NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation document

Prontosan for acute and chronic wounds

How medical technology guidance supports innovation

NICE medical technologies guidance addresses specific technologies notified to NICE by companies. The 'case for adoption' is based on the claimed advantages of introducing the specific technology compared with current management of the condition. This case is reviewed against the evidence submitted and expert advice.

If the case for adopting the technology is supported, the specific recommendations are not intended to limit use of other relevant technologies that may offer similar advantages. If the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.

1 Recommendations

1.1 Prontosan shows promise for chronic wounds. However, there is not enough high quality evidence to support the case for routine adoption. The case for adopting Prontosan for acute wounds is not supported because the evidence is very limited.

1.2 A randomised controlled trial is recommended on the effectiveness of Prontosan wound irrigation solution compared with saline or water in chronic wounds of different types. Wounds should be followed up until completely healed, and time to healing should be measured. Find out more details in further research.

Why the committee made these recommendations

Care of acute or chronic wounds aims to improve their condition, help with healing and minimise risk of complications. Usually wounds are cleansed with saline or water.

Prontosan is available in 3 different formats: a solution, a gel, and extra thick gel. The solution is used for rinsing and soaking wounds. It can be used alone or with one of the gels. After soaking, the gel is applied to the wound and is left in place until the next dressing change. It aims to prevent build-up of microbes such as bacteria in the wound to help with healing.

Most of the evidence about Prontosan's effectiveness is not of good quality. It may speed up wound healing and reduce infections compared with saline in chronic wounds, but more evidence is needed to confirm this. There is very little evidence about using Prontosan in acute wounds.

Cost analyses suggest that Prontosan is cost saving compared with saline in chronic wounds. But there is not enough good quality evidence about its clinical effectiveness. So, more research is recommended to address the uncertainties.

2 The technology

Technology

2.1 Prontosan (B Braun) is a range of topical solutions and gels used for cleansing, rinsing and moistening acute and chronic wounds. Prontosan includes:

- Prontosan Wound Irrigation Solution, which is used for rinsing wounds or applied to gauze as a soak. It is available as a 350 ml bottle, as 40 ml single-use pods and as a 1,000 ml bottle for instillation.
- Prontosan Wound Gel, which is applied to the wound bed after cleansing during dressing changes and before further dressings are applied. It is available as a 30 ml bottle. It can be used in deep and tunnelling wounds, wound cavities or wounds that are difficult to access.

- Prontosan Wound Gel X (extra thick gel), which is applied in the same way as the Wound Gel. It is available as a 50 g or 250 g tube. It can be used in flat wounds or wounds with a large surface area, such as leg ulcers.

2.2 Prontosan received a CE mark in February 2009 as a class 3 medical device. The CE mark covers the Prontosan solution and gels.

Innovative aspects

2.3 The solution and gels contain an antimicrobial polyhexanide (0.1% polyhexamethylene biguanide) and a betaine surfactant (0.1% undecylenamidopropyl betaine). Prontosan is the only wound cleansing solution or gel that contains these 2 active ingredients. The company claims they work together to prevent biofilm forming in the wound bed and break it down if it has formed. The company claims that it cleanses and removes slough, devitalised tissue and other wound debris.

Intended use

2.4 Prontosan is intended for cleansing, rinsing or moistening acute and chronic wounds. It can be used by healthcare professionals in community and acute care settings, such as outpatient clinics, hospital inpatient care, GP surgeries, postoperative care and at the patient's home. The company states that brief training may be needed, but this is likely to be unnecessary for staff who are already trained in cleansing wounds with saline or water.

Costs

2.5 Prontosan is available in several forms, quantities and costs:

- Prontosan Wound Irrigation Solution: £5.03 for a 350 ml bottle (cost per dressing change £0.57); £0.62 per 40 ml ampoule
- Prontosan Wound Gel: £6.71 for 30 ml
- Prontosan Wound Gel X: £12.29 for 50 g (cost per dressing change £2.51); £32.89 for 250 g (cost per dressing change £1.34).

For more details, see the website for Prontosan.

3 Evidence

NICE commissioned an external assessment centre (EAC) to review the evidence submitted by the company. This section summarises that review. Full details of all the evidence is in the project documents on the NICE website.

Clinical evidence

The main clinical evidence comprises 18 studies

3.1 The evidence assessed by the EAC included 18 studies. Sixteen were full-text peer-reviewed publications and 2 were unpublished studies. Of the included studies, 9 were comparative studies (7 randomised controlled trials and 2 observational studies) and 9 were non-comparative observational studies. The comparative evidence included a total of 792 people, of which 415 had Prontosan, 281 had saline, 53 had saline or Ringer's solution, 23 had silver sulfadiazine, and 20 had sterile water. For full details of the clinical evidence, see section 4 of the assessment report. Find the assessment report in the supporting documentation file in the project documents on the NICE website.

The randomised controlled trials and the comparative and non-comparative studies were heterogeneous and at high risk of bias

3.2 The EAC considered the strength of the evidence to be limited, with only 1 randomised controlled trial at low risk of bias. The remaining studies were considered to be at high risk of bias. Further limitations of the evidence base included the following points:

- Most of the included studies had small sample sizes and some of the larger randomised controlled trials were underpowered (meaning they do not have enough people to answer the research question).
- Prontosan was not used consistently across the studies. It was not always used in a way that reflects NHS practice, or in line with the company's instructions for use.

- Outcomes were not always clearly reported and similar outcomes were reported differently across different studies. This made it difficult to make comparisons and draw conclusions across the evidence base.

There are 4 comparative studies for venous leg ulcers

3.3 Four studies were included for venous leg ulcers, 3 randomised controlled trials (Borges 2018; Harding 2012, unpublished; Romanelli 2010) and 1 comparative retrospective analysis (Andriessen 2008). All 3 randomised controlled trials had a small sample size and may have been underpowered. The control group in Andriessen 2008 had either saline or Ringer's solution. The clinical experts advised the EAC that Ringer's solution is not routinely used in the NHS to cleanse wounds. However, they explained that there is a dressing that contains Ringer's solution available and this would be used if clinically indicated for debridement (rinsing the wound and removing dead tissue and debris). Reported outcomes included wound healing, wound infection and pain.

There is limited evidence for burn wounds with no NHS comparators

3.4 Only 3 studies were included for burns, 1 randomised controlled trial (Wattanaploy 2017) and 2 non-comparative studies (Ciprandi 2018; Kiefer 2018). The sample size in the randomised controlled trial was small, saline was used in both arms, and the comparator was silver sulfadiazine. This was not considered to be standard care in the NHS so was not included in the scope for this guidance as a comparator for Prontosan. However, the EAC stated that silver sulfadiazine would be an appropriate treatment for burns. Reported outcomes included wound healing, wound infection, pain and treatment satisfaction.

There is limited evidence for surgical site wounds

3.5 Only 1 study, a randomised controlled trial, was included for surgical site wounds (Saleh 2016). This study had a small sample size, and the comparator was sterile water. The EAC included this study because surgical site wounds were considered relevant to the decision problem. The EAC noted that although the study compared Prontosan with sterile-

water soaked dressings, only one dressing was applied after surgery. This treatment approach may have limited applicability to the NHS. The study outcomes included wound infection but not wound healing.

The evidence for different types of chronic wounds was varied with 3 comparative studies

3.6 Different types of chronic wounds were included in 10 studies; 2 randomised controlled trials (Bellingeri 2016; Valenzuela 2008), 1 comparative cohort study (Assadian 2018) and 7 non-comparative studies (Atkin 2020; Ricci 2018; Moore 2016; Durante 2014; Moller 2008; Horrocks 2006; Orropallo, unpublished). Bellingeri 2016 was at low risk of bias, but the study was underpowered and at risk of selective reporting. Valenzuela 2008 used the gel only. This may not be applicable to the NHS because the wound would usually be soaked before the gel was used (see section 4.2 of the assessment report). Assadian 2018 had a small sample size and had limited applicability to the NHS because only a single application of Prontosan was used. Reported outcomes included wound healing, wound infection, pain, dressing changes and quality of life.

It is not certain if Prontosan has better outcomes than saline

3.7 In total, 6 randomised controlled trials compared Prontosan with saline alone. Wound healing was reported in 1 study (Harding 2012, unpublished), wound size in 2 studies (Romanelli 2010; Valenzuela 2008) and wound condition improvement in 1 study (Bellingeri 2016). Of these 4 studies, there was only 1 study that showed statistical significance in wound improvement (Bellingeri 2016). Infection rate was reported in 1 study (Harding 2012, unpublished), bacterial burden in 2 studies (Assadian 2018; Romanelli 2010), bacterial load in 1 study (Borges 2018), inflammation score in 1 study (Bellingeri 2016), and microbiological cultures in 1 study (Valenzuela 2008). Of these 6 studies, there were only 2 studies that showed statistical significance, a reduction in bacterial burden (Romanelli 2010) and a reduction in inflammation score (Bellingeri 2016). Pain was reported in 3 studies (Bellingeri 2016; Harding 2012, unpublished; Romanelli 2010). Only 1 study found a significant reduction

in pain when using Prontosan (Romanelli 2010). The EAC concluded that Prontosan appeared to be effective for some clinical parameters in chronic wounds, but there is not enough good quality comparative evidence with saline.

Prontosan is safe, easy to use and has potential benefits but evidence is limited

3.8 Prontosan is safe, adverse events are rare, the products are easy to use and it has the potential to improve wound pain but the evidence is limited.

Cost evidence

The company's cost modelling finds Prontosan to be cost saving

3.9 The company submitted 2 de novo cost analyses with different model structures. One used a Markov model (wound closure model) that compared costs for Prontosan with saline to treat venous leg ulcers until full wound closure. The time horizon was 1 year. The clinical experts advised the EAC that when using Prontosan wounds healed within a year. The company provided 2 alternative data sets for rate of wound healing for this model (Andriessen 2008 and Harding 2012, unpublished). The other model was a simple cost model (wound bed preparation model) that compared costs for Prontosan with saline to treat chronic wounds (for example, leg ulcers and pressure ulcers) until the wound bed is fully granulated. This means that there are visible signs that the wound is healing. The time horizon used was the time to reach a Bates-Jensen wound assessment tool (BWAT) score of 14. The BWAT score is a clinical tool used for scoring wound healing. The time taken to reach a score of 14 was 4.1 weeks for Prontosan and 11.3 weeks for saline (Bellingeri 2016). The company reported base-case cost savings per person with Prontosan of £1,118.26 and £1,188.47 for the wound closure model (with data from Andriessen 2008 and Harding 2012, unpublished, respectively) and £1,134.40 for the wound bed preparation model. For full details of the cost evidence, see section 9 of the assessment report.

The EAC agrees with the company's cost models but the key limitation is that the clinical evidence is uncertain

3.10 The EAC agreed with the structure of both of the company's models and its assumptions and made minor alterations to the costs and resource use. This had little impact on the cost savings (for full details see section 9 of the assessment report). The EAC noted that the inputs for wound healing and infection rates in the wound closure model were uncertain, as were the inputs for wound bed improvement in the wound bed preparation model. It made the following comments:

- Andriessen (2008) is a retrospective comparative case series of 112 patients with venous leg ulcers with a follow-up time of 6 months. The EAC considered that Andriessen 2008 was a suitable data source because of the larger number of patients and longer follow up. However, the study was at high risk of bias because of potential selection and reporting bias.
- Harding (2012) is a small, unpublished, UK pilot randomised controlled trial 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 about the randomisation process.
- Bellingeri (2016) is a randomised controlled trial of 289 patients with pressure ulcers or vascular leg ulcers at low risk of bias. The follow up was 28 days, and wounds were assessed using the BWAT score. The company used an Excel trendline to extend the graphs to reach a mean BWAT score for both arms. However, there were concerns about the data. The study seemed to use only 8 out of the 13 dimensions of the BWAT. This meant the overall score was not on a scale of 13 to 65, but on a scale of 8 to 40. As a result, the EAC could not be confident that a reported BWAT score of 13 or 14 in Bellingeri (2018) accurately corresponded to a wound approaching healing or one that has healed. However, no improved data source has been identified.

The EAC base case uses the wound closure model with inputs from Andriessen 2008 and estimates a cost saving of £951.01 per person

3.11 The EAC considered that the wound closure model with clinical inputs from Andriessen 2008 was the most appropriate base case. It concluded that Andriessen 2008 was the most suitable data source and provided the most robust estimates for wound improvement, deterioration and recurrence that reflected the clinical reality of treating chronic wounds. This model estimated a cost saving from the use of Prontosan compared with saline of £951.01 per patient over a time horizon of 1 year.

4 Committee discussion

Clinical effectiveness overview

Prontosan shows promise but there is not enough evidence of its clinical benefit

4.1 The committee noted that much of the evidence comparing Prontosan and saline in chronic wounds was of low quality and at high risk of bias. The committee noted that there was very limited evidence for acute wounds. The committee agreed that the technology showed promise based on clinical expert advice, but that this was not supported by the evidence. The committee concluded that that there was not enough good quality evidence to make a clear judgement about the benefits of Prontosan compared with saline or water.

The evidence is heterogeneous in terms of wound type

4.2 The committee noted that the patient populations in the evidence were heterogeneous, including different wound types such as venous leg ulcers, chronic wounds of mixed aetiology, burns and surgical site wounds. The clinical experts agreed that Prontosan could be used for a broad patient population with acute or chronic wounds, although the committee considered that there was not enough clinical or cost evidence to make a judgement on its use in acute wounds. The committee understood that there is a diversity of wound type in the chronic wound

population. It considered it difficult to generalise the evidence from trials, which included relatively narrow subgroups of this population (for example, pressure ulcers, arterial leg ulcers, venous leg ulcers, among others), to the total population with chronic wounds.

The evidence is heterogeneous in terms of how Prontosan was used

4.3 The committee noted that how Prontosan products were used ranged across the studies. Prontosan solution was used alone, with the gel or gel X, or the gel or gel X was used alone. The clinical experts agreed that the solution is used to irrigate and clean acute wounds (when clinically necessary) and can also be used as a soak for chronic wounds. The clinical experts noted that the gel is used less often, and always in combination with the solution to support and maintain the soak process. The clinical experts said the gel is most often used for more complex and chronic wounds and for people with a history of recurrent infections. The committee recognised the heterogeneity in the way the Prontosan products were used and concluded that this makes it difficult to draw conclusions about the evidence.

Side effects and adverse events

Prontosan has plausible benefits

4.4 The clinical experts noted that, in their experience, using Prontosan on static (non-healing) chronic wounds with a dull brown colour causes the wound bed to change to vibrant red granulated tissue (tissue in the process of healing). No adverse events or allergic or instant reactions to Prontosan were observed by the clinical experts. The clinical experts said that Prontosan is easy to use, soothing and does not sting. The committee recognised that pain is an important consideration when treating chronic and acute wounds and concluded that Prontosan has plausible benefits.

Outcome measures

Complete wound healing is the preferred outcome

4.5 The clinical experts said that Prontosan should be used until wounds are healed, or close to healing, and not just until the wound bed condition is improved. The clinical experts clarified that wounds can epithelialise (when a layer of new tissue forms over the wound) and close, but this does not mean the wound is healed. For people with a history of recurrent infection the wound can break down again if treatment is stopped before the wound is healed. Some types of chronic wounds, specifically leg ulcers, often deteriorate and recur. Chronic wounds can be complex and may become static or have high levels of recurrence. The clinical experts noted that some patients have wounds for 2, 3 or even 4 years. To measure Prontosan's effectiveness compared with saline, the committee concluded that evidence is needed that follows wounds until they are completely healed. This evidence should also measure the time it takes for complete healing to happen.

Uncertainties in the reporting of the BWAT score from Bellingeri 2016

4.6 The most robust evidence (a randomised controlled trial by Bellingeri 2016) was at low risk of bias but underpowered and showed a significant reduction in Bates-Jensen wound assessment tool (BWAT) score for Prontosan compared with saline. The EAC noted that it is unclear from the study whether all 13 dimensions of the tool were used. It was not confident that a reported BWAT score of 13 or 14 in this paper can be interpreted as wounds that have healed, or that are approaching healing.

Relevance to the NHS

The evidence from Bellingeri 2016 may not be generalisable to NHS clinical practice

4.7 In both the Prontosan and control (saline) groups of Bellingeri 2016, the protocol included irrigation (20 ml to 30 ml) followed by a 10-minute soak. There are no clear guidelines for cleansing wounds and the clinical

experts said that the decision to irrigate or cleanse the wound lies with the assessing clinician. This decision depends on the condition of the wound and the person's risk factors and environment. The clinical experts also suggested that soaking with saline is not routinely done in the NHS. Although the protocol in Bellingeri 2016 makes it easier to understand trial outcomes, the committee recognised that it may not reflect the variability in care in NHS clinical practice.

NHS considerations overview

Prontosan does not add to the appointment time if the soak is applied at the start of the appointment

4.8 The clinical experts told the committee that Prontosan solution is often applied as a soak (for 10 to 15 minutes) for chronic wounds. The experts noted that this can lead to an increase in appointment times in some cases (primarily wound clinics) but that if the tasks are switched around and the soak is applied at the start of the appointment this should not extend the appointment time. The committee concluded that some education and training may be needed to ensure healthcare professionals know to soak with Prontosan solution at the start of an appointment.

Prontosan is part of a wound care package so the treatment effect is hard to establish

4.9 The committee noted that Prontosan is part of a wound care package and not used on its own. This means it is difficult to isolate the treatment effect of Prontosan on chronic wounds. The clinical experts stressed the importance of using a locally agreed wound care pathway and explained that treatments are selected using a holistic approach and clinician experience. People with chronic wounds do not necessarily see the same clinician, and use of products and dressings can vary between visits based on what is available. One clinical expert said it would be easier to use one solution consistently rather than decide between multiple solutions (water, saline or Prontosan). The committee concluded that it is

hard to isolate the direct effect of Prontosan and recognised the need for an appropriate wound care pathway for chronic wounds.

Cost modelling overview

The cost models are acceptable but any cost modelling using the available evidence is likely to be flawed

4.10 The committee agreed that the clinical and cost case were dependent on each other. Prontosan would result in cost savings even if there was only a small benefit in healing rate or reduction in infection rate. The clinical inputs in the model were of low quality and at high risk of bias and subject to the same uncertainty as discussed in the clinical evidence section. It concluded that more research was needed to establish the clinical and cost benefits of using Prontosan in the NHS. Until then, any cost modelling is likely to be flawed.

Further research

Randomised controlled trials comparing Prontosan solution with saline or water in the NHS are needed

4.11 The committee concluded that research is needed to address the uncertainties about the clinical effectiveness of Prontosan wound irrigation solution compared with saline or water. It recommended that randomised controlled trials should be done in the NHS. These should compare Prontosan solution with saline or water in different types of chronic wounds. The randomised controlled trial needs to be well designed to detect clinically meaningful results in subgroups (for example, pressure ulcers or venous leg ulcers). The committee agreed that a key outcome should be time to complete wound healing. Other important outcomes should include pain and wound odour, measured using patient-reported outcome measures (PROMs). The number of dressing changes should also be recorded for each wound included in the study.

Real-world observational studies in the NHS are encouraged

4.12 The committee considered the low number of patients in the existing evidence and encouraged real-world observational studies. Real-world data collected from large cohorts would be helpful to understand differences in wound care in the NHS, including how different types of wounds are treated and how Prontosan would be used. For example, when using Prontosan solution and gel together would be clinically needed, and the effect of using Prontosan solution and gel together. Outcomes such as pain and wound odour should be measured using PROMs.

5 Committee members and NICE project team

Committee members

This topic was considered by NICE's medical technology advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of the medical technology advisory committee, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each medical technologies guidance topic is assigned to a team consisting of 1 or more technical analysts (who act as technical leads for the topic), a technical adviser and a project manager.

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