3 and 4. These indicate that the models are driven by faster wound healing in the Prontosan group, with lower probabilities of the wound being infected in the Prontosan group compared with saline.

Reflecting the Markov trace, the cost comparison indicates Prontosan is a cost saving option compared with the standard saline. Table 9 describes the cost for wound care over a 12 month period for Prontosan and saline based on the data sources for the model (Harding 2012; Andriessen and Eberlein 2008) reported as standard cumulative and cumulative with half cycle correction. Prontosan is cost saving in both models with incremental cost saving of £1,073.10 up to £1,188.47 annually per VLU patient compare with saline.

Table 9 Annual Results per patient

	Cumulative			Cumulative +half cycle correction		
	Prontosan	Saline	Increment	Prontosan	Saline	Increment
	Harding (2012) data					
Healthcare cost	£5,475.70	£6,757.56	**-£1,281.86**	£5,052.85	£6,396.27	**-£1,343.42**
Technology	£188.06	£21.57	**£166.49**	£175.61	£20.66	**£154.96**
Total	**£5663.76**	**£6,779.13**	**-£1,115.36**	**£5,228.46**	**£6,416.93**	**-£1,188.47**
	Andriessen and Eberlein (2008) data					
Healthcare cost	£3,702.70	£4,893.72	**-£1,191.02**	£3,223.41	£4,446.33	**-£1,222.92**
Technology	£133.85	£15.93	**£117.92**	£119.39	£14.73	**£104.65**
Total	**£3,836.55**	**£4,909.65**	**-£1,073.10**	**£3,433.04**	**£4,461.06**	**-£1,118.26**

Figure 3 Markov Trace Harding



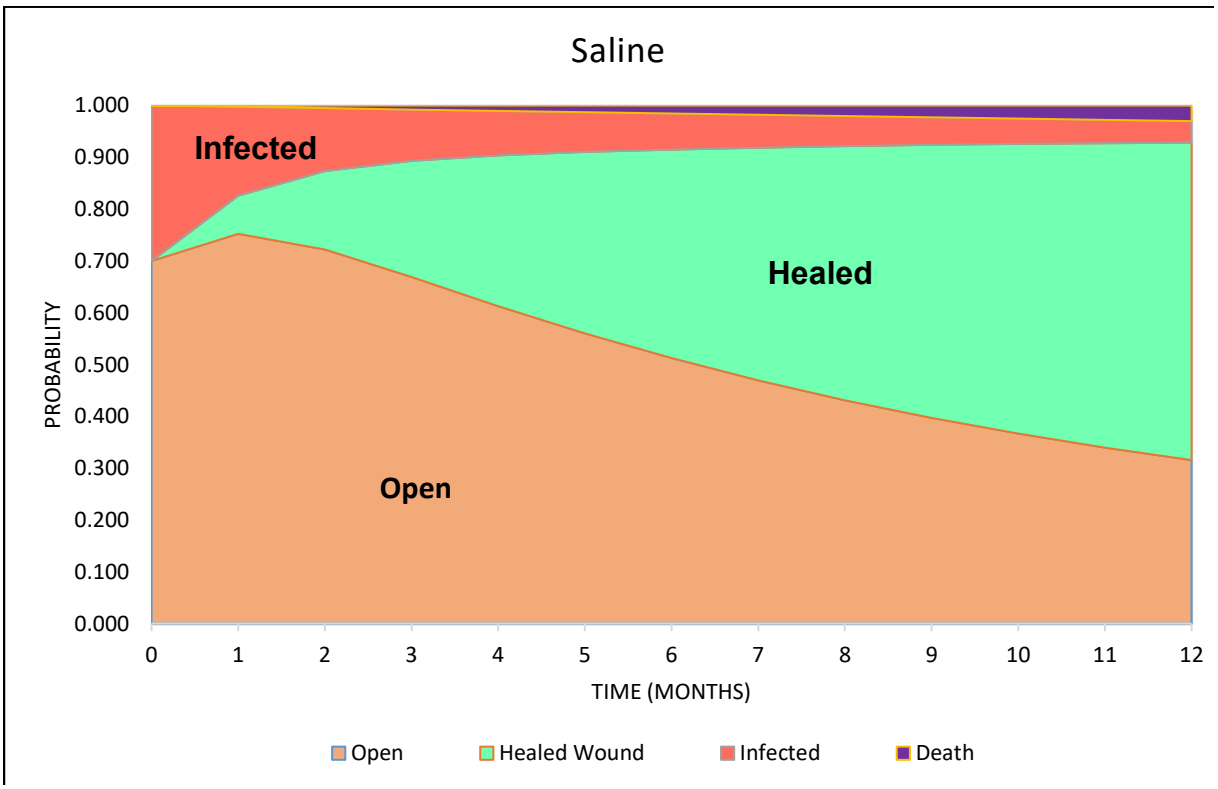
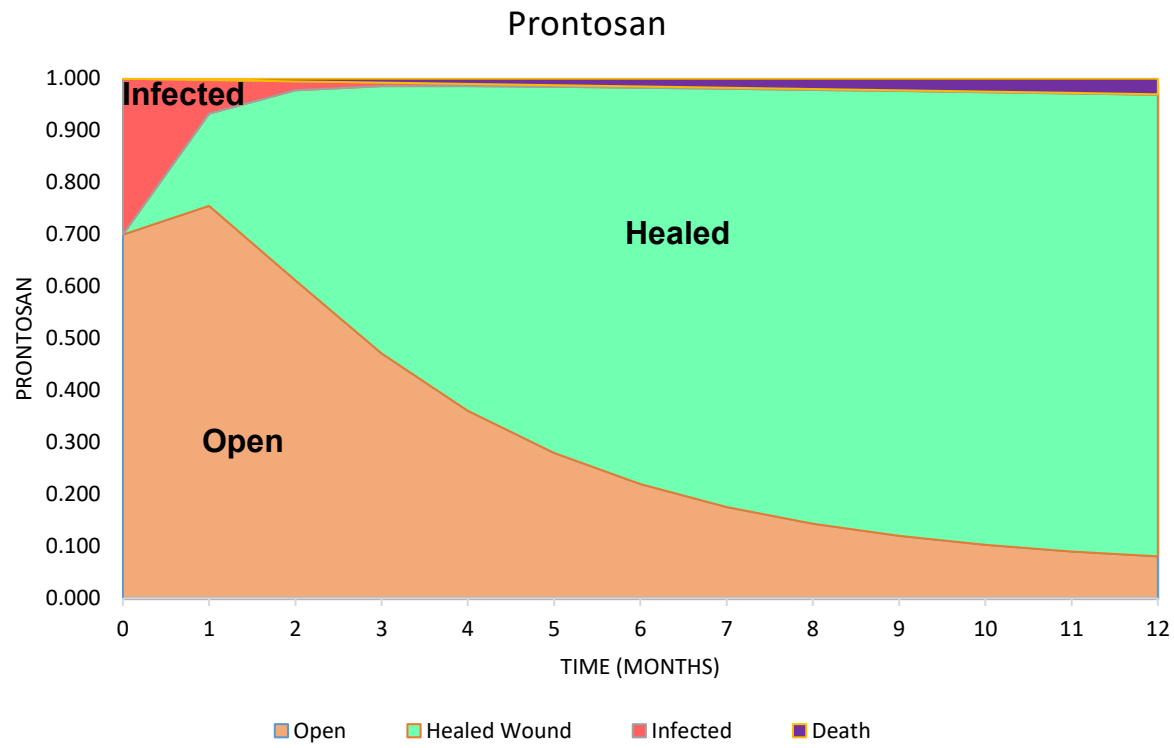
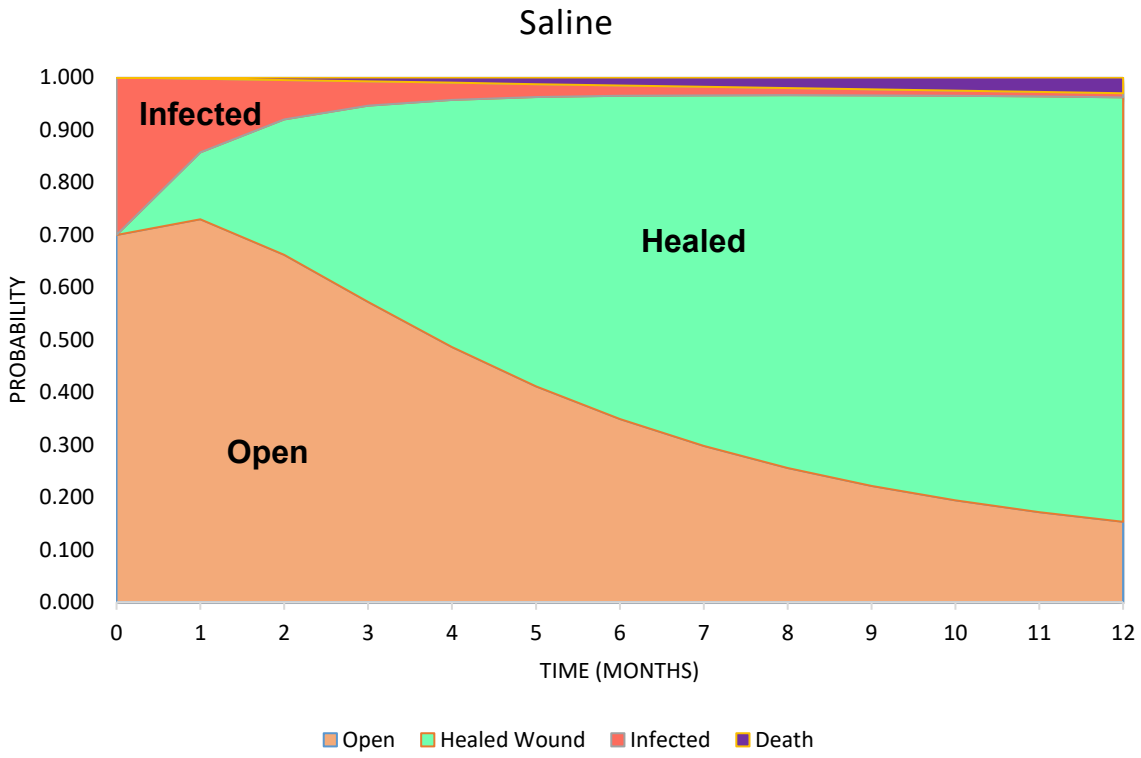


Figure 4 Markov Trace Andriessen



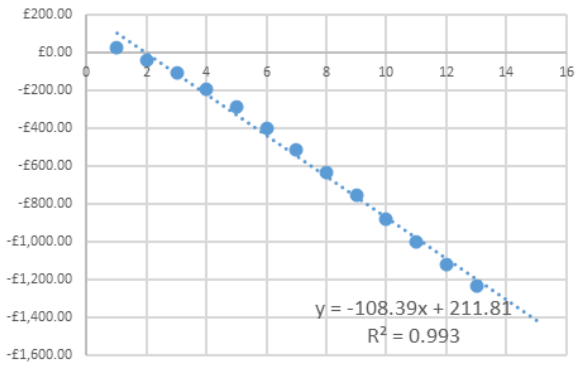


Estimated cost neutral

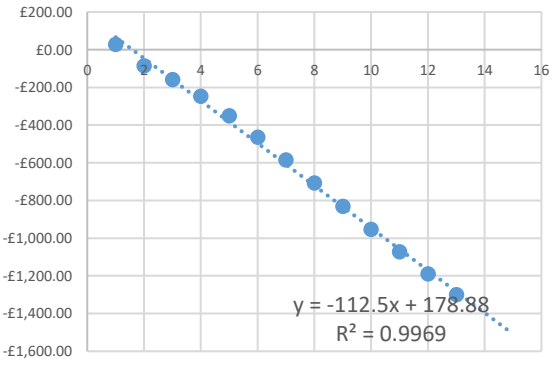
Time taken for Prontosan use to become cost neutral with use of saline (table 10) was estimated by plotting monthly incremental costs from the Markov model and fitting a linear regression (figure 5). Time to cost neutral estimates indicate that between 0.66 and 2.0 months (approximately 20 -60 days), health resource costs with Prontosan treatment become cost neutral with saline for the cumulative data. When analysing the cumulative data with half cycle correction, this reduces further (table 10).

Figure 5 Time estimation to cost neutral

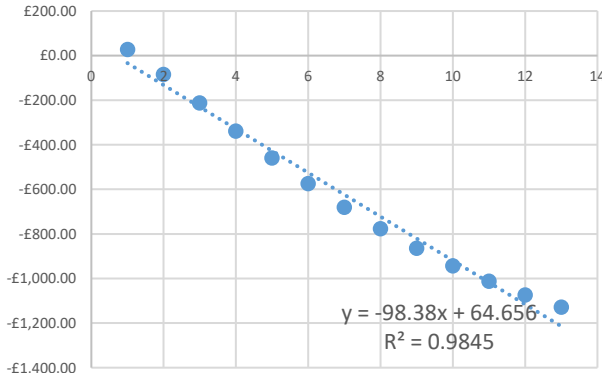
Harding, Cumulative



Harding, cumulative half cycle



Andriessen Cumulative



Andriessen Cumulative half cycle

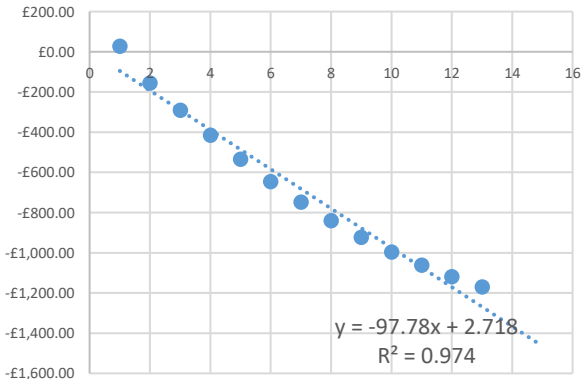


Table 10 Time estimation to cost neutral, wound closure model

	Time (months)	
	Harding Base case	Andriessen Base case
Cumulative total	1.954	0.657
Cumulative total cycle correction	1.590	0.028

Sensitivity Analysis

Transition probability sensitivity analysis

To explore uncertainty around the healing rate of Prontosan, upper and lower transition probabilities for Prontosan were calculated (Calculation 1), replacing the incremental impact estimate β_1 value with the log relative upper and lower 95%CI for Prontosan (table 3) (Harding β_1: L95%CI -0.613, U95%CI 1.621 and Andriessen β_1: L95%CI -0.11, U95%CI 0.761). This results in upper and lower monthly healing probabilities for Prontosan of: 5.84% and 43% in the Harding model and 18.02% and 34.95% for Andriessen model – baseline healing rates remain the same.

Infection rate and infection resolution rate did not have 95% CI available. Infection rate was varied by 30% and the infection resolution rate was varied by 25%. Rate of recurrence and death was not changed. Changing one parameter in the transition matrix had an impact on other parameters. Tables 10 and 11 describe the full transition matrix used as each of the parameters (healing rate, infection rate and infection resolution) were changed individually and reflects impact of the individual changes in the other parameters in the matrix.

Table 11 Upper and lower transition probabilities in sensitivity analysis, Harding

	Lower			Upper		
	Open	Healed	Infected	Open	Healed	Infected
	Healing lower			Healing upper		
Open	0.84674	0.05839	0.09233	0.47511	0.43002	0.09233
Healed	0.01553	0.98193	0.00000	0.01553	0.98193	0.00000
Infected	0.79542	0.00000	0.20204	0.79542	0.00000	0.20204
	-25% infection resolution			+25% infection resolution		
Open	0.73715	0.16799	0.09233	0.73715	0.16799	0.09233
Healed	0.01553	0.98193	0.00000	0.01553	0.98193	0.00000
Infected	0.59657	0.00000	0.40090	0.99428	0.00000	0.00319
	-30% infection rate			+30% infection rate		
Open	0.76484	0.16799	0.06463	0.70945	0.16799	0.12003
Healed	0.01553	0.98193	0.00000	0.01553	0.98193	0.00000
Infected	0.79542	0.00000	0.20204	0.79542	0.00000	0.20204

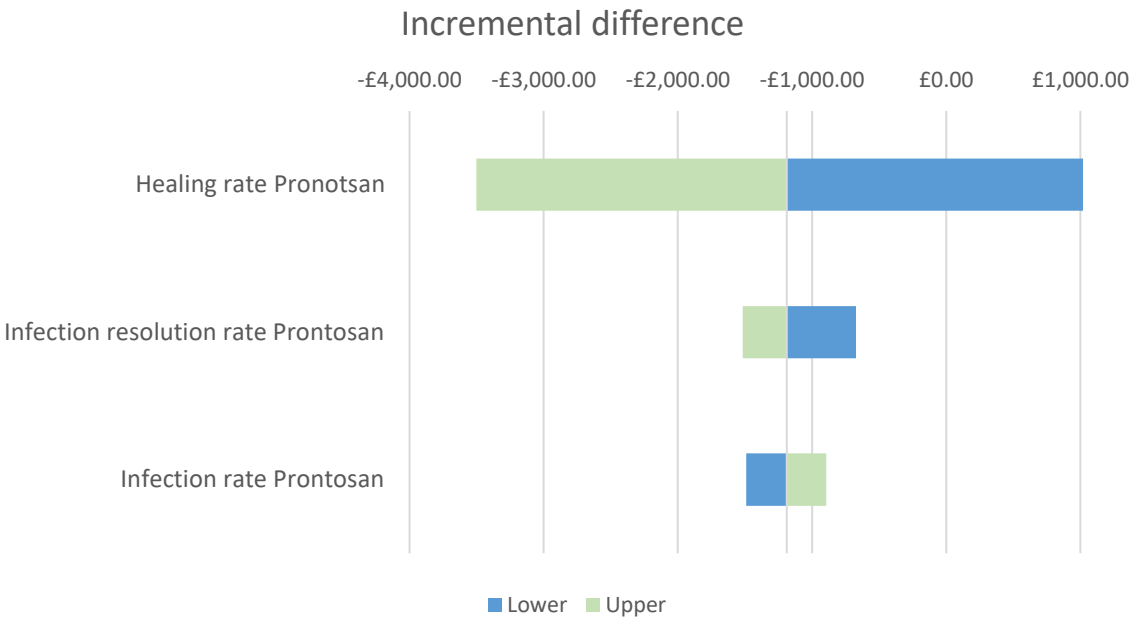
Table 12 Upper and lower transition probabilities in sensitivity analysis, Andriessen

	Lower			Upper		
	Open	Healed	Infected	Open	Healed	Infected
	Healing lower			Healing upper		
Open	0.81155	0.18018	0.00573	0.64219	0.34954	0.00573
Healed	0.01553	0.98193	0.00000	0.01553	0.98193	0.00000
Infected	0.79542	0.00000	0.20204	0.79542	0.00000	0.20204
	-25% infection resolution			+25% infection resolution		
Open	0.73827	0.25346	0.00573	0.73827	0.25346	0.00573
Healed	0.01553	0.98193	0.00000	0.01553	0.98193	0.00000
Infected	0.59657	0.00000	0.40090	0.99428	0.00000	0.00319
	-30% infection rate			+30% infection rate		
Open	0.73999	0.25346	0.00401	0.73655	0.25346	0.00745
Healed	0.01553	0.98193	0.00000	0.01553	0.98193	0.00000
Infected	0.79542	0.00000	0.20204	0.79542	0.00000	0.20204

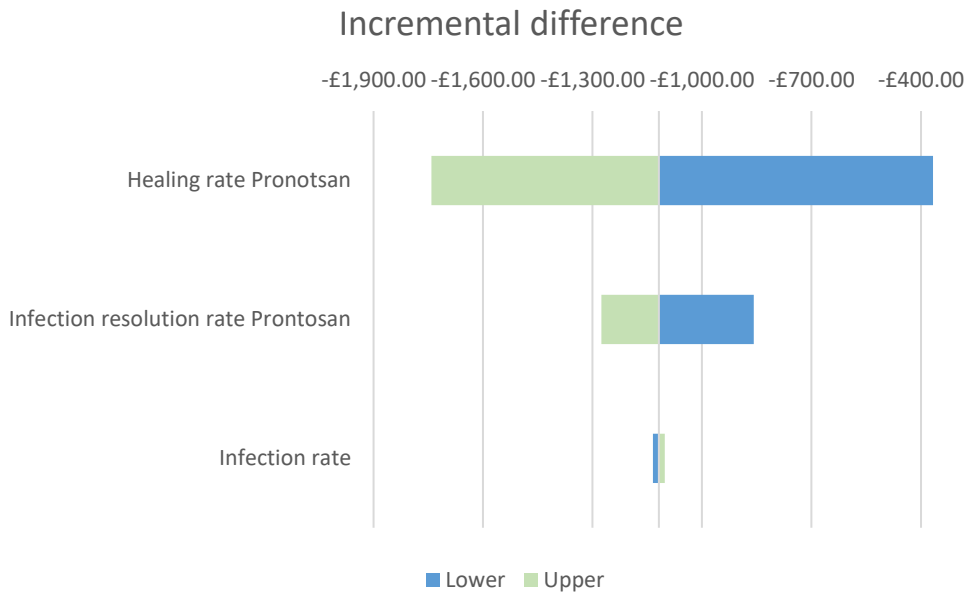
Results were similar for cumulative half cycle and cumulative. Tornados for cumulative half cycle are shown in figure 6, results for cumulative data can be found in Appendix C. When each of the transition parameters is varied by the upper and lower limits, Prontosan remains cost saving for all results in the Andriessen model (figure 6). Prontosan remains cost saving for all variants except healing rate in the Harding model (figure 6). These results are not surprising due to small study population in the Harding study (n=37) resulting in large error and 95%CI estimates, whereas for the larger study by Andriessen and Eberlein (n=119) the 95%CI (0.989) was very close to crossing 1, indicating significant impact of Prontosan on healing rate.

Figure 6 Tornado transition probabilities cumulative half cycle

Harding



Andriessen



Sensitivity analysis - Threshold analysis

Uncertainty around healing rate was tested by threshold analysis (figure 7). For data from Harding and Andriessen, all transition parameters for Prontosan were set equal to the corresponding saline values from the study, providing cost impact of no difference in treatment effect (0%). Then, only the healing rate was changed and the cost impact of only healing rate (65.5% Harding and 45.5% Andriesen) was obtained. Plotting cost impact of 0% healing with cost of 65.5% or 45.5% for Harding and Andriessen respectively, allowed for increased healing effect needed for Prontosan to break even with saline to be calculated (Figure 7 and table 13).

Figure 7 threshold analysis

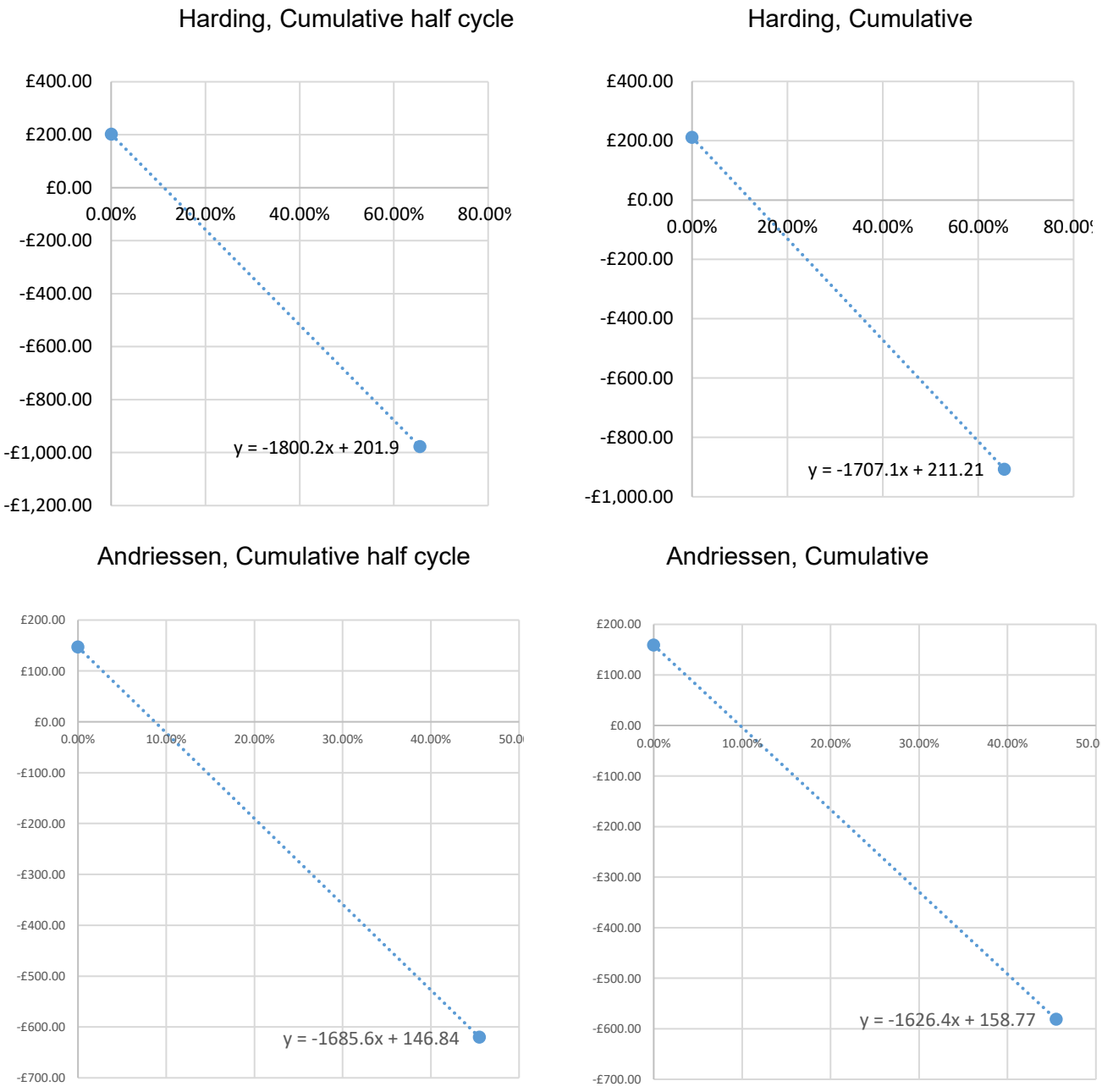


Table 13 Estimated healing rate required to break even with saline

	Harding	Andriessen
Cumulative	11.22%	8.71%
Cumulative half cycle	12.37%	9.76%

Threshold analysis shows a break even healing rate of 8.71%-9.76% for the Andriessen model and 11.22%-12.37% for the Harding model. The models returned an increased healing rate of 65.5% (SE 0.944) and 45.5% (SE 0.287) for Harding and Andriessen respectively, both of which are considerably higher than the estimated break even healing rates, indicating that Prontosan will achieve high enough healing rates to pass the breakeven threshold.

Sensitivity analysis – Univariate analysis

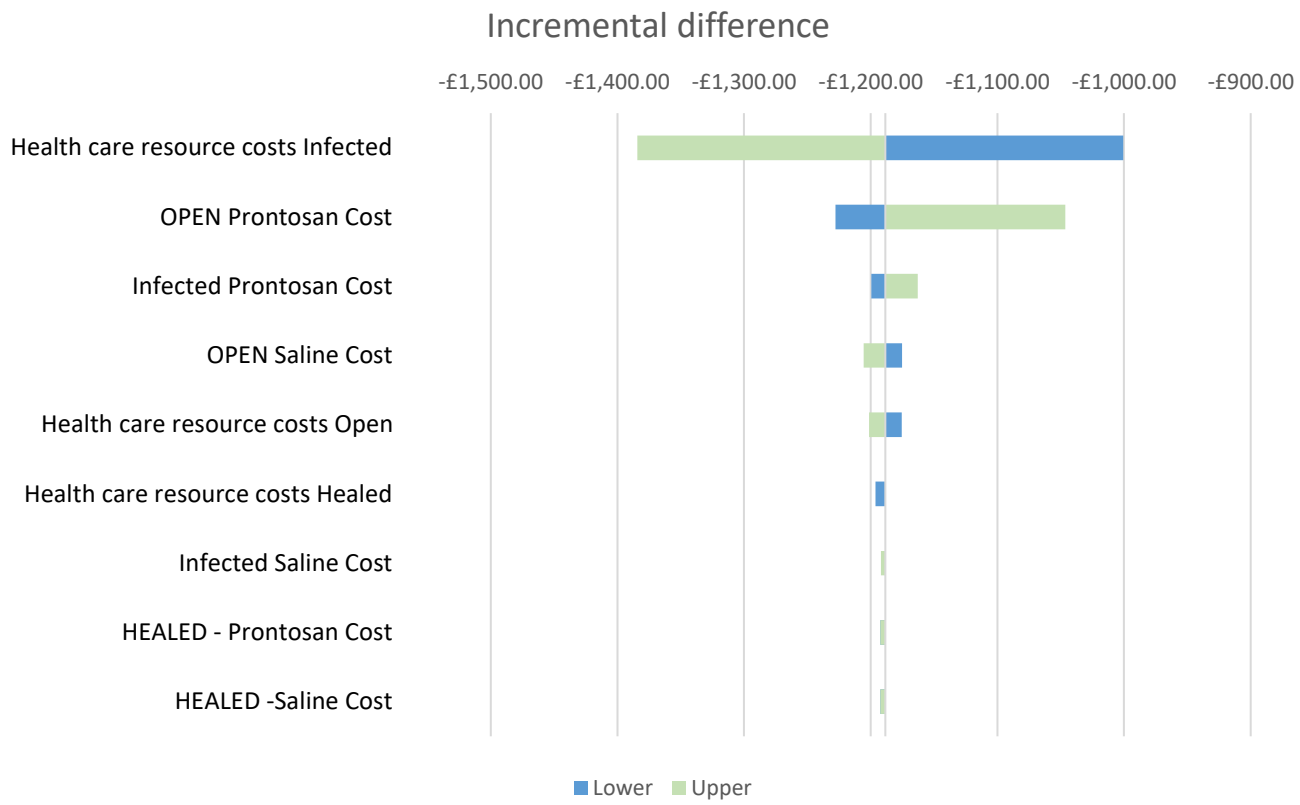
Deterministic one way sensitivity analysis was performed on healthcare resource cost and technology costs. Resource use costs were varied by calculating the 95% CI from the data provided in Harding, Posnett and Vowden (2013). Technology costs were the lower available cost of Prontosan and the upper banding was average cost of Prontosan +100%. The lower banding of saline was £0.00; indicative of tap water used for all wound irrigation and +100% saline cost for the upper banding. Upper and lower banding for resource cost are presented in table 14 and the impact on the incremental difference are expressed in figure 8 for cumulative half cycle. Similar results are seen in the cumulative data in Appendix D. The univariate sensitivity analysis revealed that when varying the technology costs, Prontosan remained cost saving over saline for all variable explored (figure 8).

Table 14 Upper and Lower banding for monthly resource and technology cost

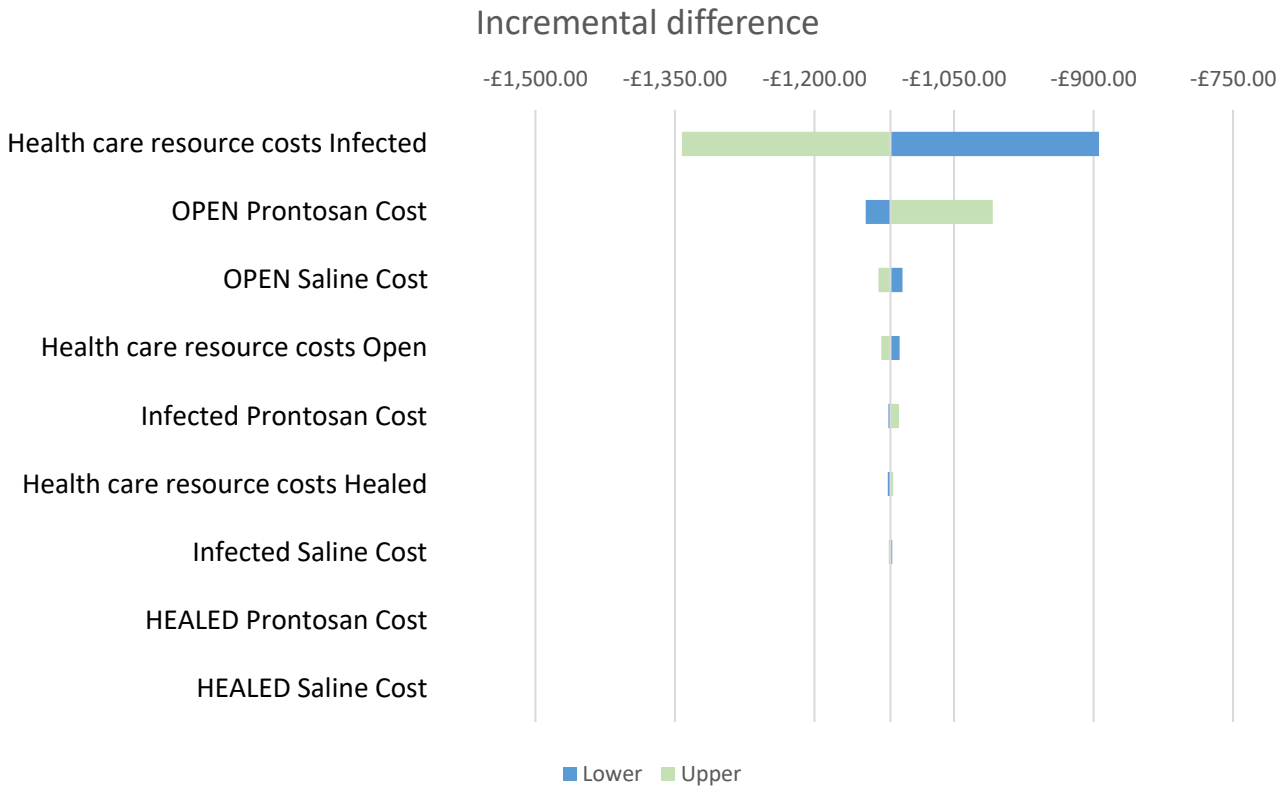
Parameter	Base case	Lower Banding	Upper banding
Healed resource cost	£42.87	£40.65	£45.10
Open resource cost	£635.76	£626.49	£644.88
Infected resource cost	£2,034.15	£1,283.52	£2,784.64
OPEN Prontosan Cost	£29.54	£22.41	£59.08
OPEN Saline Cost	£2.69	£0.00	£5.39
Infected Prontosan Cost	£36.46	£27.66	£72.93
Infected Saline Cost	£3.32	£0.00	£6.65
HEALED - Prontosan Cost	£0.00	£0.00	£0.00
HEALED - Saline Cost	£0.00	£0.00	£0.00

Figure 8 Tornado plots, resource use and technology Cumulative half cycle

Harding



Andriessen



Bivariate sensitivity analysis technology costs

Deterministic bivariate analysis was performed varying the cost of saline to be reduced to £0.00 (indicative of water use only) and the baseline price for Prontosan is + 100%. Table 15 shows the cost differential of implementing Prontosan with inclusion of saline at £0.00 or Prontosan at +100% and BOTH saline at £0.00 AND Prontosan at +100%.

Table 15 Bivariate Sensitivity analysis, Cost increment between technology

	Harding		Andriessen	
	Cumulative	Cumulative +half cycle correction	Cumulative	Cumulative +half cycle correction
Saline cost = £0.00	-£1,171.78	-£1,097.52	-£1,103.53	-£1,057.17
Prontosan cost + 100%	-£1,016.83	-£931.04	-£998.88	-£939.25
Saline cost = £0.00 AND Prontosan cost + 100%	-£996.16	-£909.47	-£984.14	-£923.32

With the assumption of no cost for current treatment and a 100% increase in Prontosan products, Prontosan still remains a net cost saving per patient when used until wound closure. It is therefore highly unlikely that savings would be reduced through any increase in costs of Prontosan or changes to comparator costs.

Sensitivity analysis conclusion

The sensitivity analysis reveals that Prontosan remains a net cost saving over saline when resource, infection rate and infection resolution rate are varied. The sensitivity analysis reveals that Prontosan remains a net cost saving over saline when healing rate is varied using the Andriessen data, however some uncertainty around impact of varying healing rate using the Harding data was identified. Uncertainty around the healing rate has been explored and both models predict an increased healing rate with treatment with Prontosan compared with saline by 46-66%; both of these results are far beyond the threshold healing rate required to break even with saline (9-12%) indicating that the model is robust to modelled scenarios.

Validation – wound closure model

Costs calculated in the models utilise monthly resources costs, calculated and inflated from weekly costs published by Harding, Vowden and Possnett (2013). Namely £42.87 per month for a healed wound, £635.76 per month for an “open” wound and £2,034.15 per month for an infected wound. The study by Harding, Vowden and Possnett (2013) is for “leg ulcers”, as such the numbers are validated here with other literature specific for VLUs. Annual average costs for VLUs are reported in the literature as £7,600 on average, £3,000 for a healed VLU and ranging between £10,777 up to £14,475 for an infected VLU per year (Guest, Fuller, and Vowden 2018). Weekly costs used in this

model correspond to £7,629.08 per year for an open wound, in line with published UK literature. VLUs are unlikely to spend 12 months in an infected state. From costs used in this model, if a VLU spent any 4 month period in the infected state, and the remaining months in the open state, the annual cost would be £13,222, this is in line with the published UK data. Literature around infection cost in the UK only describes wounds as having had an infection, duration and/or number of infections, per VLU, are not specified, therefore cost utilised here may be a conservative estimate. Clinical expert opinion varies on duration of infection, however consensus is these wounds are more costly to treat. In VLUs which heal, average healing time is reported at 3 months in the UK (Guest, Fuller, and Vowden 2018). If the monthly data used in this model is calculated for 3 months in the open state and 9 months in the healed state, the average annual cost of a healed VLU in this model is £2,293.12. All resource costs used in this model align with other reported burden costs for VLUs in the UK and the resource cost used are robust.

Clinical experts who were involved in validating the resource costs used in the model:

[redacted]

Clinical experts who were involved in validating Prontosan resource use in Practice Nurse setting

[redacted]

Wound Closure Model Summary

The cost analysis model shows implementation of Prontosan Solution and Gel X until wound closure offers net cost savings. The scenario analysis explored plausible range of assumptions about the baseline risk. The expectation that Prontosan is cost saving is robust to any of the modelled scenarios for: technology costs, infection rate and infection resolution rate - these were demonstrated as robust. The expectation that Prontosan is net cost saving is robust with data from the larger Andriessen and Eberlein study (n=112). Some uncertainty is shown from the small, unpublished RCT by Harding (2012) (n=34).

It is estimated that the annual investment per patient to introduce Prontosan Solution and Gel X, until wound closure for treatment of VLU, is £104.65-£166.49. This investment could result in an annual net cost saving of between £1,073.10 up to £1,188.47 per patient. (Table 9). Based on the cost analysis models, time to break even is estimated as less than 2 months of continual treatment (table 10), Prontosan is expected to be cost saving. These cost savings come from a reduction in healthcare resources needed due to a reduced time to healing.

Other things being equal, the net cost saving increases with the size of the healing rate. The break even for healing rate is 9-12% above saline, both studies inform healing rates far higher than this threshold (46-66% faster healing).

Budget impact on one CCG

Each CCG in the UK is estimated to cover an average of 250,000 patients (Guest et al. 2017) and recent studies estimate that 1.1% of the adult population has a VLU (Guest, Fuller, and Vowden 2020); this data would indicate that each CCG will have approximately 2,750 VLU patients. With an estimated net saving of £1,073.10 up to £1,188.47 per patient per year, if a CCG implemented Prontosan Solution and Gel X until wound closure, for the treatment of all VLU patients, for the investment of £287,787.50 up to £457,847.50 per year, the CCG could make a net saving between £2,951,025 up to £3,268,292 up to per year.

Wound bed Condition MODEL

This section shall deal with the model data, results and sensitivity analysis for wound bed preparation only

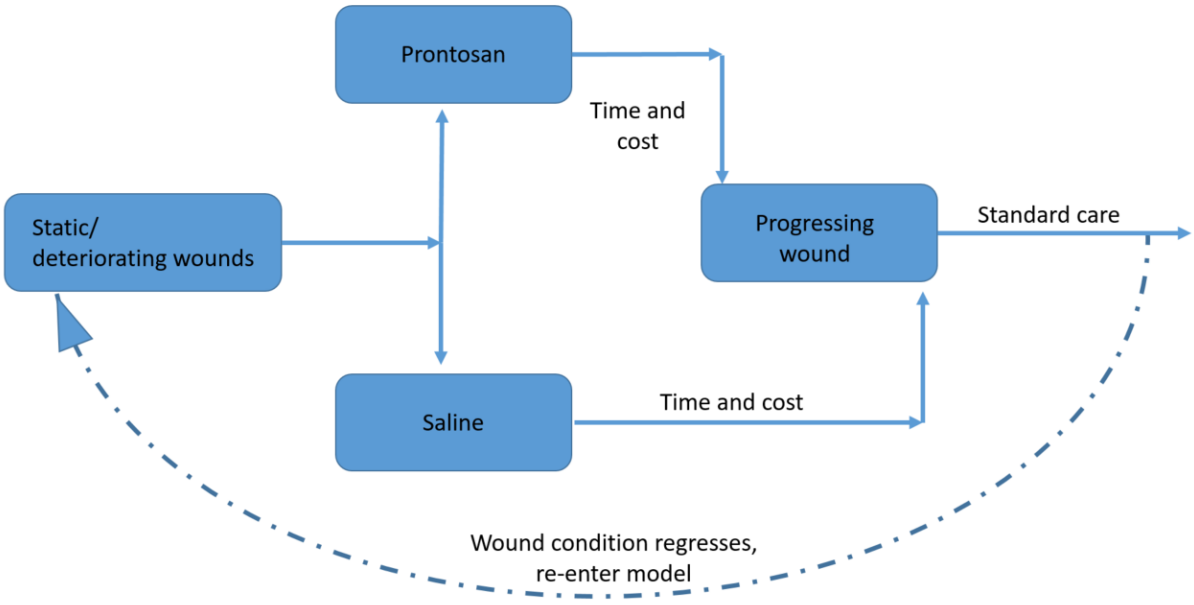
Patients - wound bed condition model

The wound bed condition model could be suitable for all chronic wounds, as all chronic wounds have their wound bed condition assessed at dressing changes and wound care treatment objectives change according to wound bed condition. The literature reporting on wound bed condition and Prontosan use covers: an RCT on venous leg ulcers; and pressure ulcers (Bellingeri 2016) as well as an RCT on wounds of mixed aetiologies (Valenzuela and Perucho 2008). As the Bellingeri et al (2016) study utilises a validated method for wound bed condition reporting (Bates-Jensen Wound Assessment tool), the model is set up using this data. Cost data comes from a UK study on leg ulcers, (Harding, Posnett, and Vowden 2013).

Model structure - wound bed condition model

This wound bed condition model is a price of therapy model, covering costs to achieve a good wound bed condition, indicative of progression to a “good” healthy wound which is progressing. The wound bed condition model covers use of Prontosan at a single point within the wound care treatment “life cycle”, and used to achieve a healthy, progressing wound condition. Wounds which are clinically “static” or “deteriorating” would enter the model, this includes wounds with the presence of any of the following: slough, excess exudate, markers of infection such as inflammation, malodour, necrosis or pain. In this wound bed condition model, Prontosan Solution and Prontosan Gel X are used at every dressing change until the wound condition is improved i.e. barriers to healing such as slough, excess exudate, markers of infection such as inflammation, malodour and/or pain are resolved and the wound condition improves to a healthy progressing wound. The wound bed condition model compares the cost of using Prontosan Solution and Gel X against using saline or water until the wound is healthy with a good wound bed condition (equivalent of BWAT 14). The lowest BWAT score available is 13, representing wounds which are 100% epithelialising and therefore in the very latter stages of wound healing (Halim, Khoo, and Mat Saad 2012), therefore scores of 14 would indicated wounds which are progressing to healing and are a suitable parameter for the model. After the wound condition is good/healthy it is assumed that all downstream care and costs are the same in both arms of the model, i.e. Prontosan treatment is stopped and standard care is continued for all wounds. The model does not cover impact on wounds deteriorating after treatment with Prontosan has stopped. If wounds deteriorate they would re-enter the model again as another incident of needing to improve the wound bed condition (Figure 8).

Figure 8 wound bed condition model



Assumptions in Wound bed condition model

Table 16 Assumptions in Wound closure model

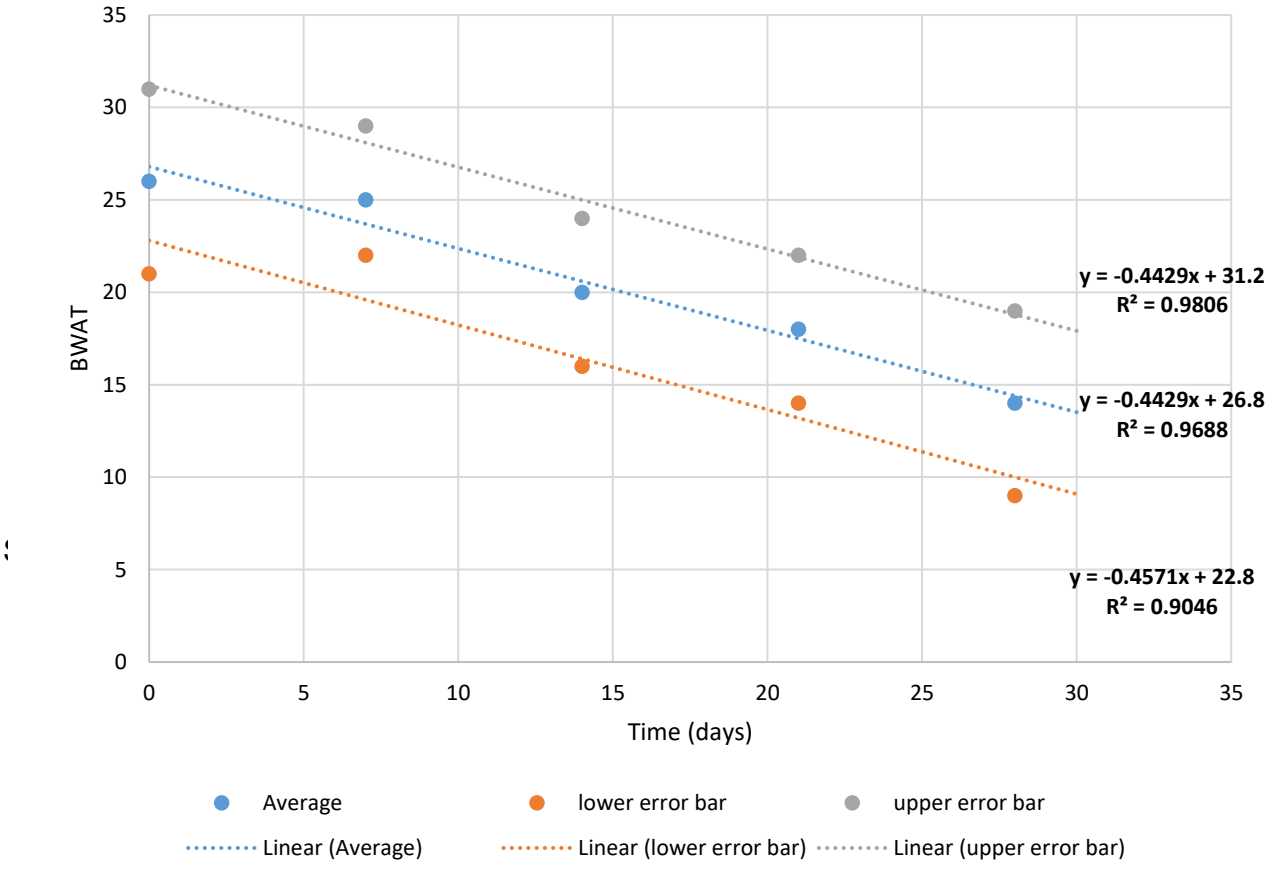
Assumption	Justification	Source
40ml Prontosan Solution per dressing change	Smallest volume able to be purchased and volume suitable to soak gauze for leg ulcers up to 52.3 cm^2	Drug Tariff Dec 2020 Clinical expert opinion December 2020
One sachet of saline (25ml) used as standard per dressing change	Clinicians provided opinion that 1 sachet would be used for an average sized wound	Clinical expert opinion December 2020
10g Prontosan Gel X used per dressing change	Gel X use will depend on size of wound. 10g is estimating for quite a large wound – circa 52.3cm^2 and 2mm thick gel per wound.	Clinical expert opinion December 2020 and company advice
Once wound is progressing cost of care is reduced	Weekly cost UK wound care cost in 2008 is reported as less for a progressive wound (£87.59) compared with a static wound (£100.27) or deteriorating wound (£159.45)	(Harding, Posnett, and Vowden 2013)
Once wound is progressing care and cost is the same for both arms and not included in model	Model represents impact on cost to achieve a healthy progressing wound only, cost will continue until wound healing but will be at a lesser extent	

Clinical parameters wound bed condition model

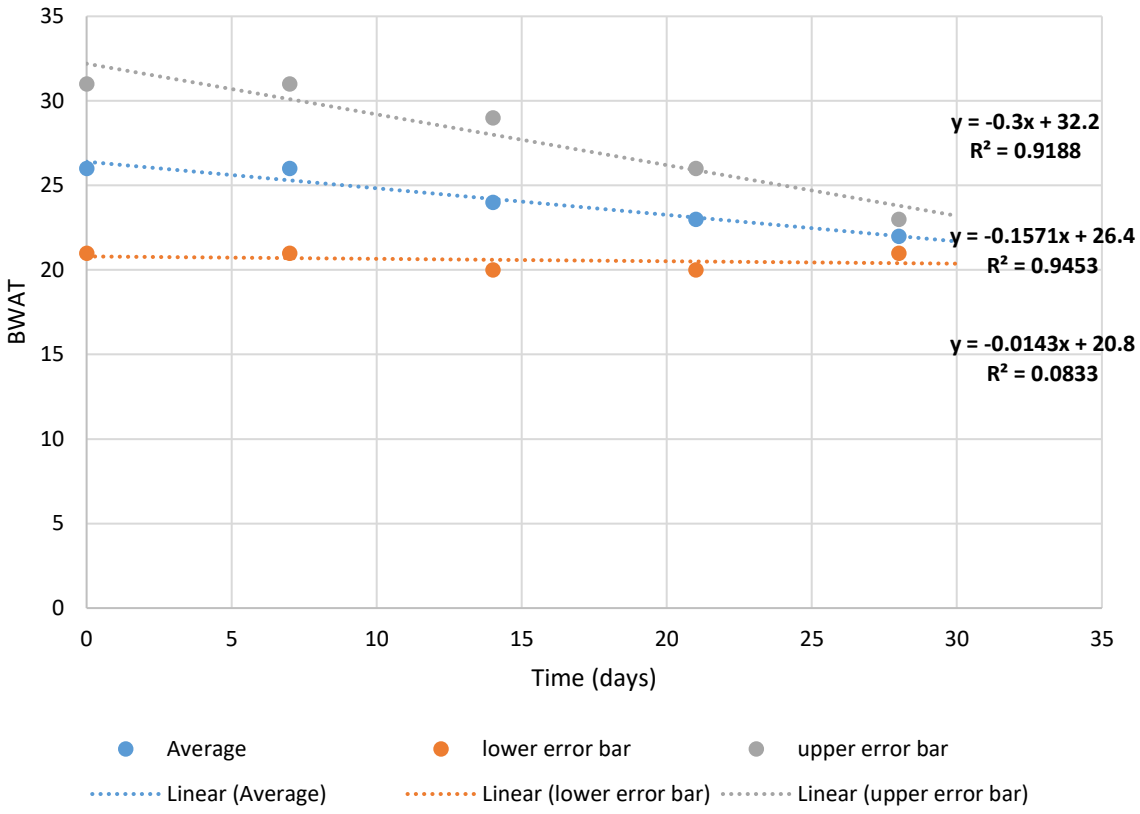
Two clinical studies compare the use of Prontosan with saline and measure wound bed condition (Bellingeri 2016; Valenzuela and Perucho 2008). Of these, Bellingeri et al (2016) uses a validated wound assessment tool to score wound bed condition - the Bates-Jensen Wound Assessment tool (BWAT) to report on wound bed condition. The RCT by Bellingeri et al (2016) report on use of Prontosan in VLUs and pressure ulcers (grades 2 or 3), reporting the average BWAT score repeated weekly over a 28 day period. Here the data from Bellingeri et al (2016) was extrapolated to estimate time to achieving a BWAT score of 14 in both arms of the study (figures 9). The lowest BWAT score available is 13, representing wounds which are 100% epithelialising and therefore in the very latter stages of wound healing (Halim, Khoo, and Mat Saad 2012), scores of 14 would indicated wounds which are progressing to healing and are therefore a suitable parameter for the model. The average, upper and lower error bars from the study were plotted separately for both study groups (Figure 9). Time (x intercept) when the wounds would be healthy and progressing (y=14) were calculated by applying line of best fit. The 95% CI around lines of best fit and intercepts were calculated by fitting linear regression using Graphpad Prism (version 8) (table 17).

Figure 9 Data extrapolation from Bellingeri et al (2016)

Prontosan



Saline



The lower error bars for the saline group returned very large estimates to achieve a healthy wound (estimated 475 days), with the 95%CI extending to infinity. Due to the overly large confidence intervals in the saline group, the 95%CI of the average was used as upper and lower limits for both groups. This was a reasonable estimation as the 95%CI time estimates for Prontosan closely matched the time estimates from the upper and lower error bars. The 95% CI estimated, offered more conservative time estimates for the Prontosan group and therefore is a reasonable data set to use in the sensitivity analysis.

Table 17 Clinical parameters, - Wound Condition model

Parameter/outcomes	Relevant results	Range	Source	How are these values used in the model?
Time to achieve BWAT 14 wound bed condition Prontosan	28.9 days	95% CI 19.25 to 38.84 days	(Bellingeri 2016)	Duration applied for Prontosan arm
Time to achieve BWAT 14 wound bed condition Saline	78.93	95% CI 58.68 to 130.6 days	(Bellingeri 2016)	Duration applied to comparator arms

Resource Identification measurement and valuation

Resource use

The same resource use from the wound closure model is used in the wound bed condition model (Harding, Posnett, and Vowden 2013). Inflated weekly cost (calculated previously for the wound closure model, with hospital admissions excluded) and number of health care visits from the "static" and "deteriorating" wounds were used to calculate a weighted average weekly cost and weighted average number of healthcare visits per week of wounds entering the wound bed condition model. The average starting score of the wounds in the Bellingeri et al (2016) study were BWAT = 26 (error bards 21-31) initially, representative that the wounds were assessed as having the presence of: excess exudate, necrotic tissue and slough (Bates-Jenson B.M. and Sussman 2012). Costs for wounds described as "severe" in Harding, Posnett and Vowden are not included, as "severe" was described as infected wounds and infected wounds were excluded in Bellingeri et al (2016).

Table 18 resource use

Resource Parameter	Relevant result	Source
Weighted average number of dressing changes per week for "static" and "deteriorating" leg ulcers	2.74	Calculated from (Harding, Posnett, and Vowden 2013)
Weighted average cost of weekly health care for "static" and "deteriorating" leg ulcers	£162.60 (£160.08 - £165.16)	Calculated from (Harding, Posnett, and Vowden 2013)

Technology use

The cost per dressing change for Prontosan Solution based on 40ml per application purchased as 40ml ampoules, use of 350ml bottles is included in the sensitivity analysis. The Drug Tariff January 2021 cost of Prontosan Irrigation Solution is £5.03 for a 350ml bottle and for 40ml ampoules (24 x 40ml £14.93, £0.62 per 40ml ampoule). The more viscous, Prontosan Gel X, is the most appropriate of the gel products to use on large flat wounds such as VLUs. Amount of Prontosan Gel X used per dressing changed is estimated at 10g per dressing change (approximate volume required for 2mm thickness of Gel X used on 52.3cm^2 wound). Saline is purchased in single use sachets. Clinical experts reported that a single sachet would be used to irrigate wounds at each dressing change. According to NHS drug tariff saline is available as follows: Irripod; 25 x 20ml £5.90 cost per 20ml sachet £0.24, Steripod; 25 x 20ml £5.07 cost per 20ml sachet £0.20 and Normasol; 25 x 25ml £6.62 cost per 25ml sachets £0.26, the average of these costs have been applied at £0.23. Number of HCP visits per month, determined by wound state, were calculated above and used to calculate cost of the technology (Prontosan or comparators) per month based on wound condition (table 6). As tap water is reported as used to irrigate wounds, the impact of a cost of £0.00 is included in the model.

Table 19 technology cost per dressing change

	Cost per dressing change	Total cost
Prontosan Solution 40ml pod	£0.62	£3.08
Gel X 10g	£2.46	
Prontosan Solution 350ml bottle per 40ml	£0.57	£3.03
Gel X 10g	£2.46	
Saline	£0.23	£0.23
Tap water	£0.00	£0.00

Adverse event costs

No adverse events cost are included.

Table 20 Other parameters in the model

Parameter	Description	Justification	Source
Time horizon	Until healthy wound condition "BWAT 14"	UK papers report over a 12 month period	(Guest, Fuller, and Vowden 2020)
Discount rate	N/A	Time horizon less than 1 year	NICE

Results

Results – wound bed condition

Results are presented for the wound bed condition model in table 21. Prontosan is a net cost savings compared with the standard of Saline (-£1,134.40) or tap water (-£1,127.29). The cost savings in this model come from reduced time taken to achieve a healthy "good" wound condition with Prontosan, by reducing the number of days a wound incurs higher costs. Prontosan reduces the duration of higher treatment cost, by 50 days (7.15 weeks) compared to saline (table 17).

Table 21 Wound bed condition cost to achieve a healthy wound bed condition

	Technology costs (40ml ampule)	Saline costs	Tap water costs	Difference in resource use costs (technology vs Saline)	Difference in resource use costs (technology vs Water)
Cost technology/ comparator	£34.87	£7.12	£0.00	£27.75	£34.87
Healthcare cost	£671.33	£1,833.48	£1,833.48	-£1,162.15	-£1,162.15
Total costs	£706.20	£1,841.28	£1,834.60	**-£1,134.40**	**-£1,127.29**

Sensitivity analysis

Univariate sensitivity analysis

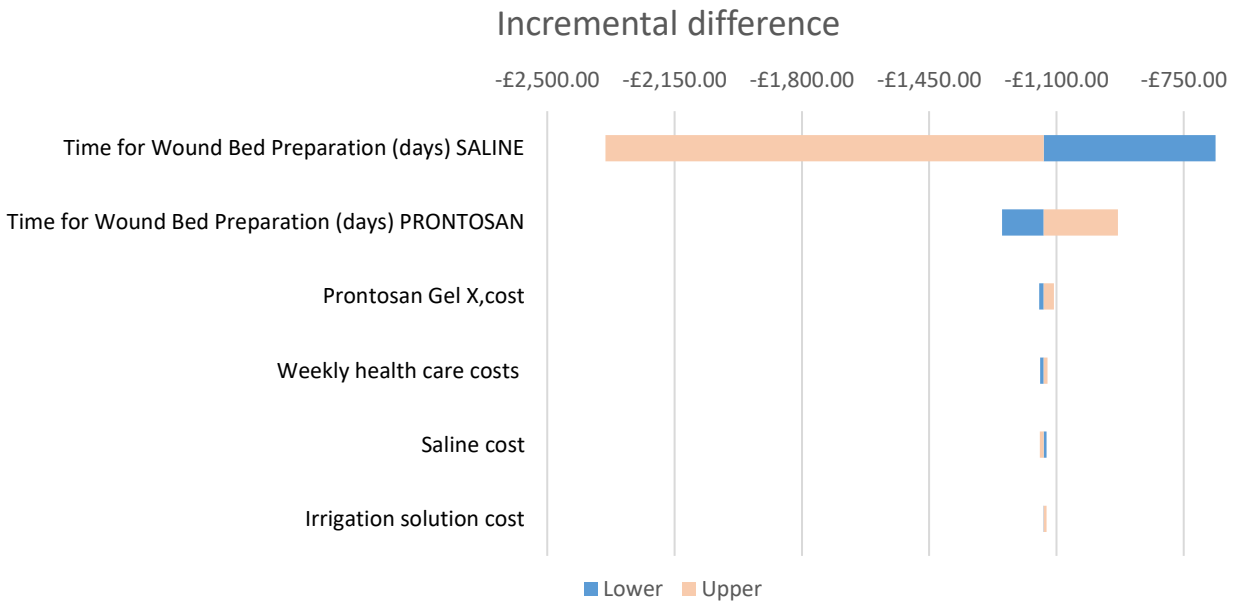
Deterministic one way sensitivity analysis was performed on time taken to achieve a healthy wound condition for both Prontosan and saline weekly health care costs and technology cost. Time taken to achieve the improved wound bed condition and weekly healthcare costs were varied by 95% CI. Cost of Prontosan Solution and Gel X were increased by +100% as the upper banding. For the lower cost banding for Prontosan the larger volumes available to purchase were used: 350ml bottle for Prontosan Solution and 250g tube for Prontosan Gel X. Saline was varied by +100% for upper banding and a cost of £0.00 (indicative of use of water) for the lower banding.

Table 22 Upper and lower parameters in Sensitivity analysis

	Base	Lower	Upper
Prontosan Solution per dressing change	£0.62	£0.57	£1.24
Prontosan Gel X per dressing change	£2.46	£1.32	£4.92
Prontosan time for wound bed condition	28.90	24.21	37.24
Saline time for wound bed condition	78.93	58.68	130.60
Weekly health care costs	£162.60	£160.08	£165.16

When each of the parameters were varied by the upper and lower limits, Prontosan remained a net cost saving, indicating the model is robust.

Figure 10 Tornado chart



Wound bed condition Model - Summary

Introduction of Prontosan Solution and Prontosan Gel X to improve the wound bed condition offers a net cost saving over use of saline. It is estimated that the investment of £27.75 per patient (per episode of wound bed improvement) to introduce Prontosan Solution and Gel X, until wound bed condition has improved, could result in a net cost saving of £1,134.4 per patient per episode compared with saline (Table 21). Savings are driven by reducing the time taken for the wound to reach a healthy wound state following Prontosan treatment compared with standard treatment of saline. Once the wounds are "healthy" the cost of care reduces (Harding, Posnett, and Vowden 2013) and this model assumes that treatment of Prontosan ceases as long as the wound remains "healthy" i.e. none of the following are present: slough, excess exudate, malodour, necrosis or pain. This does not account for deterioration of the wound once treatment with Prontosan is stopped. If wounds deteriorate they would re-enter the model.

Prontosan for wound bed condition, budget impact on one CCG

Each CCG in the UK is estimated to cover an average of 250,000 patients (Guest et al. 2017) and recent studies estimate that 1.1% of the adult population has a VLU (Guest, Fuller, and Vowden 2020), this data would indicate that each CCG will have approximately 2,750 VLU patients. With an estimated net saving of between £1,134.40 per patient in the base case, if a CCG implemented Prontosan for all VLU patients the CCG for an investment of £76,312.5 could result in a net saving of £3,119,600 if all VLUs required one episode of wound bed improvement.

Prontosan for wound bed condition improvement for other wounds

Recent UK literature reports that 51% of chronic wounds in the UK do not heal in a 12 month period (Guest, Fuller, and Vowden 2020). Wounds which are static or deteriorating will not heal (Milne 2015). National literature indicates that up to 51% of chronic wounds are not in a healthy wound state. Two RCTs report on wound condition improvements in VLUs and PUs as well as chronic wounds of various aetiologies (Bellingeri 2016; Valenzuela and Perucho 2008). The model could be applied to other chronic wounds due to Prontosan demonstrating significant improvements in wound condition in various wounds, discussed in detail in Part 1 of this submission (Valenzuela and Perucho 2008).

Recent UK literature reports that 3.1% of the adult UK population has chronic wound (defined as diabetic foot ulcer, Leg ulcer of any kind or pressure ulcer). In a CCG of 250,000 patients this would estimate that 7,753 adults have a chronic wound in each CCG. If 51% of these wounds (3,954 chronic wounds) were in a "static" or "deteriorating" (i.e. poor) wound bed condition and in need of wound bed improvement in order to progress to healing, implementation of Prontosan for one

episode of wound bed condition improvement per wound would be an estimated investment of £109,723.50 and return a net cost saving of £4,485,417.60.

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

Evidence supports the case for Prontosan as an option for: treatment of VLUs until wound closure and for the treatment of stagnant and deteriorating wounds to improve wound condition.

Wound Closure Model

The *de novo* wound closure cost models apply healing and infection rates from two comparative studies in VLUs, with the addition of infection resolution rates from another RCT.

The modelling shows an increased healing probability resulting in a reduced resource cost to the NHS. The driver of the cost saving is reduction in resource required to treat the wounds in the open state due to faster healing times with Prontosan. QALY gain was not measured, however it is logical to assume QALY gain as patients in the healed wound state would have higher QALY score.

The results are robust to plausible values of all the key parameters in the model. The breakeven values of the healing rate (9% to 12%) are substantially lower than the healing rate (46% and 66%) reported in the literature, providing a large margin to indicate that Prontosan is likely to be cost saving.

Wound Bed Condition Model

The *de novo* wound bed condition cost model applies cost resources required to achieve a healthy "progressing" wound bed condition based on a VLU population.

The model shows a reduction in time to achieve a healthy, "good" progressing wound bed condition and a reduction in resource cost to the NHS. The driver of the cost saving is reduction in duration in the more expensive "static and deteriorating" wound conditions and a faster move to the less expensive "progressing" wound condition. Results are robust to plausible values of all key parameters in the model.

While wound bed condition and wound healing are addressed as two separate models, the real life situation is likely to involve a combination of the two models. Based on literature reporting on wound bed preparation and wound condition (Milne 2015), it is reasonable to assume that the wounds which healed more quickly in the clinical studies (Andriessen and Eberlein 2008; Harding 2012) were able to do so due to early and maintained improvements in wound condition. However, not enough comparative information in the Prontosan literature is available to include extra wound

states in the wound healing model and hence two separate models are provided. Evidence supports that effective wound bed preparation along with improving and maintaining good wound condition (Milne 2015), supports faster healing and is in line with the clinical observations and similarities between outcomes in the two models.

Briefly discuss the relevance of the evidence base to the scope.

The evidence is directly relevant to a comparison of Prontosan with saline in both wound healing and wound bed preparation for chronic wounds defined as VLUs.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

Costs calculated in the models utilise monthly costs calculated and inflated from weekly costs in the Harding, Vowden and Possnett (2013). Namely £42.87 per month for a healed wound, £635.76 per month for an "open" wound and £2,034.15 per month for an infected wound. The study by Harding, Vowden and Possnett (2013) is for "leg ulcers" as such the numbers are validated here with other literature specific for VLUs. Annual UK costs for VLUs are reported in the literature as: £7,600 as an overall average, £3,000 for a healed VLU and ranging between £10,777 up to £14,475 for an infected VLU per year (Guest, Fuller, and Vowden 2018). Weekly costs used in this model corresponds to £7,629.08 per year for an open wound, in line with published UK literature. VLUs are unlikely to spend 12 months in an infected state. From costs used in this model if a VLU spent on average 4 months in the infected state and the remaining in the open state the annual cost would be £13,222, in line with the published UK data. In VLUs which heal, average healing time is reported at 3 months in the UK (Guest, Fuller, and Vowden 2018). The monthly data used in this model is calculated for 3 months in the open state and 9 months in the healed state, the average annual cost of a healed VLU in this model is £2,293.12. All resource costs used in this model align with other reported burden costs for VLUs in the UK and the resource cost used are robust.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The wound healing model is indicative for VLUs. Based on the literature it would not be feasible to extend this model to other would types without further research in the area.

The wound condition model is presented for VLUs. Two RCTs report on wound condition improvements in VLUs and PU as well as chronic wounds of various aetiologies (Bellingeri 2016;

Valenzuela and Perucho 2008). Wound condition can vary irrespective of the wound type, a good wound condition is a requirement for all chronic wounds to heal (Milne 2015). The model could be applied to other chronic wounds due to Prontosan demonstrating significant improvements in wound condition in various wounds, discussed in detail in Part 1 of this submission (Valenzuela and Perucho 2008). Recent UK literature reports that 51% of chronic wounds in the UK do not heal in a 12 month period (Guest, Fuller, and Vowden 2020) and may be indicative of wounds not progressing and therefore considered as wounds which are static or deteriorating and will not heal (Milne 2015).

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

There are no economic models in the literature for Prontosan, only *de novo* models which utilise the data from clinical literature.

The wound closure model uses two comparative studies reporting directly on wound healing with Prontosan treatment compared with saline. The rate of healing within in the saline groups differed between the two studies, which may be indicative of different countries of origin and differences in practice between the two studies. However, the impact of Prontosan compared with saline was consistent. Both comparative studies report large increases in the rate of healing (46% and 65%) and reductions in time to healing (36 weeks reduces to 21,75 for Harding and 20 weeks reduces to 13.5 weeks in Andriessen) in the Prontosan groups compared with control.

The model utilising Harding (2012) reports a 66% faster healing rate with Prontosan Solution and Gel X while the Andriessen and Eberlein model reports a 46% faster healing rate with Prontosan Solution. The wound closure model has included the cost for both Prontosan Solution and Gel X rather than using the products from the literature to the corresponding study. This could be viewed as a limitation, however, it allows for the impact of the different studies to be compared with the same cost comparators and may actually present a more conservative estimate for the Andriessen model. It would be of interest to explore in future studies, if the faster healing rate in Harding (2012) corresponds to the addition of the Gel X product. I.e. does Prontosan Solution in addition to Prontosan Gel X results in faster wound healing compared with Prontosan Solution alone. This could be a likely outcome due to the continuous contact of Prontosan Gel X with the wound bed in between dressing changes potentially having more impact on the wound.

The wound closure model could not inform on impact of different wound condition states (progressive, static or deteriorating) separately, due to lack of reporting of wound condition in the

wound healing studies. The clinical literature indicates that treatment with Prontosan improves the condition of the wound and the wound condition model indicates cost savings through improvements in wound condition. The improved healing rates may well be driven by improved wound condition, which would correspond to literature (Milne 2015), although this combined information is currently missing from the Prontosan literature, the current wound closure model may underestimate savings if wound condition were also able to be included.

The wound bed condition model is only able to model cost impact of Prontosan until the wound condition improves. As this model assumes treatment with Prontosan stops after the wound bed reaches a healthy progressive wound bed condition, it is not able to model for impact of any wound regressing into a “poor” wound state after treatment with Prontosan has stopped. Long term impact of Prontosan on wound condition is not available in the literature, the improved healing rate observed in longer studies (Harding 2012; Andriessen and Eberlein 2008) could be driven by the improved wound condition allowing for wounds to progress. This is logical and wound condition is associated with wound healing (Milne 2015), there is currently a lack of information reporting impact of long term wound condition and healing with Prontosan treatment compared with saline.

Both models report on literature for VLUs and utilise cost data from a UK study on “leg ulcers” (Harding, Posnett, and Vowden 2013), which may encompass cost for VLU as well as other leg ulcers. Validation of the resource costs with other UK data sources on VLU (Guest, Fuller, and Vowden 2020; Guest, Fuller, and Vowden 2018) indicated that the resource costs utilised while limited were reasonable.

Detail any further analyses that could be done to improve the reliability of the results.

There are no economic models in the literature for Prontosan. The results here would benefit from the addition of “Real World Evidence” studies to inform on healthcare costs in the UK or comparative clinical studies including economic impact of Prontosan in comparison with saline.

References

Please include all references below using NICE's standard referencing style.

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Appendices

Appendix A: Search strategy for economic evidence for Prontosan

Date search conducted:	13.10.2020
Date span of search:	All time

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Set	Search	CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	
		Type	**Outcome**
S1	Wound*	Title	126,748
S2	Ulcer*	Title	161,885
S3	Burn*	Title	115,346
S4	S1 OR S2 OR S3	Title	395,084
S5	Econom*	Title	194,481
S6	Price	Title	69,145
S7	Budget	Title	31,244
S8	Cost	Title	305,915
S9	Financ*	Title	78,307
S10	S5 OR S6 OR S7 OR S8 OR S9	Title	661,722
S11	Prontosan	All text	506
S12	S4 AND S10 AND S11	All text	**3**

Set	Search	PubMed	
		Type	**Outcome**
S1	Wound*	Title	68,820
S2	Ulcer*	Title	104,141
S3	Burn*	Title	53,468
S4	S1 OR S2 OR S3	Title	217,101
S5	Econom*	Title	54,177
S6	Price	Title	6,176
S7	Budget	Title	5,144
S8	Cost	Title	78,180
S9	Financ*	Title	18,142
S10	S5 OR S6 OR S7 OR S8 OR S9	Title	158,160
S11	Prontosan	All text	31
S12	S4 AND S10 AND S11	All text	0

Set	Search	Cochrane			
		Type	Reviews	Prontocols	Outcome
S1	Wound*	Title	56	15	6,295
S2	Ulcer*	Title	121	38	13,872
S3	Burn*	Title	16	7	2,999
S4	S1 OR S2 OR S3	Title	184	58	22,388
S5	Econom*	Title	20	4	3,616
S6	Price	Title	1	0	168
S7	Budget	Title	0	0	101
S8	Cost	Title	5	4	12,725
S9	Financ*	Title	12	1	671
S10	S5 OR S6 OR S7 OR S8 OR S9	Title	30	9	16,707
S11	Prontosan	All text	0	2	17
S12	S4 AND S10 AND S11	All text	**0**	**2**	**2**

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Additional sources added from company data bank

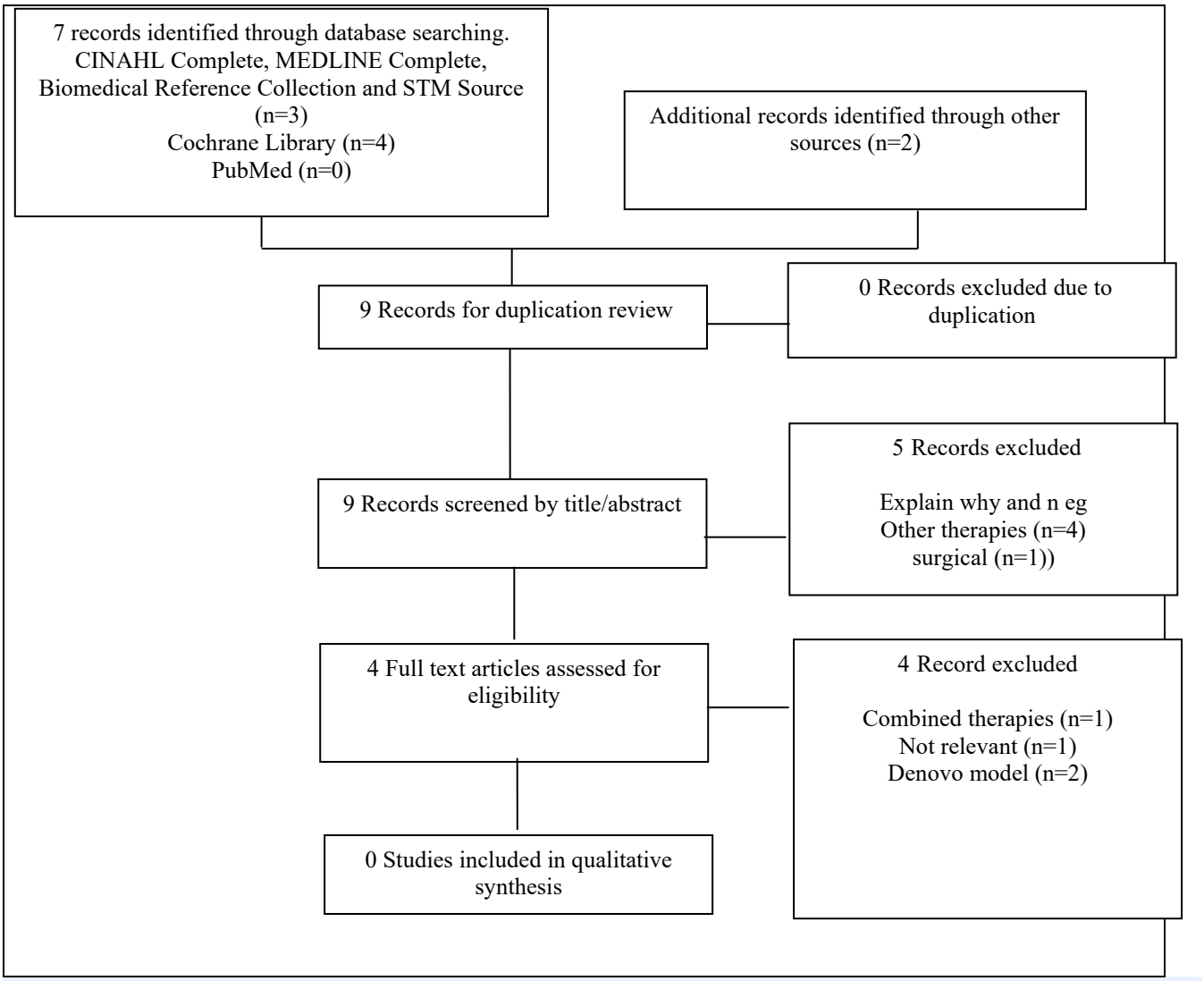
Data abstraction strategy:

Study search results was completed by two reviewers independently

Inclusion criteria	
Population	Age: any Gender: any Race: any Condition: All chronic wounds associated with, pressure ulcers, leg ulcers (venous and arterial), foot ulcers (inc diabetic), cellulitis. Acute wounds including burns and infected wounds.
Intervention	Prontosan (gel, gel X or solution)
Outcomes	Resource use, economic outcomes, cost, ICER cost per patient
Study	Modelling economic studies
Language restrictions	English
Dates	No restrictions
Exclusion criteria	
Population	Surgical wounds, trauma
Intervention	Other topical agents containing PHMB not prontosan solution, gel or gel X
Outcomes	No economic outcomes reported
Study	In vitro, review or discussion articles
Language restrictions	Non-English Language
Dates	N/A

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

PRISMA Prontosan economic search



Appendix B: Search strategy for resource use in wound care in the UK

Date search conducted:	02.02.21
Date span of search:	01.01.2009-present

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

	Term	Type	Hits		
			EBSCO	PUBMED	Cochrane
1	Wound*	Ab	128,304	107,399	15,466
2	Ulcer	Ab	47,874	25,047	5617
3	Burn	Ab	28,483	16,776	2282
4	1 OR 2 OR 3		187,407	140,405	21,109
5	Economic*	Ti	37,960	24,385	2617
6	Price	Ti	6,758	2,742	98
7	Budget	Ti	4,862	1,960	87
8	Cost*	Ti	102,052	63,796	9517
9	Financ*	Ti	15,832	7,914	644
10	5 OR 6 OR 7 OR 8 OR 9		162,575	97,876	9334
11	UK	Ab	93,101	72,794	13,609
12	"United Kingdom"	Ab	47,244	21,629	2503
13	England	Ab	48,087	27,738	2793
14	Scotland	Ab	11,752	7,873	792
15	Wales	Ab	18,924	11,709	1110
16	"Northern Ireland"	Ab	13,651	2,396	277
17	NHS	Ab	33,265	21,603	3509
18	11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17		225,928	137,023	16,904
19	#4 AND #10 # AND 18		**180**	**92**	**25**

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Enter text.

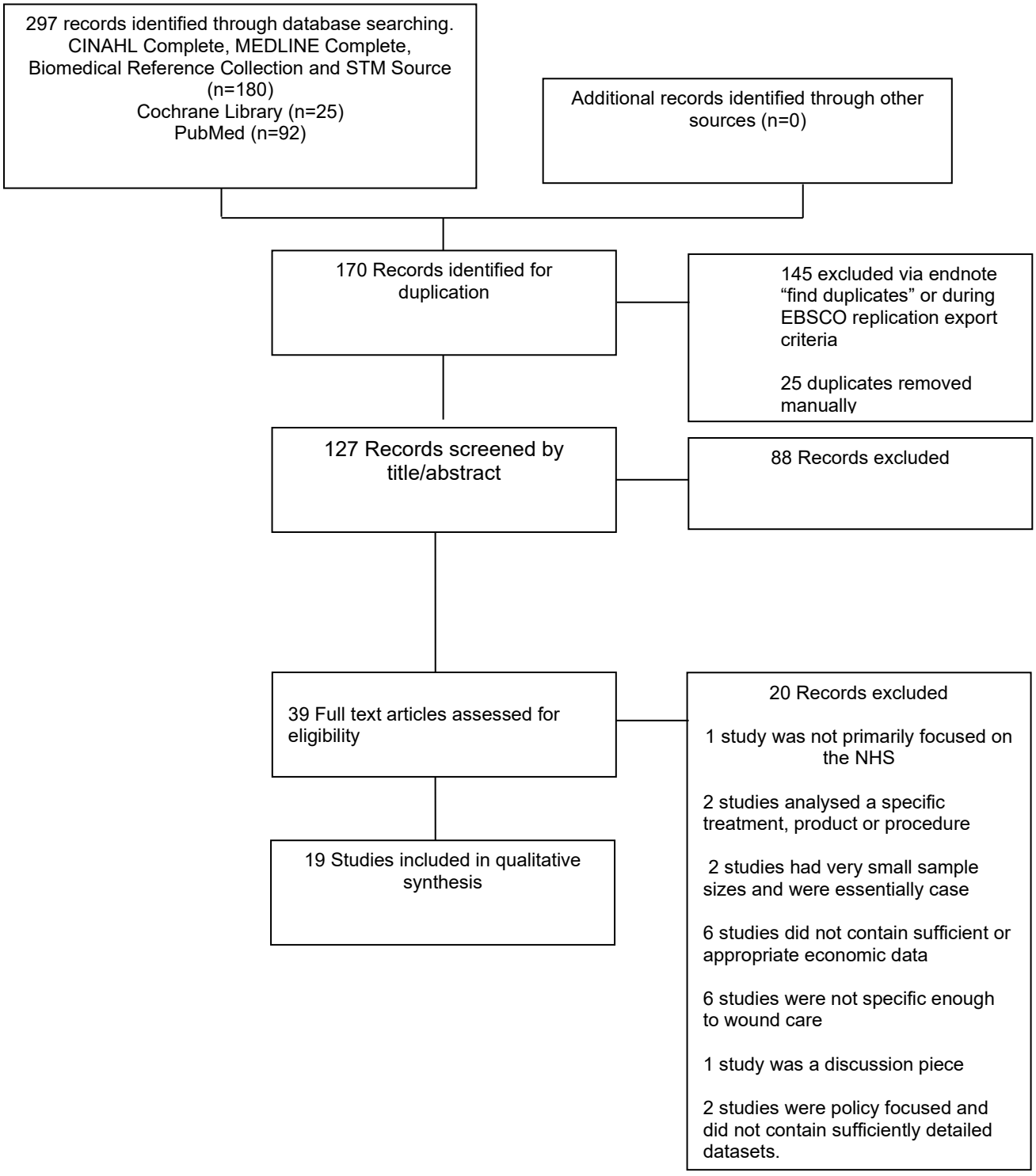
Data abstraction strategy:

Study search results was completed by two reviewers independently

Inclusion criteria	
Population	Age: any Gender: any

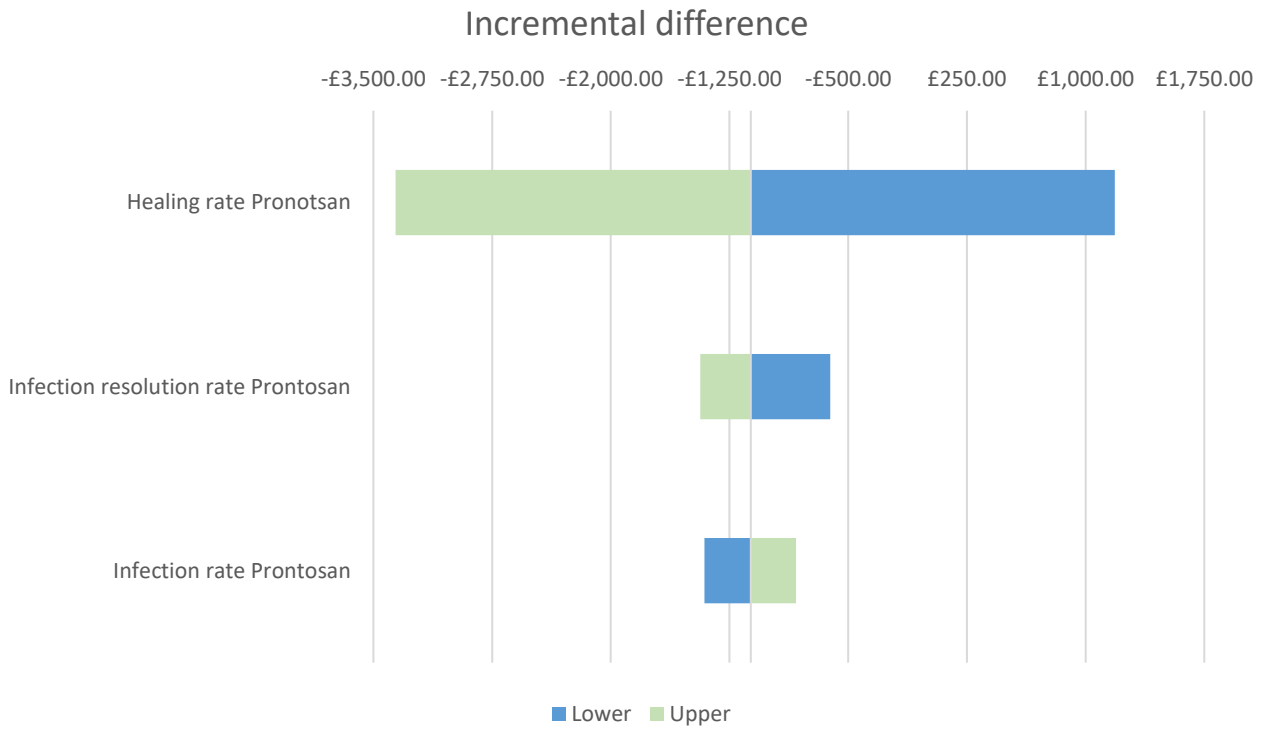
	Race: any Condition: All chronic wounds associated with, pressure ulcers, leg ulcers (venous and arterial), foot ulcers (inc diabetic), cellulitis and unhealed surgical wounds.
Intervention	Standard wound management
Outcomes	Resource use, economic use, cost, cost per patient
Language restrictions	English
Study	Modelling, economic studies UK perspective
Dates	Jan 1st 2009 onwards
Exclusion criteria	
Population	Surgical wounds, trauma, surgical site infections, other acute wounds
Intervention	Prevention, diagnostic, decision making tools. Topical antiseptics, product specific analysis, procedure specific analysis.
Outcomes	No economic or resource use reported
Study	In vitro, review, discussion articles or letters in response to authors which provide no additional data. Not UK. Policy related publications
Language restrictions	Non-English Language
Dates	Before Jan 1st 2009

PRISMA Resource use in UK wound care

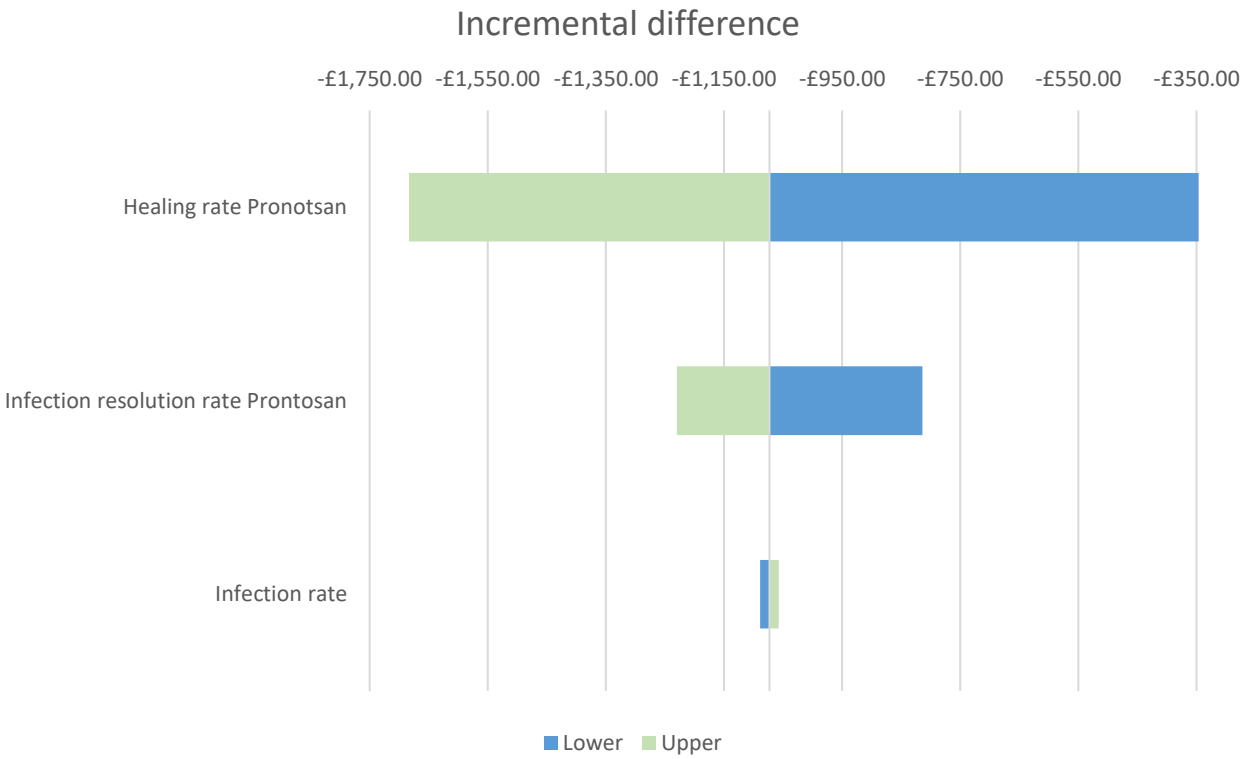


Appendix C: Additional Tornados for cumulative data: Transition probabilities

Harding

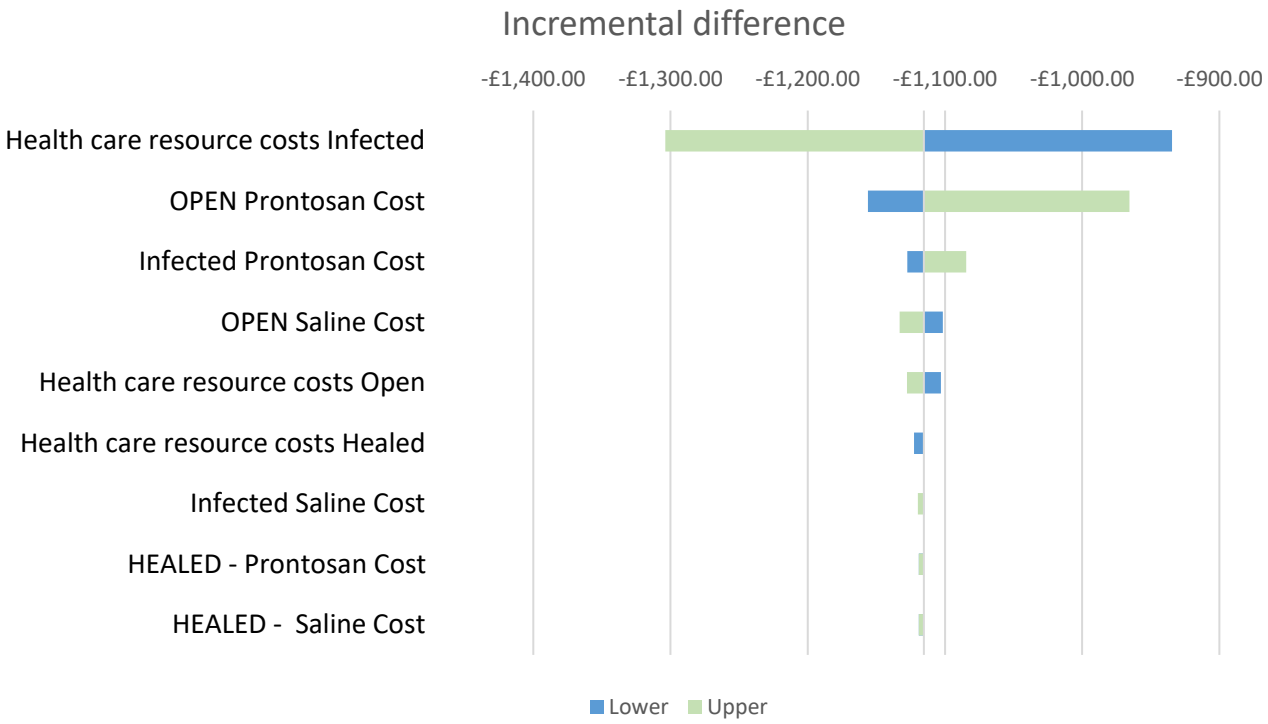


Andriessen

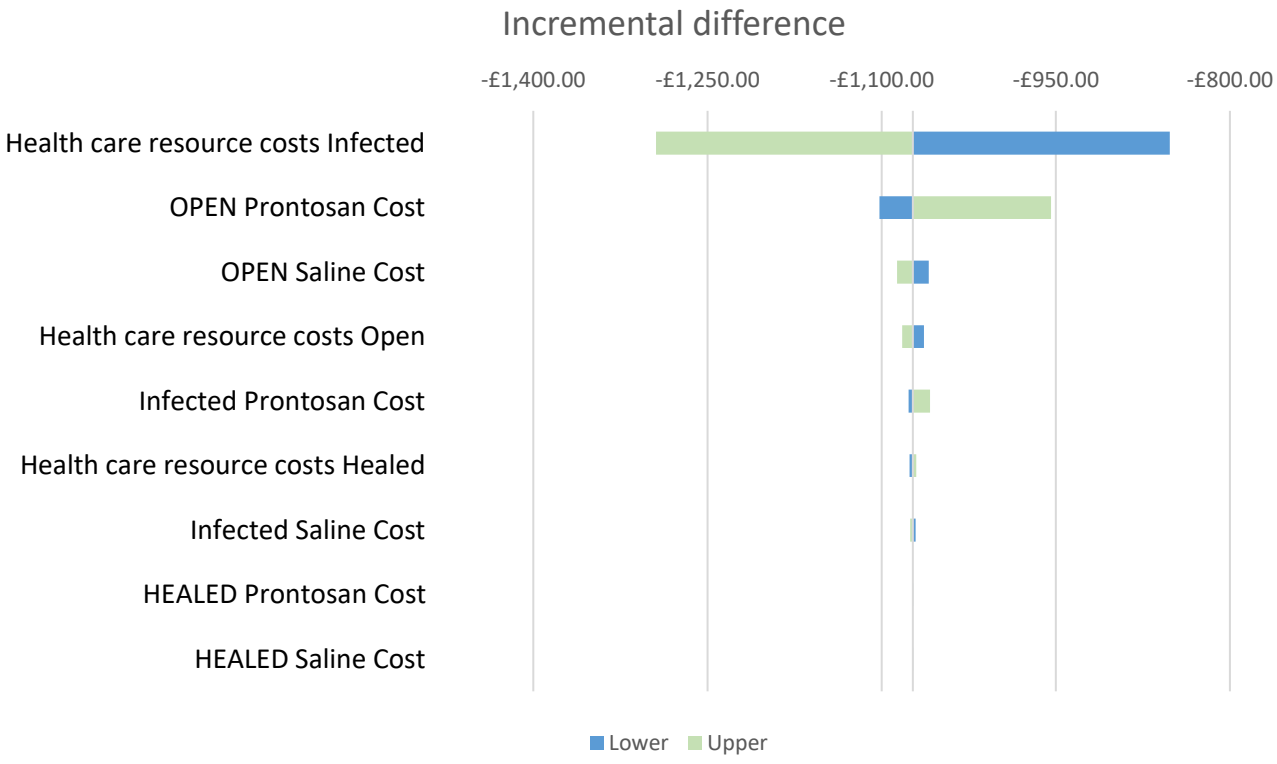


Appendix D: Additional Tornados for cumulative data: Resource use

Harding



Andriessen



Appendix E: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#14	☒ Commercial in confidence ☐ Academic in confidence	UK sales information for product	Forever
Details	**Enter text.**		
#26	☒ Commercial in confidence ☐ Academic in confidence	Private contact details for Clinical experts	Forever

Details	Enter text.		
Details	Enter text.		
Throughout	☐ Commercial in confidence ☒ Academic in confidence	Data from unpublished study assigned academic in confidence throughout part 1	On going.

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly

if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.
Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		Date:	16/02/2021
Print:	Dr. Tarik Yalaoui	Role / organisation:	Chief Medical Officer
Contact email:			

National Institute for Health and Care Excellence

Collated comments table

MTG Medtech Guidance:

Expert contact details and declarations of interest:

Expert #1	Name, job title, organisation, email address : Kimberley Wilde, Advanced Podiatrist, Manchester Foundation Trust
	Nominated by: Company
	DOI: NONE
Expert #2	Name, job title, organisation, email addres: Dr Fania Pagnamenta, Nurse Consultant (Tissue Viability), The Newcastle upon Tyne Hospitals NHS Foundation Trust
	Nominated by: NICE
	DOI: NONE
Expert #3	Name, job title, organisation, email address: Baljit Dheansa, Consultant Burns and Plastic Surgeon, Queen Victoria Hospital
	Nominated by: NICE
	DOI: NONE
Expert #4	Name, job title, organisation, email address: Haitham Khalil, Consultant Oncoplasty and Reconstructive Surgeon, University Hospitals Brimingham
	Nominated by: NICE
	DOI: NONE
Expert #5	Name, job title, organisation, email address: Heather Hodgson, Lead Nurse Tissue Viability, NHSGGC
	Nominated by: Company
	DOI: NONE
Expert #6	Name, job title, organisation, email address: Katie Bennett, Wound Care Lead Nurse, Westbury Group Practice
	Nominated by: Company
	DOI: None
Expert #7	Name, job title, organisation, email address: Mark Collier, Nurse Consultant and Associate Lecturer – Tissue Viability, Independent with affiliations to the Universities of Lincoln and Hertfordshire
	Nominated by: Company

	DOI: Has attended and participated in various meetings – National and International - discussing the clinical benefits and potential further development of the use of the product (2010 to current).
Expert #8	Name, job title, organisation, email address: Patricia Littlewood, Lead Tissue Viability Clinical Nurse Specialist, Frimley Health Foundation Trust
	Nominated by: NICE
	DOI: NONE
Expert #9	Name, job title, organisation, email address: Denise Woodd, Independent clinical nurse specialist – wound care and leg ulcers, NHS PORTSMOUTH CCG AND SOLENT NHS TRUST
	Nominated by: Company
	DOI: Has done teaching or support work in local trust with an honorary contract, BBraun support these hours (2017 to current)

1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it? Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake? Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another	Expert #1: I have ten years' experience of using the technology. I use the product daily in my clinical practice. The podiatry team I work with also use it regularly because it is our product of use for cleansing and decontaminating wounds. The district nurses and tissue viability in my locality also use it. I have worked in a number of trusts within the Manchester area and have used this product in all of these trusts.	

	specialty for this procedure/technology, please indicate your experience with it.	I am an Advanced Podiatrist so I develop plans of care for patients for other staff members to follow. I prescribe the product regularly for my patients and my colleagues will use it on my recommendation.	
		Expert #2 I have used Prontosan for at least the last 10 years. This product has been on our Formulary for many years. Yes Yes Yes Yes	
		Expert #3 As a burns surgeon I have experience of managing wounds and cleansing wounds with a wide variety of products including antiseptic agents. This product is used in a variety of settings: cleansing wounds in the community, decolonising skin of MRSA carriers, wound cleansing in secondary care, skin cleansing. It is used by some in burns management for wound cleansing.	

		It is often used in chronic wounds to help address the biofilm.The product is standard of care in some regions in community nursing. Some feel it is essential as it may be beneficial for wounds while others are not sure it is required. This centres around claimed benefits. Much of the research related to this product is of poor quality or at risk of bias. Often the aims or objectives of the research may not be clinically relevant. Burns has long used a variety of antiseptic or antimicrobial products and this product is one of them. The complexity of burns wound care and the variation ion practice means that the impact of this kind of product would need very carefully constructed research with large numbers to show if it had a true impact.	
	–	Expert #4 I have used prontosan with negative pressure wound therapy instillation (NPWTI-(Verflow) as anti-microbial agent for irrigation of mainly acute infected wounds. I have been using the verflow technology for more than 4 years now which we mainly started with saline solution. However, when more contamination, bacterial count load and mature biofilm were encountered, antimicrobial prontosan was used especially with pseudomonas aeruginosa. I have previously Acted a s advisor for NICE with regards the NPWTi-Verflow and has been a game changer in my practise for management of infected wounds. The addition of prontosan to this technology and	

		widened the spectrum for its use to manage these complex wounds. Prontosan Wound Irrigation Solution; contains 2 active ingredients, an antimicrobial polyhexanide (polyhexamethylene biguanide [PHMB]), and a betaine surfactant (undecylenamidopropyl betaine). I haven't used the Gel form yet I am aware that prontosan is used with Verflow technology for wound irrigation in several trusts in the West Midlands mainly in orthopaedic and plastic and reconstructive surgery disciplines Yes, In addition to the plastic and reconstructive surgery disciplines it has been used mainly in orthopaedic, Colorectal surgery and thoracic surgery Any patient with acute or chronic deep infective wounds especially if foreign prosthesis is in place e.g breast implants, cement mesh, titanium plates	
	–	Expert #5 I am a daily user of the product and have developed wound care formulary and protocols which feature this product including: 1. Maternity wound guidance 2. Wound cleansing (National document) 3. NHSGGC acute wound care formulary	

		4. Burns and trauma guidance This product is used widely throughout all departments involved in wound care.	
	–	Expert #6 I am very familiar with the technology, I have been using prontosan products for approximately 7 years, in the area I work we have a care pathway for prontosan irrigation fluid and wound gel x. The criteria for use is non- healing wounds, wounds in need of debridement and all wounds with a recurrent infection. This includes acute wounds for example pilonidal sinus wounds, these tend to have a cavity so often difficult to see the wound bed and are at risk of recurrent infections and chronic wounds eg ulcers, diabetic foot ulcers etc. Theses wounds are prone to biofilms. Prontosan irrigation fluid is applied to a wound for 10mins by soaking gauze in the solution, the wound gel x is applied directly to the wound bed followed by a simple non- adherent dressing. I am not aware how widely this technology is used in the NHS, I know that it is used frequently in the area I work.	
	–	Expert #7 I was first introduced to the product in 2010 and having reviewed the available evidence at the	

		time, set up and supervised a six-month clinical evaluation of the product on a rage of surgical patients (acute wounds) in 20ll, with a follow up period of six months (again in the same surgical setting) in 2012. Further to an analysis of the results obtained from the above and after discussions with a number of relevant members of the multi-disciplinary team (MDT), I introduced the product on the Wound Management Formulary for the Trust that I was working for at the time and continued to use the product for the cleansing of all wounds (both acute and chronic) until I retired from my NHS post at the end of 2018. When I get the opportunity to work with patients my cleansing solution of choice is always Pronotosan - if available. Yes, as above. A large number of Trusts (both Primary and Secondary) have already listed the product on their Wound Management Formularies Yes, as relevant e.g. Stoma Therapists, Dermatology and Vascular Nurse Specialists Have used the product clinically for the last 9 years with results as anticipated and no reports/observations of patient reactions to the same. I have found the product to be efficacious, clinically beneficial and cost effective.	

	–	Expert #8 I have used the irrigation solution many times over the last 4 or 5 years – mostly in conjunction with VAC Veraflo pumps. We are currently using the product and would like to extend the use in practice as it has ben found to be very effective in cleansing wounds. I do not know how widely it is used elsewhere It is used in one other department that I know of other than my own. We have recommended the solution to other areas and it has been received well.	
	–	Expert #9 I am familiar with the product and have been using it for over since 2009 Clinically I use it on all chronic wounds in an advisory capacity and in my own clinical practice I have not been involved in any research etc I teach over 5 counties and work clinically and it is seen in community and practice nurse settings extensively It has been on our pan (acute and primary) Hampshire Wound Formulary for over 6 years now	

2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1: I have completed a case study evaluation on the product and presented this at the European Wound Management Association Conference.	
		Expert #2 I have done bibliographic research on this procedure. I have done clinical evaluation using prontosan involving patients.	
		Expert #3 Other (please comment): I have researched methods of wound cleansing and the use of cleansing agents in burns specifically. I have reviewed papers on Prontosan. There are significant methodological or bias issues associated with many of these papers. The objectives are not always appropriate or clinically relevant. Often the comparator was not necessarily ideal e.g. saline rather than another antimicrobial or lack of clear approach to the mechanical cleansing of wounds which may also have an impact.	
	−	Expert #4 I have already published on verflow technology with using saline and in the process of publishing on the use of prontosan with verflow technology in	

		infected breast implants post reconstruction and chest wall reconstruction. e.g Haitham Khalil et al. Negative Pressure Wound Therapy Instillation for Management of Intrathoracic Chronic Infection. Plast Reconstr Surg Glob Open, 2019 Jul 29;7(7):e2323	
	–	Expert #5 I have done bibliographic research on this procedure.	
	–	Expert #6 I have had no involvement in research on this procedure.	
	–	Expert #7 I have done clinical research on this procedure involving patients or healthy volunteers. I have published this research. Other (please comment) Have discussed the clinical benefit and use of this product at a number of conferences around the world and listened to numerous other clinicians' positive experiences of using the same on a variety of patients with a variety of wounds.	
	–	Expert #8 I have had no involvement in research on this procedure.	

	–	Expert #9	

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1: Established practice and no longer new.	
		Expert #2 This is no longer innovative, it has been used in standard care for a number of year. Established practice and no longer new.	
		Expert #3 Minor. Many others claim to be able to address biofilm in their products too. Established practice and no longer new.	
		Expert #4 The combination of NPWTi –Verflow with antimicrobial agents adds a combined effect in reducing the number of viable microorganism and thus creating a suitable environment for the enhancement of the neovascularization and promotion of the granulation tissue for appropriate wound healing or preparing the wound for reconstructive surgery. I believe the combination	

		would add to the armamentarium of wound management technique especially with complex and resistant wounds A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.	
		Expert #5 Innovative due to consistency of the GEL X – this product does not require a secondary dressing for it to be effective Established practice and no longer new, this product has been used since 2012 in NHSGGC and has been an integral component of wound care since then.	
		Expert #6 I feel the technology is a novel approach, tap water will cleanse a wound but it does not cleanse and reduce bacteria burden. Definitely novel and of uncertain safety and efficacy.	
		Expert #7	

		It could be seen as a minor variation on current practice however the combination of its constituents is unique. A minor variation on an existing procedure, which is unlikely to alter the procedure's safety and efficacy.	
		Expert #8 The product is highly effective in my opinion Established practice and no longer new.	
		Expert #9	
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1: It could be used to replace current standard care which is the use of saline or water	
		Expert #2 Yes, if supported by NICE medtec, prontosan could replace normal saline as standard wound cleanser.	
		Expert #3	

		It could replace other methods of burn wound cleansing if shown to be superior in terms of wound infection (NOT bacterial presence) and wound healing time (NOT reduction in wound size).	
		Expert #4 It would be an addition to an existing NPWTi-verflow	
		Expert #5 This has replaced standard care in maternity services	
		Expert #6 I feel it has the potential to replace current standard of care but also be used in addition to existing care, for example a patient with a leg ulcer can still have his leg washed in a bowl of warm tap water and then a prontosan soak to the wound.	
		Expert #7 Has the potential to replace existing wound cleansing / management procedures.	
		Expert #8 I would certainly consider encourage using the solution in replacement of normal saline for all infected wounds.	
		Expert #9	

		The underlying purpose/rationale of why staff irrigate and clean wounds has not changed by using Prontosan It is a change to approach by educating nurses to cleanse and soak to effect improved outcomes	

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1: Current standard of care for wound irrigation is water or saline	
		Expert #2 Wounds are cleansed either with normal saline, tap water (chronic wounds) or prontosan. Prontosan is used predominately as a soak.	
		Expert #3 There is no standard of care in burn wound cleansing or management of chronic wounds. It varies from plain water, saline, antiseptics, antimicrobials and mechanical methods including surgery.	

		Expert #4 Mainly VAC therapy (Vacuum assisted closure)	
		Expert #5 The use of saline or potable tap water to cleanse wounds	
		Expert #6 Wounds are cleansed with warm tap water, if we are not following the care pathway.	
		Expert #7 Sterile Normal Saline or Sterile Water or Tap Water in some clinical situations for wound cleansing. The use of a range of interactive dressing products for the breakdown / control of Biofilm formation	
		Expert #8 Normal Saline solution is normally used to cleanse wounds in this Trust. Sadly not many trusts use the VAC Veraflo	
		Expert #9	
6		Expert #1:	

	Are you aware of any other competing or alternative procedure/technology available to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Octenilin – but this does not have the same action on biofilms and does not have the same supporting evidence	
		Expert #2 Yes – other similar products are available in the UK.	
		Expert #3 Lots. See above. They all vary in terms of antimicrobial activity but it is unclear if this makes any difference to wound healing. For example Kerra-Contact is a silver based dressing that claims to reduce biofilm and reduce healing time.	
		Expert #4 There are other Antimicrobials that could be used as Povidone Iodine and antibiotic solution with gentamycin and rifampicin. I have had experience with using gentamycin	
		Expert #5 Similar products with slightly different constituents, reportedly less effective - Octenalin	
		Expert #6 No	
		Expert #7 Oxytenalin	

		The constituent parts and actions of the product.	
		Expert #8 We only have two options for use in the Veraflo – saline or Prontosan and we are slowly encouraging clinicians to consider the use of more prontosan as we have found it very effective. I am not aware of any other products that are licenced for use with Veraflo.	
		Expert #9 Yes They don't include both key ingredients of Prontosan which the information has directed is needed for reduction of infection and interruption of the biofilm found in chronic wounds	
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1: Improved wound outcomes	
		Expert #2 Better wound cleansing may reduce wound infection.	
		Expert #3 Reduced wound infection, more rapid wound healing. This would lead to reduced costs. Costs can be challenging to work out and if a whole service introduces it then one should be able to demonstrate a significant reduction in actual expenditure (NOT theoretical) and reduced clinical burden. However there is no clear good quality evidence that indicates it does.	

		Expert #4 The combination of NPWTi –Verflow with antimicrobial agents adds a combined effect in reducing the number of viable microorganism and thus creating a suitable environment for the enhancement of the neovascularization and promotion of the granulation tissue for appropriate wound healing or preparing the wound for reconstructive surgery. I believe the combination would add to the armamentarium of wound management technique especially with complex and resistant wounds	
		Expert #5 Simple to use, reduces requirement for secondary dressing, rapid response to treatment	
		Expert #6 Reduction in recurrent infection- with infection comes deterioration to a wound, delayed healing, increased pain and discomfort for patients. Increased healing rates Patients find dressing changes comfortable as the products keep the wound bed moist so the dressing does not adhere to the wound bed. I have found a reduction to wound odour, odour can be very distressing for a patient, the products clean a wound of bacteria and devitalised tissue	
		Expert #7 Enhanced wound cleansing - associated psychological benefits / Minimisation of the risk of Hospital Acquired Wound Infections / The Prevention and minimisation of the	

		development a Biofilm / Improved Patients Wound Healing potential	
		Expert #8 Cleansing wounds rapidly of harmful infection	
		Expert #9 Reduction and prevention of wound infection Interruption and dissolving of biofilm and maintenance to prevent reformation Removal of non-viable tissue and 'foreign bodies' in the wound bed	

Potential system impact

8	Are there any groups of patients who would particularly benefit from using this procedure/technology?	Expert #1: Patients with acute or chronic wounds	
		Expert #2 Patients with wounds.	
		Expert #3 Those with infected wounds or chronic wounds.	
		Expert #4 I believe the combination would add to the armamentarium of wound management technique especially with complex and resistant wounds in high risk patient e.g diabetic smoker,	

		obese, trauma, ischemic wounds etc especially in the presence of foreign prosthesis e.g breast implants, cement mesh, titanium/metal plates	
		Expert #5 All patients but Prontosan and Prontosan Gel x are included in numerous guidelines including wound cleansing, maternity wound, paediatric, burns and plastics and trauma. It has proved to be a go to product to treat facial wounds in patients with Covid arising from proning	
		Expert #6 I feel Diabetic patients would particularly benefit from the technology as they are more prone to infection. Also patients with leg ulcers as these wounds are prone to biofilms which can delay healing. The technology helps to remove the biofilm and prevent it from reforming by continually cleansing the wound.	
		Expert #7 All patients with a Chronic wound	
		Expert #8 Patients with infected post-operative wounds or those who have infected or colonised chronic leg ulcers. Trauma wounds.	
		Expert #9 All patients with a wound that needs cleansing, esp the vulnerable patient and/or chronic ones	

9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1: This product could benefit current wound pathways by improving healing rates. It could improve patient outcomes, reduce treatment times and have a cost saving on staff/clinic time	
		Expert #2 Yes – might offer improved outcome.	
		Expert #3 It may create a more standard approach to burn wound cleansing and possibly improve wound healing/reduce infections. But currently there is no good quality data to support this.	
		Expert #4 The combination of NPWTi and Prontasan would accelerate wound healing or preparation for reconstructive surgery to mange complex wounds therefore would reduce length of hospital stay in general which I personally experienced, The negative side is that still there is no agrred pathwyas for it to be used on outpatient basis which if provided this would add more cost-effectiveness to the combined technology however that will be subject to safety and education of the use by patients district and community nurses etc.	
		Expert #5 Yes , inclusion in pathways ensure appropriate effective care leading to improved clinical outcomes for patients with wounds	

		Expert #6 With a reduction in wound infections and improved healing rates there is then a reduction on the need for wound swabbing, antibiotics, dressing changes and also potential hospital admissions.	
		Expert #7 Yes Yes	
		Expert #8 Yes I believe it would.	
		Expert #9 Yes it could for those not yet using it and I believe does Its for prevention as well as treatment Reduced incidence of wound infection and biofilm formation Reduced recurrence of infection esp in high risk groups like SSI, compromised patients and chronic wounds	
10	Considering the care pathway as a whole, including initial capital and possible future	Expert #1: Cost would be more than using saline	

	costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #2 No, Normal saline in sachets and/or pods cost almost the same as prontosan.	
		Expert #3 Yes, more. The product is more costly than water and many other cleansing agents. Many burns wounds need repeated, regular cleansing and are often very large meaning that a very large amount of the product would be required.	
		Expert #4 I would say it is likely to cost more to start with however on the mid & long term it will be very cost-effective especially as the use of the technology becomes more widely available and used	
		Expert #5 Cost less due to: fewer wounds breaking down quicker healing time less wound products required	
		Expert #6	
		Expert #7 Unit cost is likely to be increased however as the length of a patient's treatment time is similarly likely to be reduced, in this	

		clinician's opinion the product will be cost effective if used appropriately and as pre manufacturer's instructions	
		Expert #8 I think that if there was an increase in cost it would be counterbalanced by the improved outcomes and earlier discharges.	
		Expert #9 Initially marginally more cost, but the research and studies have demonstrated efficacy in prevention therefore there are long term cost savings financially and in the patient journey	
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1: Cost would be less overall because it would impact wound healing by reducing healing times and thus this would impact on reduced visits, less dressing costs	
		Expert #2 Staff training	
		Expert #3 It will be more costly	
		Expert #4 As I said it is likely to cost more to start with however on the mid & long term it will be very cost-effective especially as the use of the technology becomes more widely available and used	

		Expert #5 Same as standard care and in some instances less than standard care depending on products used for example Prontosan solution V Saline Prontosan Gel x via Flaminal	
		Expert #6 There is likely to be an increase in initial cost but looking at the whole package, with a reduction in infection, improved healing rates, when all added up it could cost less.	
		Expert #7 Slight increase in unit cost (see also above response) but no increase in staffing or equipment costs whatever the Healthcare setting in which it is used	
		Expert #8 I understand that the cost is similar to that of saline.	
		Expert #9 Minimal, it is easily available, simple to use, the company have good education resources and pathways in use No change to staff or setting at all	
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1: Non	
		Expert #2	

		Minimal changes to existing facilities	
		Expert #3 None	
		Expert #4 No change to hospital clinical setting, however will be beneficial and cost-effective to add the community setting to support outpatient basis treatment	
		Expert #5 None	
		Expert #6 I can't see any clinical facilities that will be needed to use technology safely.	
		Expert #7 None	
		Expert #8 Education of staff and the time to do this!	
		Expert #9	

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1: no	
		Expert #2 No more than any other wound care product.	
		Expert #3 The instructions for use are fairly straightforward and easy to understand	
		Expert #4 Yes, surely the doctors, Tissue viability nurses (TVN) nurses (hospital, community) will require to be familiar with the technology, mode and dose of administration to ensure efficacy and safety	
		Expert #5 Very little training required – knowledge required on: Type of wounds How to use Wear time Contraindications	
		Expert #6 The products are very easy to use, I do not think any specific training is needed	
		Expert #7	

		Some training re specifics of use of the product to enhance the potential of positive outcomes as a result of the product	
		Expert #8 It is always difficult to bring change but the evidence would speak for itself once people see the improved outcome.	
		Expert #9 Minimal education required	

Other considerations

14	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events	Expert #1: There are no potential harms or risks using the product. I have never had any issues with the product during the time I have used it.	
		Expert #2 None known	
		Expert #3 It may promote bacterial resistance, cause skin reactions/rashes. Cases of anaphylaxis have been reported. Cell toxicity may occur (reducing wound healing potential). It may interfere with the effectiveness of dressings applied to the wound. Systemic toxicity from absorption -	

		especially in large wounds. Adverse effect on skin grafting or biological dressings. Hirsch T, Seipp HM, Jacobsen F, Goertz O, Steinau HU, Steinstraesser L. Antiseptics in surgery. Eplasty. 2010 May 27;10:e39. PMID: 20526354; PMCID: PMC2878193. Olivieri J, Eigenmann PA, Hauser C. Severe anaphylaxis to a new disinfectant: polyhexanide, a chlorhexidine polymer. Schweiz Med Wochensch 1998; 128: 1508-11. Kautz O, Schumann F, Degerbeck L, Venemalm L, Jakob T. Severe anaphylaxis to the antiseptic polyhexanide. Allergy 2010; 65: 1068-70.	
		Expert #4 As with any antimicrobial agent even with topical application that should be discontinued of any of adverse reaction develops for example prontosan usually should be stopped after 2 weeks of usage.	
		Expert #5 Allergy to any of the constituents	
		Expert #6 Nil	

		Expert #7 None known To the best of my knowledge, none to date As above None known None known	
		Expert #8 Potential allergic reaction but I have seen no evidence of this. None seen Not aware of any	
		Expert #9	
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1: Wound bed preparation by reducing inflammatory signs Accelerated healing	
		Expert #2	

		Reduction of bioburden	
		Expert #3 Wound infection rate (NOT positive bacterial swabs or bacterial counts), time to full wound healing (NOT wound size reduction).	
		Expert #4 In my experience combining it with NPWTi; Acceleration of reducing contamination and bacterial load, hence providing a more suitable environment for development of granulation tissue, reduce hospital stay	
		Expert #5 Prevention of wound breakdown Improved clinical outcomes in terms of quicker wound healing rates	
		Expert #6 Improved healing rates, reduction in recurrent infections, good patient experience	
		Expert #7 Enhanced wound cleansing / Reduction in the incidence of Hospital Acquired Wound Infections / The Prevention and improved Management of Biofilms / Improved Patients Wound Healing potential	
		Expert #8 Reduced secondary infections.	

		Expert #9	
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1: None	
		Expert #2 User's error	
		Expert #3 It may not have any significant clinical effect compared to other wound management strategies	
		Expert #4 The possibility of preservation of foreign prosthesis if encountered is still questionable	
		Expert #5 Nil	
		Expert #6	
		Expert #7 None known	
		Expert #8 None	
		Expert #9	

17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1: No	
		Expert #2 Perceived costs in terms of a) product cost and b) time – prontosan is known as a soak which necessitate 10-15 minutes. Prontosan can also be used to cleanse wounds. However staff are unaware of the cost of normal saline.	
		Expert #3 Yes, see above (2, 6, 7, 10, 16). This product may be a costly way of making no difference to chronic wounds. There does not seem to be any data showing decreased costs or reduced clinical burden in those services that have instituted it as standard care.	
		Expert #4 The possibility of preservation of foreign prosthesis if encountered is still questionable	
		Expert #5 Nil	
		Expert #6 None that I am aware of.	
		Expert #7 No	

		Expert #8 None that I am aware of	
		Expert #9	
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1: Most or all district general hospitals.	
		Expert #2 All hospitals and community settings.	
		Expert #3 Most or all district general hospitals in a generic sense (general wound care) and all specialist burns services for burns specifically. This therefore will have a potentially very large cost impact.	
		Expert #4 Most or all district general hospitals.	
		Expert #5 Most or all district general hospitals.	
		Expert #6 Most or all district general hospitals.	

		Expert #7 Most or all district general hospitals.	
		Expert #8 Most or all district general hospitals.	
		Expert #9	
19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1: ***Bellingeri et al. (2016)*** 289 people with chronic wounds (vascular leg ulcers and pressure ulcers) in a single-blind randomised controlled trial. ***Romanelli et al. (2010)*** 40 people with chronic venous leg ulcers in a single-blind prospective controlled trial ***Ciprandi et al. (2018)*** 198 children with burns in a retrospective data review. ***Ricci (2018)*** 70 people with chronic wounds (older than 6 weeks) in an observational study	

		Durante et al. (2014) 124 adults and children with chronic wounds in a multicentre observational study. ***Andriessena and Eberlein (2008)*** 112 adults with venous leg ulcers in a retrospective review of records. I completed a case study in 2019 that included five patients with foot wounds. I had successful results in wound improvement using prontosan solution/prontosan pads and prontosan gel x.	
		Expert #2 None	
		Expert #3 None	
		Expert #4 Not aware of Shamaila Tahir et al. The Effect of Negative Pressure Wound Therapy with and without Instillation on Mature Biofilms In Vitro. Materials (Basel), 2018 May 16;11(5):811	

		Expert #5	
		Expert #6 Please see attached article I wrote for B Braun earlier this year.	
		Expert #7 Due to COVID19 and the cancellation of almost all National and International Conferences due to take place this year (although some virtual shortened versions have taken place) I am unaware of any significant studies that you will not come across during your planned Literature search.	
		Expert #8 None that I am aware of	
		Expert #9 No I have only heard lately of it being used in synergy with some antimicrobial dressings as this has increased the effect of wound infection resolution	
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1: Not that I am aware of	
		Expert #2	

		Not to my knowledge.	
		Expert #3 None that I am aware of.	
		Expert #4 Not aware of	
		Expert #5	
		Expert #6 None that I am aware of.	
		Expert #7 None known to this clinical for the same reason as above - lack of access to information regarding the same due the cancellation of numerous conferences / focus groups / review meeting and other planned face to face educational events.	
		Expert #8 Not known	
		Expert #9	
21	Approximately how many people each year would be eligible for an intervention with this procedure/technology, (give either as an estimated number, or a proportion of the target population)?	Expert #1: 4.5% of the UK population	
		Expert #2 Almost all patients with wounds.	

		Expert #3 16000 people are admitted with burns injury every year and it would be expected that many will be appropriate for this if shown to be beneficial. Over 200 000 people sustain burns requiring hospital attendance and at least a third of these may also be eligible as they may attend a specialist service.	
		Expert #4 Difficult to quantity, but in the scenario being combined as an irrigation solution with NPWTi I would say in our organization could be 25-50 cases/year	
		Expert #5 Within NHSGGC alone approximately 4000 per year – 50% of all referrals to Tissue Viability Service	
		Expert #6	
		Expert #7 100 per cent of all patients with Chronic Wounds (prevention and management) and approximately 25 per cent of all patients with Acute Wounds (primarily for Prevention if the patient has been assessed at risk of or has a history of recurrent wound infections (e.g. SSI's)	
		Expert #8 We have used it on multiple patients if they are referred to us and have infected post operative	

		wounds possibly in the region of 20 a year but the number is going up as we see the outcomes	
		Expert #9 95-100%? I probably wouldn't advise it on a self-caring small, acute trauma wound on a healthy patient initially. However, as a wound care educator it is easier and facilitates a far better impact to do a 'whole swap' in care pathway in order to streamline/standardise care and there is evidence this is not going to be cost inhibitive	

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1 no	
		Expert#2	
		Expert#3 It may reduce the likelihood of clinical staff mechanically debriding a wound or seeking other approaches to wound care.	
		Expert #4 No	
		Expert #5 No	
		Expert #6 No	
		Expert #7 Not in my experience	
		Expert #8 The bottle is sometime difficult to connect to the machine	
		Expert #9 None experienced or known	
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1 no	
		Expert#2 n/a already in use.	
		Expert#3 Cost and appropriate effectiveness (see above).	

		Expert #4 No	
		Expert #5 Already adopted	
		Expert #6 No	
		Expert #7 No	
		Expert #8 Fear of the unknown!	
		Expert #9 No	
24	Is there any research that you feel would be needed to address uncertainties in the evidence base	Expert#1 Research into the effect the product has on biofilms	
		Expert#2 n/a	
		Expert#3 Well designed, large numbers with a number of effective antimicrobial agents or mechanical methods as comparators. Outcomes should be healing time, numbers of infections, pain scores, convenience, time, service costs.	
		Expert #4 Not that I am aware of	

		Expert #5 No	
		Expert #6 No	
		Expert #7 Further research would always be indicated for any product. In this case, a Patient acceptability and/or a Health-Related Quality of Life study could be undertaken to ascertain the patient's opinion of the use of this product on there wound and what effects the use of the same had on their Quality of Life / daily activities.	
		Expert #8 None specifically	
		Expert #9 No	
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe: − Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured.	Expert#1 Beneficial outcome measures: Adverse outcome measures:	
		Expert#2 Beneficial outcome measures: Adverse outcome measures:	

	− Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured		
		Expert#3 Beneficial outcome measures: Outcomes should be healing time, pain scores, rates of infection, convenience, time, service costs. Till the wound is healed or patient discharged from the service. Adverse outcome measures: Infections, pain, costs, time	
		Expert #4 Beneficial outcome measures: Rate of achievement of negative microbiological swabs Rate or preservation of foreign prosthesis Adverse outcome measures: Toxicity level Documentation of reaction either local or systemic	

		Expert #5 Beneficial outcome measures: Patient feedback Data on wound breakdown specifically where this product is used as part of a protocol for example episiotomy wounds Adverse outcome measures:	
		Expert #6 Beneficial outcome measures: Adverse outcome measures:	
		Expert #7 Beneficial outcome measures: Improved Wound Dimensions Improved Wound Healing Rates Reported Patient outcomes – e.g. improved mobility / improvements in daily activities Patient acceptability of the use of the product Reduction in the incidence of SSI's Reduction in the incidence of Wound Infections Adverse outcome measures: Reports of any pain associated with the use of the product	

		The incidence of Surgical Site Wound Infections (SSI's) within 30 days of the Surgical Procedure The incidence and location (Primary/Secondary/Nursing Home/Private Care setting) of Wound Infections further to the use of a wound cleansing solution i.e. Prontosan	
		Expert #8 Beneficial outcome measures: Reduced numbers of infections measured against use of saline to cleanse wounds. We are year on year increasing the number of patients that we use this product on as it certainly reduces the bacterial load – particularly in deep cavity wounds. Adverse outcome measures:	
		Expert #9	
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology,	Expert#1	
		Expert# 2	

		Expert#3 Mechanical debridement has not been compared directly with the product. Nor has effectiveness in very large wounds.	
		Expert #4	
		Expert #5 NHSGGC protocols can be supplied	
		Expert #6 During the recent pandemic I have been encouraging patients to self-care at home to reduce visits into the surgery. I have been issuing prontosan irrigation fluid for patients to cleanse their wounds with. Patients have found it very easy to use, by applying the soaked gauze I know that the wound is being cleansed without disturbing any healthy granulation tissue, reducing the risk of cross infection from contamination	
		Expert #7 None other than as a result of my own clinical experiences and observed wound and patient improvements, I do hope that this product is adopted as part of a standard wound cleansing procedure throughout the NHS in the not too distant future.	
		Expert #8	

		We are year on year increasing the number of patients that we use this product on as it certainly reduces the bacterial load – particularly in deep cavity wounds.	
		Expert #9 As well as the knowledge of infection and biofilm reduction., I have experienced many times the 'build up' of residual products 'left' in the wound beds eg. alginate fibres etc and Prontosan has released these enabling the wound bed to be stimulated, change colour and kick start healing. It is difficult to describe, but rather experience that notes the wound bed is healthier in colour and integrity so allowing the wound to recommence healing. It is observational rather than evidence based Non-sting, simple to teach and demonstrate	

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

GID-MT551 Prontosan

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)* *Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*
1.	14/01/2021	BBraun	Start-up videoconference with the company. A list of questions was sent to the company in advance of the meeting covering key topics such as: • Use of Prontosan in the NHS • Wound care pathways • Prontosan solution versus gel versus gel X • Economic approach	Full responses, verified by the company are detailed in Appendix 1

2.	20/01/2021	Clinical Expert Engagement Meeting	A meeting with all clinical experts to discuss Prontosan	Full meeting notes, verified by the clinical experts are detailed in Appendix 2
3.	25/02/2021	Company Engagement Meeting		Full responses, verified by the company are detailed in Appendix 3
4.	23/02/2021	E-mail sent to clinical experts		Responses in Appendix 4
5.	09/03/2021	E-mail sent to clinical experts		Responses in Appendix 4
6.	17/03/2021	E-mail sent to clinical experts		Responses in Appendix 4
7.	08/03/2021	E-mail sent to company		Responses in Appendix 5

Appendix 1. Company start up meeting notes

GID MT551: Prontosan for acute and chronic wounds

Start-up/Clarification Meeting with BBraun

Date: 14/01/2021

Attendees:
NICE: Kimberley Carter, Lirije Hyseni, Juliet Kenny
EAC: Rhys Morris, Susan O'Connell, Megan Dale
BBraun: Dawn Cooper, Sarah Richardson

Scope Section	Question	Company Response
Population		
	The population in the scope is very broad – are there any particular groups of interest?	The majority of the evidence for Prontosan relates to use in Chronic wounds although there is some evidence in acute wounds, specifically burns. In the UK the focus would likely be chronic wounds because of the slough and prevention and removal of biofilm, potentially leading to bigger benefits.
	Are there any groups who should avoid using Prontosan?	There are some contraindications which are outlined in the instructions for use. There have been some reported sensitivities: rare number of patients who are sensitive to PHMB – may also be sensitive to chlorhexidine, so if they are, monitor use of Prontosan. The company checked quality and complaints department, it can't be ruled out but it is extremely rare.
Current pathway (page 21 of clinical submission)		
	Should the comparator include Ringers Solution?	Ringers solution is not standard in the UK but is a suitable comparator and will likely be mentioned in some of the evidence. In the UK it is only likely to be used in specialised situations such as dermatology but in Europe it is the equivalent of saline in terms of use.
	One study (Wattanaploy 2017) used silver sulfadiazine as a comparator,	

	is this a standard treatment in the NHS for burns?	
	Cleanse vs Irrigate It states that it is habitual practice to irrigate wounds during wound dressing changes. NICE adoption team's initial engagement with clinical experts noted that wounds were only cleansed when 'not healing well' or had visible debris or biofilm. We understand practice is likely to differ for different wound types and will be discussing with a wider group of clinical experts. Are there any sources or guidelines on cleansing that we may not be aware of?	The company suggest that it will be really important to distinguish between cleansing a wound and irrigating a wound. Cleansing – would be wound bed preparation, with treatment objectives – removal of biofilm and slough etc. to cleanse you need longer time and normally an active ingredient. Normal practice is to irrigate a wound with saline however this is also commonly called cleansing. Water can be used instead of saline. Irrigation: pouring saline over the wound, no active 'cleansing' ingredients in saline and unless additional cleansing agent or mechanical cleansing (debridement) used, then no wound cleansing. With Prontosan, active cleansing ingredient means that using Prontosan as irrigation also has a cleansing effect due to surfactant (betaine) and no additional cleansing agent required. Mechanical cleansing (debridement) may also be done in addition. With active cleansing, there is a difference between wound bed cleansing or cleansing around the wound, which is commonly referred to as peri-wound skin cleansing. With Prontosan, the wound bed is cleansed. District nurses more likely to use irrigation and do more dressing changes whereas tissue viability nurses more likely to cleanse. There is a Cochrane Review which reports saline or water not appropriate for cleansing.
	Time to Cleansing Is there a specific time frame recommended for cleansing with saline, water or Ringer's solution? Does it differ between the different wound types and different solutions?	Irrigation with saline takes minimal time, no soaking is necessary with saline as it does not have any benefit. Prontosan: different time for soaks for cleansing depending on wound condition (minimal slough mean shorter soak times). Even the longest soak times fit within a standard appointment – nurses prioritise getting the Prontosan soak on at the beginning of the appointment and then do other tasks. Part of the education package from the company is to highlight this so nurses can plan appointments.

	Is there anything that would be applied to the wound bed or dressing when the secondary dressing is applied?	If you had an infected wound could use it as part of wound bed preparation, but clinicians will use antimicrobial dressing to deal with a confirmed infection in addition, when the infection resolves Prontosan can still be used to maintain the wound bed once the antimicrobial dressing has been stopped . Prontosan has a preventative effect and anti-biofilm effect, but isn't an "anti-microbial". If wound not confirmed as infected and nurse suspects something, they might start using antimicrobials in practice. Then, there is the possibility that they don't need silver dressings etc. because the use of Prontosan, but a grey area and depends on practitioners' use. Prontosan Gel and Gel X are part of wound bed preparation, not same as a secondary dressing. Swabbing wounds and testing for infection isn't straightforward as biofilm is not necessarily ubiquitous throughout wound bed. Getting clinical defined infected wound isn't straight forward. If high exudate, slough, redness etc. then it's indicative of infection. A lot of the wounds dressing, pain management etc are managing symptoms and Prontosan can help with managing the cause (eg. biofilm / slough).
	Access for wound condition / patient should be 'Assess wound condition / patient'?	Yes – this was a typo. Thank you.
	Could the company please run through the clinical pathway for current standard care and for Prontosan? • Prontosan irrigation solution as a replacement for saline? • Prontosan gel alternative to dressing types or as an addition to the pathway Refer to page 20/21 of clinical submission where both prontosan solution and gel are used.	Prontosan irrigation is a replacement for saline and may replace the need for additional cleansing. It is not a replacement for antimicrobial agents. In infected wounds, an additional antimicrobial/antimicrobial dressing will be used. Wounds with suspected infection use both Prontosan and antimicrobial dressings too. The decision on wound infection and treatment approach is a clinical decision. There are no standard guidelines for defining wound condition, although tissue type % is often present on wound assessment tools. Gel or Gel X is applied to wound before dressing and is additional to standard practice however the potential impact is that use of gel may mean less advanced dressing can be used.

	What is the difference between Prontosan Gel and Prontosan Gel X? How is the decision made on which one to use?	Gel has a more runny consistency and is more suitable for cavity wounds because it can fill the cavity. Gel X is thicker, stays in place better and is more suitable of larger wounds such as leg ulcers.
	Acute wound care flow-chart: 1) There are three wound conditions. For burns and / or infected wounds it does not say whether irrigation or soak is recommended. I assume this should be soak. 2) What types of wound conditions come under 'patients at high risk as per trust policy'? 3) Prontosan can be used for first- and second-degree burns. Can it be used for third degree burns? 4) Are trauma wounds covered in this pathway? If not, should this be included?	1) Yes, it should be soak 2) This relates to patients at high risk of wound infection and will be a clinical judgement based on patient characteristics (e.g. poorly controlled diabetes, immune disorders). 3) Yes, it can be used for all burn types 4) The focus is mainly on burns. Acute wounds are usually healing more quickly and not really followed up. It can be used for trauma wounds 5) Trauma is covered in the left hand arm of this diagram.
	For chronic wounds: Wound condition, are these three categories presented the main wound conditions? Do all chronic wounds follow the same process? Do certain wound types fit best in one of these wound conditions or can they apply to all wound conditions?	4 stages of healing and progress through all stages. Some chronic wounds develop from skin breakdown and loss of skin integrity – doesn't always come from an acute wound that doesn't heal and they can follow a different healing journey i.e. usually chronic wounds persist in the inflammatory stage. Chronic wounds add a level of complexity. The wound healing can go backwards, and forward and chronic wounds may get stuck in the inflammatory phase. Clinically nurses look for granulation tiisue presence as a sign of wounds progressing to healing. Wound healing is a continuum and wounds can improve, stall and regress over time.
	Is it appropriate to include the acute patient pathway? Are burns the only wounds of relevance? How are acute/chronic wounds defined?	No, there is evidence on trauma in one of the UK adoption studies, but there isn't a lot of evidence. Can be used for burns, surgical sites and trauma. An acute wound can become a chronic wound (depending on patient risk) and may want to use Prontosan preventatively to be careful if patient has risk. Chronic pathway - hard to define chronic and there is no standard definition of a chronic wound. Markov

		model because it can go up and down. Don't have a standard definition of what a chronic wound is.
Economics		
	Can you please offer any insight into the company's plans for the economic model? 1) Model structure (decision tree or Markov) 2) Time perspective 3) Software package used 4) Comparators 5) Clinical outcomes intended as model inputs 6) Sensitivity analysis (deterministic or probabilistic) 7) Thank you for the very helpful diagrams of proposed pathways. There are 3 separate products (solution, gel and gel X), which may be used separately or together in 2 different pathways (chronic and acute wounds), which will have very different patient populations. Are all of these combinations being modelled, or is there a focus on one scenario? 8) The economic modelling will vary depending on which size of product is used and the assumptions around this. Are there different options being modelled or a focus on one product?	• Excel • Markov model • Population is venous leg ulcers and hopefully burns • Time Perspective has not been decided but is likely to be 3, 6 and 12 months • Comparator is Saline with cost taken to 0 to reflect use of tap water • The maximum cost will be modelled using Prontosan, both the solution and Gel X.
Literature Search		
	Can you please provide a rationale for the date restriction (from 2005)?	
	There are 2 PRISMA diagrams in the appendices both with different results and neither result matches the number of papers included in the review. Can you please run through the literature selection process during the meeting?	Something went wrong in the submission and the company will provide the correct ones.

Additional information provided after the meeting in a follow-up email included:

Comparators

1) The comparators in the scope are saline, water and Ringer's solution. Do you have an estimate of what proportion of wounds are currently treated in the NHS for each of the comparators?
    - It will be varied depending on local policy – as it's not a prescribed item then water usage is very diificul to measure.
2) How are the decisions made to use saline, water or Ringer's solution? Is this related to the wound type? Wound condition?
    - No – it tends to be habitual for the nurse or depending what is historically used in the local area, personal opinion, and infection control oversight
3) One study (Wattanaploy 2017) used silver sulfadiazine as a comparator, is this a standard treatment in the NHS for burns?
    - It is well known and used widely in burns units to our knowledge, dependent on local policy

Wound types

4) The results were summarised by wound type (p101) and include leg ulcers, DFU and acute wounds (burns). Pressure ulcers were not included as a specific group. It seems that it is included in studies with mixed aetiologies. Is there no evidence summarising PU separately?
    - That is correct.
5) Evidence is provided for burns which are acute wounds. Can you confirm that no evidence was available for other acute wounds?
    - That is correct.

Appendix 2. Clinical Expert Engagement Meeting Notes

Notes from Expert Engagement Meeting for MT551 Prontosan for acute and chronic wounds

This document summarises the discussions that took place at the expert engagement meeting for MT551 Prontosan for acute and chronic wounds, which took place on Wednesday 20th January 202112:30-14:00

Patient population

1. Which wound types are likely to benefit from Prontosan/cleansing? The evidence covers a wide range of wound types (including, venous leg ulcers, diabetic foot ulcers, arterial ulcers, pressure ulcers, non-healing surgical wounds, burns, 'chronic wounds', 'mixed ulcers' and 'mixed wounds'), where is cleansing most commonly used in wound care practice?

All clinical experts had some personal experience of using Prontosan in their own practice. They all noted that Prontosan was suitable for a wide range of wound types and settings. Specific experiences of using Prontosan described by the experts:

- Every wound on a trauma/surgical ward because all wounds are at risk of infection.
- Use it on wounds that need cleansing, and those with history or risk of surgical site infection.
- Most chronic foot ulcers and venous/arterial leg ulcerations – biofilm is a major issue in these wounds and Prontosan helps.
- For cleansing leg ulcers by 1 expert working between primary care and community care
    - The expert described Prontosan as their go-to product for chronic wounds because it is a safe, simple to use product which helps with biofilm, de-sloughing and wound bed preparation.
- In oncological reconstructive surgery
    - The expert gave breast reconstruction surgery as an example of when he uses Prontosan in current practice. He noted that the added value of using Prontosan to treat infected surgical wounds can depend on time of presentation. In his view, Prontosan is likely to be most effective when used early.

- This expert also noted that Prontosan can help to prevent biofilm formation around prostheses.

General comments from experts included:

- There are resource implications but there is a developing awareness that not all wounds need to be cleansed at every dressing stage. Patient profile has changed, patients older, lots of co-morbidities affecting the healing process which means ordinarily acute wounds have a higher risk of becoming chronic/non-healing wounds.
- If Prontosan is accepted, there should be clear guidelines on what wounds would benefit such as surgical site infection risk and/or long-term chronic wounds.
- One expert said that there is a paper that demonstrates that Prontosan was no more effective than saline in some cases.
- One expert stated that there is a need to define what is a chronic wound because they felt Prontosan was being used too much and a clear place for the product needs to be defined. For example, in acute care for leg ulcers, water would be used instead of either saline or Prontosan.
- Some non-acute wounds may be treated in an acute setting however – if a Negative Pressure Wound therapy with instillation is needed this would not be classed as an acute wound. NPWT is 'commonly' used in the Acute care setting for post-surgical wounds that are classed as dirty infected wounds (SSI Guideline) but may also be used the management of a patient whose wound is at risk of infection (e.g., surgery involving the insertion of a prosthesis) or on occasions for the management of a patient who has been admitted for the management of a chronic wound

Follow-up question from NICE: Can the terms 'acute' and 'chronic' become somewhat arbitrary? Is there a better way to group wounds?

Two experts suggested using the National Wound Care Strategy definition of a chronic wound: all wounds are defined as chronic after two weeks if non-healing as it will capture different wound types.

One expert explained that in Glasgow, Prontosan soak is also used prophylactically following episiotomy where suturing is delayed because delayed suturing increases the risk of infection and chronic wound development. In this setting Prontosan would be indicated as a cleansing agent to minimise the risk of infection post episiotomy (due to the anatomical location of the same) in which case either a Prontosan soak might be considered for immediate use (pre suturing) and Gel X might be considered for the maintenance of risk minimisation as it would be impractical to cover the suture line with a traditional interactive dressing product

2. Is Prontosan/cleansing appropriate for children? Are there significant differences in cleansing protocols for adults and children?

None of the clinical experts had any reasons why Prontosan could not be used for treating wounds in children.

a. One expert stated is no evidence looking at use of Prontosan in children but they use it. One expert noted there is a paper looking at Prontosan in burns in children. The EAC has checked and confirmed this, the paper is Ciprandi et al (2018).

b. One expert stated that there are specific guidelines in Scotland relating to its use in children.

c. One expert stated that the company only suggest it should not be used in neonates

Evidence

3. Is it appropriate to generalise evidence on cleansing from 1 patient group to another – for example adults with burns to children with burns? Or from 1 chronic wound type to another?

Clinical experts largely agreed that it was appropriate to generalise evidence from different patient groups however raised specific concerns around vascular wounds which led on to further discussion about the potential benefits of using Prontosan prophylactically to maintain the health of the wound bed.

- One expert stated that the reason for a chronic wound didn't matter when it came to treatment/management approaches as there are commonalities within the patients groups in terms of why a wound is chronic or non-healing.

- One expert noted that treating all chronic wounds the same was potentially problematic for vascular wounds where a poor blood supply is going to impact wound healing and if the blood supply cannot be improved, the product used to treat the wound won't matter. This concern was acknowledged and supported by other experts.

- Two experts suggested that in cases where patients were waiting for surgery to improve blood supply, Prontosan may be used prophylactically to manage the wound and prevent infection. This was supported by one expert who suggested that in these wounds they try to avoid sharp debridement to avoid further damage in already hard to heal patients but if there is some debris then Prontosan can provide a gentle debriding effect which can be beneficial.

4. Is it appropriate to consider evidence collected from studies that included a mix of chronic/non-healing wound aetiologies?

The experts agreed that, in the absence of evidence for specific populations, and taking account of the fact that most chronic wounds are treated in a similar way and have similar prognosis, evidence from mixed studies could potentially be suitable for decision making..

Current practice

5. Are there any professional society guidelines or local practice guidelines on cleansing that we should refer to?

Specific guidelines in Scotland include general wound care guidelines, maternity guidelines and paediatric guidelines. [The National Association of Tissue Viability Nurses, Scotland (NATVNS) guideline was shared with NICE after the meeting]

Throughout the discussion, the experts also referred to National Wound Care Strategy Programme, and existing NICE guidance.

6. What is the role of cleansing in infected wounds?

Clinical experts suggested that there is a difference between irrigation and cleansing. There was some discussion around whether wounds in different settings were cleansed or irrigated and how often wounds needed to be cleansed. The general consensus appears to be that the decision will be clinical judgement based on the condition of the wound at dressing change appointments.

There was a broader discussion around the management of infected versus non-infected wounds with a general consensus that in infected wounds, Prontosan is used as an adjunct to antimicrobial management to help deal with the underlying cause of infection (it helps to remove deeply embedded debris, slough and biofilm) but in non-infected wounds, prophylactic use of Prontosan might prevent infection.

- One expert stated that if Prontosan was not used or not available then most people will be using an antimicrobial dressing.
- One expert noted that Prontosan does have an antimicrobial effect within the wound margins but the product is not classed as an antimicrobial product.
- One expert noted they were not aware of any clinical issues / reported adverse reactions further to the combination of the use of Prontosan (in whatever form) with any current antimicrobial dressing product on the market.
- One expert stated they were not aware of any specific contraindications.
- One expert explained that they used Prontosan Solution for prevention (biofilm formation), treatment (when biofilm and/or infection is see/suspected and prophylactically on the at risklimb/foot/wound/patient. They used Prontosan gel as an AM treatment instead of an AM dressing.

Follow-up question from NICE: What is the purpose and duration of Prontosan treatment when used prophylactically?

There was consensus among the clinical experts that the aim of prophylactic treatment is to try to maintain the health and integrity of the wound prior to surgical closure and that treatment would be time-limited by local protocols (max 2 weeks).

- One expert said that use of Prontosan in post-partum care (see previous comments) was a good example of prophylactic Prontosan use.
- Another expert explained that the timeframes used for post-partum perineal wounds would also be relevant to wounds (chronic or acute) that are scheduled for surgical debridement or grafting. In these situations, Prontosan is used prophylactically prior to surgery as a bridging treatment.

A general comment by one expert was to note that Prontosan is not the only product on the market and some places may look for cheaper products. A second clinical expert noted that there is no 'like for like' product available. Different products have different constitutions/make-ups and may have different actions.

7. Are there any wounds that would always be cleansed during dressing changes?

The consensus among the clinical experts is that there are no specific wound types that would be cleansed at every dressing change. The decision to cleanse will be made based on clinical need following wound assessment (e.g. clinicians will consider presence of slough, devitalised tissue, patients at high risk, pressure ulcers etc).

- Two experts agreed the soak was the most important part of the process but that this can be challenging due to the time involved (5-15 mins depending on wound size/condition).
- One expert noted that if the soak was applied at the start of the appointment then no additional time was added to the appointment and stated that their appointment protocols now say that the soak should be applied straightaway.

Query from the EAC: Are we talking specifically about the use of Prontosan irrigation solution? What about the use of Prontosan gel/gel X?

The consensus among the experts is that the soak using the irrigation solution is the most important element.

- One expert stated they didn't routinely use the gel but may use it to support the post cleansing process.
- One expert stated that the gel would be used to support and maintain the irrigation/soak process.

- One expert noted that the gel is part of the 'toolkit' to carry on the work of biofilm disruption... and applying a 'hydrogel' to lift and soften any resistant infected slough which may be apparent. If the slough/wound bed is not clinically infected, then a non-antimicrobial gel will do the job

There was a wider discussion around the difference between irrigation and cleansing/soaking including instillation.

- One expert stated that irrigation is just to remove superficial debris/infection whereas instillation works at deeper levels of the wound/tissue. Instillation is specific to negative pressure wound therapy and although negative wound therapy is used in the community for very hard to heal wounds, the installation aspect may not occur in the community. One expert noted that the use of NPWT and other wound management techniques are likely to increase in all primary healthcare settings in light of current the NHS plan (more patient being cared for in their own home) and the recommendations within the National Wound Care Strategy.

- One expert noted that this may be a major consideration for the cost effectiveness as not all wounds would require instillation (much more Prontosan used) but noted that it is less commonly used and only in acute setting. The clinical expert also noted that the time for using Prontosan is immaterial, as the whole process takes 3-4 hours so when instillation is used appropriately, you are just comparing the price of the products.

8. Would cleansing be done until the wound closes or is cleansing stopped before then? What indicates that a wound no longer needs cleansing?

The clinical experts agreed that once wounds began to epithelise or if the wound bed was quite shallow then the wound would not be cleansed or the use of any cleansing solution or soak should only be dictated by clinical need further to an assessment of the wound and if addressing only is used, would prefer the use of an interactive dressing (as in NICE SSI Guideline)

- One expert noted that the type of secondary dressing may have an impact on the decision to cleanse as some dressing have cleansing properties.

- One expert noted that they may use Gel X if they have a known history of infection but that this is rare. Another expert said that it is very expensive. They stated that the choice to use irrigation solution versus gel is not an 'either or or' because they have different indications.

- One expert noted that Gel X would be used in the maternity setting and has the advantage of not requiring a secondary dressing.

- One expert advised that they would consider the use of gel like an antimicrobial. It should not be used in place of a standard hydrogel to hydrate wounds due to the cost.

9. Is saline the most appropriate comparator? Would saline be appropriate for cleansing burns?

The general consensus is that saline or water is the most appropriate comparator for Prontosan irrigation solution except in a burns setting where buffer solutions would be used. However, one clinical expert noted that their experience with burns was only in an acute setting before a patient is moved to a specialist burns unit.

10. Do patients report pain when wounds are cleansed with saline or water?

- One expert noted that neither solution per se causes pain. It is rather that the wound bed is painful and therefore any solution or interference could cause pain. If the solutions are below body temperature too, this can cause pain at dressing change.

- It is the action of cleansing the wound or removal of a dressing product that cause pain rather than the solution used.

11. How often is Ringer's solution used to cleanse wounds in the NHS?

The clinical experts agreed that Ringers solution is not routinely used in the NHS to cleanse wounds but noted that there is a dressing which contains Ringer's solution available and that this would be used if clinically indicated for debridement.

12. How long does cleansing of a wound typically take? What does this depend on?

The clinical experts agreed that the time taken would depend on the wound/wound condition but typically a Prontosan soak would take between 5-15 minutes depending on wound condition, but most soaks were 10 minutes. Specific comments included:

- One expert stated that it is not appropriate to compare Prontosan with saline cleansing times as there is no cleansing/soak with saline.

- One expert said that if the wound is granulating then the soak would only take about 5 minutes.

- Experts noted that in some areas education on wound care is still lacking.

Follow-up Query form EAC: Does the use of Prontosan have an impact on a standard appointment time?

The experts agreed this was not an easy question to answer. They all agreed that the appointments often over-run and managing the patient list is really difficult particularly in the primary care and community settings. Experts all agreed that provided the application of a

Prontosan soak was done at the start of an appointment then no additional time was needed. Specific comments included

- Chronic wound appointments in wound clinics typically need 30 to 45 minutes however this time may not be allocated in the non-specialist clinics. Experts said that longer appointments were likely to be more acceptable to both health care professionals and patients if they resulted in shorter healing times.
- Only the cost of the product needs to be added to the appointment. No additional time/resource.
- Time needed for the appointment will depend on wound condition not on type of dressing. One expert said that in a wound clinic the wound dressing may not take long but the wound assessment and determining a treatment plan are also included in this time (i.e. holistic wound assessment and documentation).

Using the technology

13. Do you use the range of preparations of Prontosan (solution, gel, single use pod)? Do they have different applications?
    - Two experts stated the whole range as needed.
    - One expert noted that irrigation solution is always used and the gel sometimes. Cost effectiveness is considered in Primary and Community Care and many patients have a 350ml bottle as this is more prudent and is for single patient use which is left in the patient's home or brought with the patient to the GP surgery. Acute areas nearly always use the pods
    - One expert noted that solution and single use pod – wound cleansing or soak; Gel – maintenance of wound bed condition / minimisation of risk of infection and/or when not practical (anatomically) to use a dressing product
14. Is Prontosan gel an alternative to advanced dressing types or as an addition to the pathway?
    - One expert stated that they would rarely use 2 anti-microbial products in a wound. If the gel is applied, then it would just require a secondary dressing.
    - One expert noted this can be based on ongoing wound assessment
15. Are the training resources and customer support offered by the company of good quality?
    - From two experts - Yes

- One expert specifically noted that they are excellent with good support. Ethical when demonstrating and knowledgeable. Good visual resources for the staff too with application guides

16. Will it be used in community, primary and secondary care?

    - Any setting where chronic wounds are found or suspected

17. Is it more likely that health care professionals will use ampules or containers that can be used for several dressings, and will that vary across settings?

    - Acute settings more likely to use smaller containers of the solution (as clinically dictated) whereas primary care settings are more likely to consider the use of larger containers of the chosen product that can be left in the patients home for ongoing use for that patient in an effort to be more cost effective.

18. How do these products relate to topical antimicrobial treatments or dressings?

Questions 13-18 were not discussed explicitly during the call, although the experts answers to previous questions indicate that Prontosan is used in community, primary and secondary care. Alternative questions related to the use Prontosan gel and the use of Prontosan products have been added to the list of follow up questions below along with questions 15 and 17.

Follow-up questions

1. What are the key risk factors for delayed wound healing?

    - age?
    - vascular disease (is it the disease alone or the presence of specific complications of vascular disease that matters?
        - Vascular inefficiency as stand-alone is key. Complications can be pain, neuropathy, skin disorders (varicose eczema etc), oedema etc-all resulting from vascular disease.
    - immunosuppression?
    - presence of infection?
    - anything else?

- The variables are far ranging-concordance, pain, lifestyle, BMI, nutrition, mobility, understanding, practitioner skill, pressure, site etc. But the topics listed already are key factors I would agree

2. Please can you describe any situations when Prontosan gel is used:

- Instead of Prontosan irrigation solution?
  - From one expert:
  - Always an addition, not stand alone. The solution is the default cleaning and preparation for the wound bed and for the gel application if required. I use it instead of an advanced (anti-microbial) dressing. Not as well as. 'Mixing' advanced dressings will make it unclear which product produced the most effect plus cost considerations.
  - From one expert: Post discharge from an acute setting if the patient has been assessed as at risk of wound infection and the interval between dressing changes/reassessment are likely to be extended for whatever reason.
- In addition to Prontosan irrigation solution?
  - Known history of previous wound infection
- Instead of an advanced dressing?
  - From one expert: Most likely to be Maternity and Post Natal settings or if the anatomical location of the wound negates the use of an interactive dressing (e.g. has been tried but for a number of potential reasons the dressing does not stay on or in some case the patient refuses to have a dressing
- In addition to an advanced dressing?
  - From one expert: not commonly used in conjunction with an advanced interactive dressing unless the patient is thought to be at high risk or has had a history of recurrent wound infections.

Instead of another inert hydrogel?

- The gel is used primarily to combat infection or if infection suspected within slough on the wound bed and this needs hydrating and clearing. If no infection seen or suspected I would choose a standard amorphous gel to encourage debridement and cleaning.

- From one expert: The use of hydr0gels (for rehydrating a wound bed) has significantly decreased in the past decade, due to the advent other advanced wound management products; improved understanding of wound management techniques and better hydration of the patient in general. In my clinical experience, I have never used Prontosan Gel X instead of an inert Hydrogel.

- Appendix 3. Notes from Company Engagement Meeting for MT551 Prontosan for Acute and Chronic Wounds

Notes from Company Engagement Meeting for MT551 Prontosan for Acute and Chronic Wounds

This document summarises the discussions that took place at the company engagement meeting for MT551 Prontosan for acute and chronic wounds which took place on Thursday 25th February 2021, 9:00am-11:00am.

- General question around the academic data and confidentiality marking
    - Harding et al (2012): ITT data is marked up as confidential but it's the Per Protocol data that is in the public domain. Intention to treat data which is used in the model is confidential as it is not in the public domain.
    - Company to discuss what they can do about the extent of the marking.
    - EAC to share document which cross checks the AiC data with public domain data

- Question around the 'wound closure' model being generalisable from venous leg ulcers to all chronic wounds?
    - Prontosan would be used in all chronic wounds but the model is based on venous leg ulcer data as this is what is available. Validation from clinical experts suggest that the underpinning process of removing biofilm and improving condition is what moves to healing pathway and all wounds would go through this process. The company recognise that key clinical inputs are taken from a study that is specific to people with venous ulcers however they consider that evidence from VLUs likely to therefore be generalisable to other chronic wounds.
- Time Horizon: We'd like to understand a bit more about how the time horizon was chosen and if any other time periods were tested
    - Spreadsheet models every month up to 12 months
    - Took guidance around other models e.g. national work by Guest et al 2012 – 2020, and what time horizons might be appropriate as well as with wound healing pathways, what seemed appropriate. Advice suggested most impact is assessed at 12 months but the company noted that they could extend the model to 5 years.

- Choice of exponential extrapolation
    - The company explained that they worked with an external advisor. All standard parametric models were tested. The Weibull model provided the best fit to the observed data but the exponential model was considered preferable choice overall because it incorporates a hazard function that is constant over time , which is better suited to generating inputs required for a Markov model (one off/constant transition probabilities).The exponential model produces a more conservative estimate of the

wound healing risk, therefore the worse fit to the observed data is unlikely to result in an overestimation of cost savings
    - The company can send the Weibull data but this is not to be shared beyond EAC for reference.

- Using gel for the whole pathway
    - Addition of gel makes it more expensive so more conservative model
    - Gel provides longer contact between active ingredients and wound with gel application so more likely to have results due to consistent application
- The instructions for use say that Prontosan can be used in infected or non-infected wounds but the company say it is not a treatment for infected wounds. Clinical experts have said they believe it prevents infection however. Could the company clarify the role Prontosan plays in the management of infected wounds and what the purpose of the antimicrobial agent is, if not to treat infection?
    - Prontosan wouldn't replace more specific infected wound treatment (e.g. silver dressings) but can be used alongside it for wound bed preparation
    - PHMB is an adjuvant to surfactant. If surfactant only would achieve most of the job, but antimicrobial minimises bioburden but wouldn't be sufficient to treat infection always. There is a synergy between two ingredients and their mechanism of action. If only using betaine for the mechanical action you take off biofilm, but don't reduce what is uncovered i.e. bioburden within the biofilm.
    - Wouldn't treat a serious infection with Pronotsan alone. The company noted that if Prontosan is used in an earlier stage, with a lower level of bioburden, it will have a bigger impact than when using it on moderate or severe infections. Prontosan can be used alongside treatments which are intended to treat a 'local or spreading, for example - use Prontosan with a silver dressing applied to address the infection.
    - Some evidence for gel and effect on biofilm included in part 1, and what it supresses, and another paper with effect on bacterial burden and species of bacteria. These are in-vitro papers on the way it works.
    - Wounds can be clinically infected and may need additional treatments, such as silver dressings, but other wounds may not have clinical signs of infection, but still have a biofilm and slough that impacts on healing negatively and this is where the Prontosan is having an impact.
    - There are real world compliance issues with dressings, dressing changes. Difficulty getting to appointments, completing appointments. District nurses not always able to get to community clinics.
    - Disconnect between what happens with TVN (in hospital) and district nurses – Prontosan used by TVN and saline used by district nurses.
    - Gel essentially maintains a good wound condition until next wound dressing change.

- Would use of gel prevent the use of any other topical agents?
    - Contraindicated for some enzyme based products but fine to use with the majority of used dressings even silver dressings/foams/alginates.

- Not an anti-microbial or an anti-septic. It is classed as a wound cleansing agent but may need to check what definition of antiseptic is used and understanding of clinicians around what is an anti-septic.
  Main disconnect is between clinical experts and understanding of how it should be used. Some clinicians (anecdotal) will keep Prontosan back for the most seriously deteriorated and/or infected wounds.

Wound bed preparation

1. How generalisable are results for this study to whole population?
   - The model inputs are taken from a study with mixed aetiology wounds so it is pretty generalisable to the whole population. The company recognised however that most of the patients in the study had pressure ulcers or vascular leg ulcers).
   - The Valenzuela paper does not have any details on which wound types are included (mixed aetiologies). It is an RCT with gel application for 2 weeks.
2. Purpose of the wound bed preparation model.
   - Broadly – Use of Prontosan to get wounds to a healthy state and then revert to standard care rather than using it all the way to wound closure.
   - There seems, from literature, to be data on use of Prontosan going to wound healing, or for short time use and the company wanted to model what is the impact of that type of use? The idea is the Prontosan would be used as short term intervention for the model, and then revert to normal care once wound is in better state. The company note that there are then there are still costs. The assumption is that the wound is then in a better state, and they would then go to saline as standard care. Wounds can change by regressing and that isn't covered in this model.
   - The company note that Prontosan should be used to wound closure but there is a possibility that using it to improve wound condition is appropriate.
   - There was a brief discussion on difference between a surgical wound and surgical intervention on a chronic wound and how these two different wound types would be managed.
   - The company noted that there is possibly a lot more interest in wound bed preparation in Asia where plastic surgeons want a quick time to get to a condition for treatment.
3. BWAT Measurements: How often were the BWAT measurements taken, and how reliable are they between different time points and health care professionals?
   - Used every 7 days (in methodology), staff who provided assessment were different from cleansing, so all part of wound association, and had training.
   - It is a validated score so appropriate for use for wound bed score.
   - Paper to share about wound assessment score tools used in the UK.
   - There is no standard reporting of wound bed condition in the UK however the company consider that clinical staff would be able to fit the wounds they manage into the BWAT score.
   - Clinical difference between score 13-14 comes down to question of epithelialisation. All scores go down to 1. 100% epithelialized would be healed and the score before

that is 75% to <100% epithelialized and so most wounds would sit in 14 for some time. 13 would be a healed wound, 14 would be well on the way to healing.
- Need to have 75% epithelialisation to get score 14.
    - Stopping Prontosan early – sensitivity analysis? Reduced costs increased cost savings but only if wounds carry on to healing and don't need to have increased treatment/interventions.

4. The model diagram appears to show a possibility that wounds break down and re-enter the model, but this does not appear to be included in the model. Is that a correct interpretation?
    - Although the model diagram includes an arrow that suggests that patients can return to an earlier state, in fact patients only move through the model once/in one direction
    - Taken to a score of 14 where they are starting to epithelialize, but important to note that wounds can regress, or stagnate.

5. For both models: are the assumptions on gel pack size, and volume used, the same for both models, and could you explain a little more about the assumptions used for the calculations
    - Wound bed condition – for base case, used 50g, for lower used 250g for upper, doubled 50g price.
    - Wound healing – looking at long term use, patients may be given larger tube even for small wounds due to the 8-week shelf life after opening. For wound bed condition, felt they may be more likely used 50g as this is achieved rapidly.
    - Shelf life after opening is 8 weeks with the exception of the 40ml ampule, clinic more likely to have an ampule. Use of smaller tube as base case conservative as less cost-effective way to purchase.
    - In clinic there are anecdotal reports that clinicians are likely to, with infection control consent, decant into a pot and then use on the person, then decant again for another patient – so may use tube multiple times.
    - The choice of tube size may also be wound dependent, if the wound is large and has slough then it is more likely to use 250g, and if it is a clear wound then 50g.

Appendix 4. E-mail clarifications to clinical experts

Additional Questions for experts – sent via e-mail
E-mail on 23/02/2021

general query about what defines a 'topical' agent?

- Would both solution and gel be classed as topical agents or just the gel as it remains in place?

One Expert: for me they both are. The gel and the solution are applied on the surface of a wound. Because the solution is often left as a soak, this for me is a topical agent, but even if it wasn't even left on as a soak I would still describe it to other nurses as a topical agent.

One Expert: A topical agent is one that is applied to the wound (from/on the outside) so would apply to both the solution and the gel, whereas a systemic agent is one that works from within the body - is ingested (e.g. a tablet) or injected (e.g. a vaccination given via an infusion device).

One Expert: I concur

- Is it possible there would be different clinical interpretations of what counts as a topical agent at all or is it a general clinical term which has a consistent meaning?

One Expert: no, not in my experience-dressings, solutions, gels etc are all expressed as topical agents in nursing woundcare terms

E-mail sent on 09/03/2021

1. What is a typical thickness of Prontosan Gel likely to be?

One Expert: In my experience – you just need to cover the surface of the wound with a tin layer of Prontosan Gel and then cover with an appropriate secondary dressing, however if not practical to cover the wound with a dressing (due to anatomical location) then it would be best to reapply a thin layer of Gel to the cover the wound surface 2 or 3 times a day to optimise the chances of achieving the assessed treatment objective.

One Expert: Instructions are 2- 4mm

One Expert: Approximately 2mm

One Expert: Approximately 0.5-1cm deep

One Expert: I tend to use the thickness of a £1-coin 3mm if thick slough and 1-3mm if minimal slough or wound bed clear when advising nurses as a guide

2. Is 52 cm^2 a reasonable mean estimate for a typical venous leg ulcer?

One Expert: OK as starting point but in my experience a little on the small side.

One Expert: According to colleagues who do this, yes

One Expert: There is no such thing as a typical venous leg ulcer or even a mean estimate – most wounds are not even measured as they have different shapes and may even cover the whole leg.

One Expert: Some can be circumferential and the length of the lower limb so that may be a bit conservative. Is that figure gleaned from somewhere?

One Expert: I don't treat venous leg ulcers

3. What would you expect a typical time for dressing changes for a single venous leg ulcer to be?

One Expert: The time taken will of course depend on the nature of the patient's ulcer and treatment plan – and If compression therapy is included? Unfortunately, appropriate Compression therapy is underused. Furthermore, to some extent time taken will also depend on the expertise of the practitioner, in addition to the experience of the patient – previous dressings changes / current symptomatology / questions they need to ask about the management of their ulcer to date etc. at the time of dressing changes. The assumptions below are therefore based on an experienced practitioner.

   a. For a practice nurse?

   One Expert: 10-15mins (without compression)
   One Expert: 30 mins according to nurses who do this
   One Expert: 20 mins
   One Expert: Single leg, single ulcer I recommend in our CCG contract 30minutes, (45 mins for 2 legs). Some surgeries however will only allow 20 minutes for this. Without compression take 10 minutes off.

   b. For a community nurse (not including travel time)?

   One Expert: 20-30mins (with compression)
   One Expert: 45 mins according to the nurses who do this
   One Expert: 20 minutes
   One Expert: Same as the procedure is the same. Community nurses have slightly more flexibility than a PN as not definitive booked timings.

One Expert: Dressing changes for leg ulceration should take between 40min to 1 hour but practice nurses have just 10 minutes (if they are commissioned to do leg ulcers they may be able to allocate more time) and community nurses are always in a hurry and therefore corners are cut.

4. In your experience would you be more likely to use the 50g volume or 250g volume gel, and the 40ml sachet or 350ml bottle of solution? Are the two sizes used for different reasons?

One Expert: The smaller volumes are more likely to be used within an acute care setting (single use of the product) or when the wound surface area is small in primary care,

whereas the larger volumes are likely to be used in primary care (such as when the product can be left in the patient's home and safely reused – as per manufacturer's instructions- or when clinically indicated for the management of very large wounds.
One Expert: Patient dependant and how long you are intending using products – more economical to use large sizes.
One Expert: 350ml bottle so it can be decanted in clinic or the patient can decant it at home on to gauze. I would be more likely to use the 50g gel because we review treatment regimes after 2 weeks and would not want wastage.
One Expert: We use 250 volume gel and use it again on the same patient. We also have both the 40mls pots and on high wound care wards, we use the solution.

One Expert: I think because of the nature of complexity for TV nurses in hospital, they find the 250g gel useful but in the community/primary care I have only ever seen the 50g tube. In hospital the 40ml pods are always used and by some GP surgeries locally, but I usually advocate the 350ml bottle as its far more cost effective and when I suggest it the bottle is rarely wasted as chronic wound will take time to heal and once commenced, I use it until point of healing

E-mail sent on 17/03/2021

- When using either Prontosan or Saline solution single sachets for irrigation, is one sachet sufficient for wound irrigation? Do you sometimes need to use more than one sachet?

  One Expert: Obviously depends on the wound size and wound bed state so it's a difficult one to state I'm afraid. In complex wounds you may often use more than I of either. I usually order the 350ml bottle as much more cost effective

- Would you use Prontosan Wound Gel X on burns

  One Expert: Gel on burns? - yes definitely

Appendix 5. E-mail clarifications to company

Email sent to company on 08/03/2021

Query

Could I please check what the reference is for the costs you used for outpatient visits in both the wound closure and wound bed preparation models? (both for the 2008 and the 2018/19 costs).

Response

- We used the PSSRU unit cost for out-patient cost
- In the 2008 document this is in the “services” document, section 6.2 “hospital costs”
- We also used the 2018/2019 PSSRU data for the updated costs in section1: “7.1 NHS reference costs for hospital services.
- It would appear that there is a typing error and I must not have explained this thought process well in the document. Please allow me to fill you in now.
- The 2008 data reports the “non-consultant” outpatient cost.
- The 2018/2019 PSSRU report data differently and includes ALL outpatient attendances.
- The 2018/2019 it not an accurate comparison to the 2008 data in our opinion, as such we used the “lower quartile” cost from the 2018/2019 data to be more representative of “non-consultant” appointments and a more accurate data set to use to be comparable with the 2008 data.
- The typing error: the cost should be £96 in 2018/2019 for outpatient he spread sheet says £97

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

Prontosan for acute and chronic wounds

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from Cedar to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **Tuesday 23 March 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

18/03/2021

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page11 Prontosan is a class III, CE marked medical device manufactured by B.Braun Medical Ltd.	Prontosan is a class III, CE marked medical device manufactured by B Braun Medical AG.	For all Prontosan Range B. Braun Medical AG, Switzerland is the responsible manufacturer; B. Braun Medical Ltd is legally a distributor. Apologies as this was probably not clear from the original MIB submission.	Thank you for the clarification, this has been corrected.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 18 company exclusion of studies not adhering to IFUs: The EAC notes that there is a possibility that Prontosan will be used in ways that are not strictly defined in the instructions, for example soak times may vary between 10 to 15 minutes despite the IFU's stating 'at least 15 minutes'.	Propose"…..example soak times may vary from irrigation to 15 minutes despite the IFU's stating from 'rinsing' to 'at least 15 minutes'."	Accuracy	Thank you for the comment. It is not quite clear what change is requested here so we have added detail to the text to be in line with the IFU for clarity

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 22 Borges "Follow up 6 months"	please change to "no follow up"	Patients were recruited over a 6 month period. Process was biopsy before cleansing then cleansing provided with 1 x 1 min irrigation with after which a second round of biopsies were taken There is no longitudinal follow up, the follow up is before after a single application of cleansing. With some patient dropping out after the first set of biopsies.	Thank you, this has been clarified in the text.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 29 – Table 9 Assadian: -Company excluded this study on the basis that it was used outside of the Instructions for Use as only a single application of Prontosan was used. EAC agree that a single application of Prontosan irrigation solution is likely to be representative of UK practice	-Company excluded this study on the basis that it was used outside of the Instructions for Use as only a single application of Prontosan was used. EAC agree that a single application of Prontosan irrigation solution is unlikely to be representative of UK practice therefore concludes this study has limited applicability.	Possible typing error	Thank you for your comment, this typo has been corrected.

therefore concludes this study has limited applicability.			

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 44: One comparative cohort study (Assadien 2018) was excluded by the company as the use of Prontosan was outside the instructions for use with a 20 minute wet-to-moist cleansing of wounds using either Prontosan irrigation solution or saline	One comparative cohort study (Assadian 2018) was excluded by the company as the use of Prontosan was outside the instructions for use due to a *single* 20 minute wet-to-moist cleansing of wounds using either Prontosan irrigation solution or saline. IFU advise frequent use of Prontosan.	Propose the inclusion of the word single to reflect the practice used in Assadian and impact expected outcome from a single application IFU state Prontosan should be applied frequently to achieve and maintain an effect Typo Assadian	Thank you for your comment. We have added text to the section for clarification. Type corrected

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 49 treatment difference of -17.6 (95% CI -14.5-49.8). Treatment difference is calculated at -14.82 (95% CI -49.82-20.35), (p=0.3968).	treatment difference of -17.6 %(95% CI -14.5-49.8). Treatment difference -14.82 %(95% CI -49.82-20.35), (p=0.3968).	Query possible typing error – should treatment difference have a % ?-	Thank you for comment, this typo has been corrected

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Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 13 Borges *Bacterial Load (CFUs/g)* Both Prontosan and saline reduced the bacterial load compared with baseline but there was no significant difference in reduction of bacterial load	Add at the start of the sentence <u>After a single irrigation,</u> both Pronotosan….."	Context of result for reader regarding single irrigation, other papers in the same tables have time frame discussed	Thank you for your comment, we had added this text.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 55 One study (Ricci 2018) reported that cleansing with a single application of Prontosan solution for 2 mins or 5 mins had no impact on *wound bed score* (reduction in score indicates improvement) compared with baseline. Cleansing for 10 minutes resulted in reductions in score in 4/10 cases and cleansing for 15 minutes resulted in reductions in 5/10 case.	Please also add details of group B "<u>In patents treated over 14 days with daily 10min applications ,an improvement in the condition of the tissue, i.e. the wound bed was cleaned and debrided in 73% of cases, was observed and Periwound skin was improved in 29/30 cases</u>"	Only data from single application discussed by EAC – issues mentioned already regarding single application – 14 day use in group B more pertinent to clinical effect and should be included by EAC	Thank you for your comment, we have added this additional text.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 57 One ter study (Ricci 2018) reported that no patient had an *infection score* higher than 2 on enrolment and at the end of observation, 1 patient recorded 2 positive signs and 5 cases reported 1 positive sign.	One other study (Ricci 2018) reported that no patient had an *infection score* no higher than 2 positive signs on enrolment, with 4 patients scoring 2, 16 patients scoring 1 and 12 patients scoring 0 upon enrolment. At the end of the 14 day observation, the number of patients scoring 1 or 2 had decreased (1 patient scored 2 and 5 patients scored 1), with infection signs overall decreased by day 14 and most patients scoring 0 (n=24)	**Typo other** Unclear interpretation of the results here reads like there is an increase in infection markers following Prontosan treatment when there is not, proposed change is accurate to figure 5 in the paper.	Thank you for your comment, we have made these amendments to the text.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 59 table 16 *Reduction of bacterial bioburden* • • Using 0.9% NaCL (saline) did not significantly reduce the planktonic bacterial burden on wounds (p=0.761). • • Using Prontosan did not significantly reduce the bacterial burden (p=0.051)	Propose add *Reduction of bacterial bioburden, after a single application* • • Using 0.9% NaCL (saline) did not significantly reduce the planktonic bacterial burden on wounds (p=0.761). • • Using Prontosan did not significantly reduce the bacterial burden (p=0.051)	For context. Other studies in the tale have the time frame indicated.	Thank you for your comment, we have made these amendments to the text.

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Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Pg 91 Table 24 – Prontosan irrigation solution sachet	Prontosan irrigation solution ampule	accuracy	Thank you, changed as requested

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 20 PICO for wound closure model. Comparator of model recorded as saline and "placebo gel"	Remove "placebo gel" – the economic model comparator was saline only	No costs for a "placebo gel" were included in the model. Use of wound gels are not common practice hence not included. Aware that only the Harding study used a placebo gel and two sub models were submitted for Harding and Andriessen with comparator being standard practice with saline	Thank you, changed as requested

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 21 Please check dates for Andriessen x3 date typing errorsin table 21	Amend typing error to for Andriessen to “2008” x 3	Typing error	Thank you, changed as requested

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Appendix D pg 179 The EAC explored the potential impact of this change by considering the cost of the “open” state for the difference in time to healing and by using these time to healing values in the wound bed preparation model (which is essentially the same procedure, but with the addition of costs for Prontosan and Saline products.	Should “wound bed preparation” model be “wound closure” model ?	Typing error-This is the Andriessen data which was used in the wound closure model not the wound bed model.	This is not an error, but may not have been sufficiently clear. We used the wound bed preparation model to estimate the potential impact of having alternative mean times to healing, as the variable transition probabilities did not readily fit in the existing model structure. We have amended the text to describe this more clearly.

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Appendix D table 2 column title "Estimation using wound bed model"	Replace with "Estimation using wound closure model"	This is the Andriessen data which was used in the wound closure model not the wound bed model, might be a typing error.	This is not an error, but may not have been sufficiently clear. We used the wound bed preparation model to estimate the potential impact of having alternative mean times to healing, as the variable transition probabilities did not readily fit in the existing model structure. We have amended the text to describe this more clearly

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Appendix D table 2 subtext It can be seen that the Weibull model results in a reduced cost saving. The use of the wound bed model can be used to estimate the size of the reduction.	Replace with wound closure model"	Typing error. This is the Andriessen data which was used in the wound closure model not the wound bed model.	This is not an error, but may not have been sufficiently clear. We used the wound bed preparation model to estimate the potential impact of having alternative mean times to healing, as the variable transition probabilities did not readily fit in the existing model structure. We have amended the text to describe this more clearly

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 28 50g and 250G gel X costs mixed up	50g = £12.29 250g = £32.89 In addition the drug tariff reported by the EAC (£32.10 and £11.99) are not current prices – propose remove all reference in the document to prices being incorrect (discussed in the text further up the document)	Accuracy of Drug tariff prices Drug tariff January 2021 prices for Prontosan gels are here and match the company submission: https://www.nhsbsa.nhs.uk/sites/default/files/2020-12/Drug%20Tariff%20January%202021.pdf The EAC figures are December 2020 and prior prices, perhaps not updated as some systems which pull these prices through can take several weeks to update. The Gel X 50g price should be less than the 250g price there has been a switch here. (Also referenced on pg 90 – we agree there is variation with the NHSSC prices which include VAT)	Thank you, changed as suggested. Although we found different prices online, the source you provided agrees with the submission, and the difference is very small. We have removed any mentions of different prices in the drug tariff and corrected the prices for the different sizes. We have left a comment that there is a variation between prices in BNF, drug tariff and NHS supply chain. Results and Appendix F have also been updated accordingly, however the impact is minimal.

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 28 weekly healthcare cost (704.61)	Add £ “(£704.61)”	typing error	Thank you, changed as requested

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 105 The clinical studies used to populate the models to not all use Prontosan solution and gel X at each visit,	"The clinical studies used to populate the models do not all use Prontosan solution and gel X at each visit, …"	Typo	Thank you, changed as requested

Ammended text in Appendix D:

The EAC consider that Weibull would be a better fit, but agree that it is not supported by the current model structure. The EAC explored the potential impact of the different mean times to healing by considering the cost of the "open" state for the difference in time to healing and also by using these mean time to healing values in the wound bed preparation model.

It can be seen that the Weibull model is likely to result in a reduced cost saving. The wound bed preparation was used to estimate the size of the reduction, however inclusion of the Weibull parameters in the wound closure model would give somewhat different results due to movement in and out of infected states, longer time horizon and costs associated with infected and healed states that don't exist in the wound bed preparation model.

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