Review report of MTG42, UrgoStart for treating diabetic foot ulcers and leg ulcers

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This medical technology guidance was published in January 2019.

All medical technology guidance is usually reviewed 3 years after publication, unless NICE become aware of significant new information before the expected review date.

This review report summarises new evidence and information that has become available since this medical technology guidance was published, and that has been identified as relevant for the purposes of this report. This report will be used to inform NICE's decision on whether this guidance will be updated, amended, remain unchanged (static list) or withdrawn.

1. Original objective of guidance

To assess the clinical effectiveness and cost of UrgoStart for treating diabetic foot ulcers and leg ulcers.

2. Current guidance recommendations

Current NICE guidance from MTG42 supports using UrgoStart dressings for diabetic foot ulcers and venous leg ulcers in the NHS, once any modifiable factors such as infection have been treated. The guidance cites evidence that UrgoStart dressings are associated with increased wound healing compared to non-interactive dressings. Cost modelling compared with standard care shows a cost saving of £342 per patient after one year for diabetic foot ulcers. UrgoStart is also modelled to be likely cost saving for treating venous leg ulcers, but the evidence is less robust. The guidance concluded that for people with non-venous leg ulcers, there is insufficient evidence to support routine adoption.

3. Methods of review

Comprehensive literature searches were carried out by an Information Specialist at NICE (Jemma Deane) on 8 September 2022. This included a wide range of databases (Medline, Embase, Cochrane, CINAHL and Epistomonikos and INAHTA) and supplementary sources (which provided information on related NICE guidance, adverse events and ongoing trials). After deduplication 800 unique records were identified. It was not felt necessary to repeat any of these searches as they were comprehensive and of recent date. For completeness, as no separate adverse event and clinical trial searches were reported, the EAG conducted these on 3 November 2022 but did not identify any additional relevant records. Citation chasing of full text included papers was carried out on 10 November 2022 and after deduplication a further 539 papers were identified for screening at title and abstract.

Potentially relevant studies identified by the company and clinical experts were initially screened by title and abstract. Records identified from the search were then screened initially by title and abstract to identify any potentially relevant studies not identified by the company and clinical experts. All potentially relevant articles were then obtained and screened as full texts. All screening was conducted by MSB with a 10% independent check by LT. Any disagreements were resolved by discussion, involving a third reviewer (SR or ECFW) if required.

All original research studies (randomised and non-randomised studies as well as systematic reviews) and UK-based case reports assessing the clinical effectiveness of all UrgoStart formulations for diabetic foot ulcers and leg ulcers published in English-language peer-reviewed journals, as English-language scientific meeting abstracts, or English-language relevant materials supplied by the company were eligible. Studies solely addressing other wound types were not included. Meeting abstracts were only eligible where the results were not already available via a full text paper.

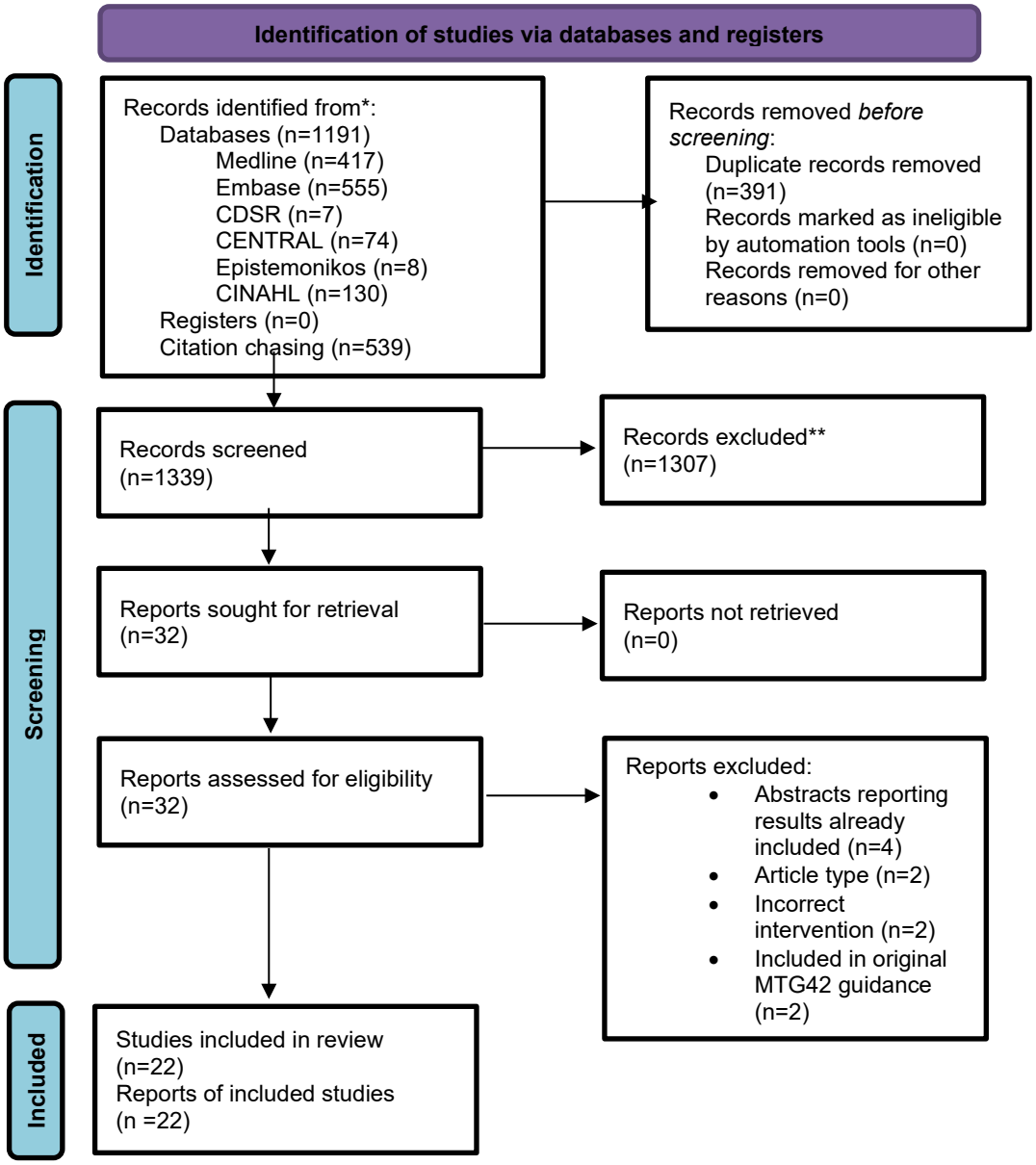
As the purpose of this review is to update the review from the original 2019 MTG42 guidance, only studies published after the March 2018 search date for the original guidance, and not featuring in the list of included or excluded studies for this guidance, were eligible for inclusion.

Data were extracted on the details of each study design, population, interventions, comparator, outcomes, statistics and effect size as well as relevant study results. Data extraction was conducted by one reviewer (MSB). Any points requiring clarification were discussed with another member of the research team (LT or ECFW). Data on other wound types within included studies were recorded as requested. NICE requested the EAG pay particular attention to any new evidence on non-venous leg ulcers, as there was insufficient evidence to recommend UrgoStart use in this population in the original guidance.

4. New evidence

A PRISMA flow diagram can be found as Figure 1

Figure 1. PRISMA flow diagram.



Note that some records in the citation chasing database duplicated records already identified due to limits of the de-duplication algorithm.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

4.1. Changes in technology

There have been no changes in the format, CE marking or other product details of UrgoStart dressings since the original guidance was issued. The UrgoStart range still comes in 5 different formats. The range of costs across

formats has increased from between £3.03 and £10.20 when the initial MTG42 guidance was issued to between £3.11 and £10.47. Considering the time period and inflation rates, the increase was considered minor.

4.2. Changes in care pathways

The NICE guideline on diabetic foot problems: prevention and management has been updated since the previous MTG42 guidance. This change relates to antimicrobial prescription for diabetic foot ulcers and does not change recommendations on wound dressing. There have been no changes to the NICE guideline on pressure ulcers: prevention and management.

Primary care prescribing data on UrgoStart usage were provided by NICE in the initial review. However, this does not fully capture UrgoStart usage, since while most people with leg ulcers are treated in the community setting, most people with diabetic foot ulcers are treated in secondary care. Therefore, usage for diabetic foot ulcers is likely to be underrepresented. The prescribed quantities of UrgoStart in primary care are 21,535 for 2019, 21,600 for 2020 and 24,355 for 2021 (NHS Business Services Authority, 2022). The vast majority of prescriptions have been by general practitioners or nurses.
The company issued a list of the top 175 UrgoStart users, including hospitals, trusts and clinical commissioning groups. The EAG was satisfied that there was a wide geographical spread in usage but noted that the list also included Scottish sites, which are outside the remit of this appraisal. All three clinical experts consulted by NICE reported using UrgoStart in their practice and none reported any concerns relating to UrgoStart use.

4.3. Results from the MTEP research commissioning workstream

NICE advised that no MTEP research was commissioned for this appraisal.

4.4. New clinical studies

A total of 22 eligible new clinical studies were identified, reported in 22 publications. One publication (Sigal et al, 2019) reported two single arm prospective cohort studies (NEREIDES and CASSIOPEE), while two publications (Lázaro-Martinez et al, 2019; Lohmann et al, 2020) both reported

post-hoc analyses from the EXPLORER trial, the primary publication from which (Edmonds et al, 2018) was included in the original MTG42 guidance. Details of each study are included in Appendix C. Key messages from the new clinical evidence are summarised below.

Three systematic reviews were identified. All addressed broader research questions; two (Nair et al, 2021; Vas et al, 2020) only reported UrgoStart studies that had already been identified through searches, while the other (Dissemond et al, 2020a) only included UrgoStart studies that had been included in the original MTG42 guidance. No new primary analyses from RCTs were identified. The only new evidence that compared UrgoStart dressings to any form of alternative treatment was two post-hoc analyses from the EXPLORER trial (Lázaro-Martinez et al, 2019; Lohmann et al, 2020), looking at diabetic foot ulcers. Both analyses supported a benefit for UrgoStart over control dressings in terms of wound healing, but Lázaro-Martinez et al (2019) noted that wound duration at baseline was an important predictor of outcome. In the UrgoStart specific cohort, wound closure by week 20 was observed in 71% of patients with a diabetic foot ulcer lasting <=2 months, but only 29% of patients with ulcers lasting 6 to <= 11 months. Two single-arm studies also provided support for superior outcomes in wounds of shorter duration. In Augustin et al (2021), wound healing rates were 59.9% for wounds that occurred in the previous month versus 36.8% in wounds that had already lasted for more than a month, across different wound aetiologies. In Dissemond et al (2020b), healing occurred in 58.3% of wounds occurring in the previous month versus 33.3% of wounds with >1 month duration, across wound aetiologies.

A total of three studies (Dowsett & Nichols, 2021; Nair, 2022; Wounds UK, 2020) comprised UK case reports or case series, across various wound aetiologies. These consistently supported a benefit for UrgoStart but are of limited methodological utility. The remaining 13 studies comprised single arm implementation, service evaluation or other observational studies. Single arm studies are also of limited methodological utility, since they cannot control, for, example for attentional biases. Results across studies were nevertheless

consistently positive for wound healing, as well as for pain, safety, tolerability, acceptability and quality of life where these were reported. This applied to both diabetic foot ulcers and venous leg ulcers. In Augustin et al (2021), by the final visit, wound closure or improvement was reported in 92.0% of treated wounds. Wound closure was achieved in 57.6% of diabetic foot ulcers, 45.6% of leg ulcers, 45.7% of pressure ulcers and 55.0% of other wounds. Median times to heal were 59 (IQR 38-84) days for leg ulcers, 56.5 (IQR 43-82) days for diabetic foot ulcers, 56 (IQR 35-84) days for pressure ulcers and 46 (IQR 32-70) days for other wounds. There was an 87.5% reduction in sloughy tissue by the final visit. Exudate decreased in 68.9% of wounds. There was a reduction in wounds with macerated periwound skin from 36.5% to 8.8%. In Dissemond et al (2020b), wound closure or improvement by the final visit was observed in 93.3% of treated wounds. Wound closure rates were 43.6% in diabetic foot ulcers, 47.1% in leg ulcers, 48.3% in pressure ulcers and 55.2% in other wounds. For all wound types, there was a continuous reduction in wound area over the course of treatment. All wound types showed a reduction in sloughy tissue, with a global reduction from 45+-30% at baseline to 15+24% at the final visit. Duration of wound at baseline had a negative effect on wound healing. Levels of exudate decreased in 67.7% of wound by the final visit. The proportion of wounds with macerated periwound skin fell from 26.2% to 3.9%. The proportion of patients with healthy skin condition rose from 5.7% to 40.6%.The one marginal exception was Richard et al (2021) in a population of diabetic foot ulcers, where only 30% of wounds had healed by the end of the study.

Studies used different products within the UrgoStart dressing range and where multiple products were used in the same study, there was no evidence of a significant difference in performance or acceptability. There was no evidence specifically presented on non-venous leg ulcers. Milne & Jones (2018) and Milne & Nichols (2021) both reported on both venous leg ulcers and leg ulcers of ‘mixed aetiology’. Evidence is limited, but may suggest comparable healing for venous and ‘mixed aetiology’ leg ulcers. However, no definition of ‘mixed aetiology’ is provided and this group does not refer

specifically to non-venous wounds, so the EAG considers this evidence to be of limited value for the current appraisal.

4.5. New economic studies

The EAG's systematic review was focused on clinical effectiveness. However, the searches identified seven new economic studies (three conference abstracts [Betts et al, 2018a; Betts et al, 2018b; Mlcoch et al, 2019] and four peer-reviewed manuscripts [Lobmann et al, 2019; Lobmann et al, 2020; Maunoury et al, 2021; Mullings & Merlin-Manton, 2018]), of which all but Mullings & Merlin-Manton 2018 were considered relevant to this review. Most of the economic studies drew on either the EXPLORER (Lobmann et al, 2019; Lobmann et al, 2020; Maunoury et al, 2021; Mlcoch, et al 2019) or CHALLENGE RCTs (Betts et al, 2018a; Mlcoch et al, 2019).

Modelling approaches included decision trees (Augustin et al, Mlcoch et al), decision tree with Markov models at terminal nodes (Lobmann et al 2019 & 2020), and Markov models (Betts et al 2018a). Betts et al 2018b evaluated a budget impact model. The time-frame ranged from 8 weeks to a lifetime horizon (40 years) and all studies included the rate, or a proportional benchmark of wound healing as the primary outcome of the study.

The EAG considered the studies broadly generalizable to the UK. Two studies (Betts et al, 2019a/2019b) were from an NHS perspective, and all other included studies were European based, including German and Czech studies. The EXPLORER trial was a multi-centre RCT spanning 43 countries across Europe and included 240 patients, and the CHALLENGE study was an RCT conducted in France with 187 patients.

In all included studies, UrgoStart was a dominant strategy (cost-saving and, where outcomes were also evaluated, at least as effective as comparator). Savings were estimated between €5 and €143 per patient per year for diabetic foot and venous leg ulcers respectively in the Czech Republic (Mlcoch et al), and €35 489 per patient over a life time horizon in France compared with neutral dressings (Maunoury et al). The large difference in cost estimates is due primarily to the scope of costs included in the analyses,

for example Maunoury et al. included risk of amputation from infected ulcers whereas Mlcoch only allowed for ‘adverse events leading to hospitalisation’. Sensitivity analysis performed across the studies suggested the results were robust to plausible changes in costs and outcomes.

The budget impact model (Betts et al, 2019b) estimated that over a five year period, a total of 1.3 million patients in the UK would be eligible for UrgoStart, yielding a cost-saving of £251.7 million, and the avoidance of 26.1 million days with ulceration over that period.

4.6. Ongoing trials.

No ongoing trials were identified by the NICE database searches or the clinical trials searches conducted by the EAG.

4.7. Changes in economic case

The EAG noted that in the initial guidance, the cost effectiveness of UrgoStart was clear for diabetic foot ulcers, probable but based on less robust data for venous leg ulcers and too uncertain to recommend routine adoption for non-venous leg ulcers. New evidence reinforces the current recommendations. There is additional evidence for venous leg ulcers, but given the limitations of study designs used, the EAG does not consider this resolves the uncertainty expressed in the current NICE guidance. There is no new evidence specifically for non-venous leg ulcers and the EAG considers that new clinical evidence, such as subgroup analyses specifically for the non-venous population, would be necessary to develop an economic case for the routine use of UrgoStart dressings in non-venous leg ulcers.

4.8. Other relevant information

The EAG did not identify any other relevant information that has not been covered elsewhere.

5. Conclusion

The EAG has not identified any evidence that contradicts the current NICE guidance for UrgoStart use. New clinical and economic evidence consistently

favours the use of UrgoStart. However, limitations in the robustness of new clinical evidence mean that the EAG considers that the uncertainties mentioned in the current NICE guidance in the context of venous leg ulcers have not been resolved. The EAG notes the dominance of single-arm studies and that the only new comparative studies available are two post-hoc analyses of an RCT that was included in the original NICE guidance. Single arm studies are unable to control for attention or other comparator effects and are generally at high risk of bias. Furthermore, the absence of clinical evidence specifically for non-venous ulcers means that the EAG considers that nothing substantial has changed for this population since the existing NICE guidance was issued. Further studies specifically on non-venous leg ulcers, or subgroup analyses for this population within existing studies could help address this uncertainty.

Appendix A – Relevant guidance

To be supplied by the NICE gIS team

NICE guidance – published

NICE guidelines (clinical, public health, social care, medicine practice guidelines, safe staffing)

Type 1 diabetes in adults: diagnosis and management (2015; updated 2022) NICE guideline NG17

Type 2 diabetes in adults: management (2015; updated 2022) NICE guideline NG28

Leg ulcer infection: antimicrobial prescribing (2020) NICE guideline NG152

Surgical site infections: prevention and treatment (2019; updated 2020) NICE guideline NG125

Diabetic foot problems: prevention and management (2015, updated 2019) NICE guideline NG19

Pressure ulcers: prevention and management (2014) NICE guideline CG179

NICE quality standards

Diabetes in adults (2011, updated 2016) NICE quality standard 6

Pressure ulcers (2015) NICE quality standard 89

Surgical site infection (2013) NICE quality standard 49

NICE technology appraisals and highly specialised technologies

None found

NICE interventional procedures, medical technologies or diagnostics guidance

Parafricta Bootees and Undergarments to reduce skin breakdown in people with or at risk of pressure ulcers (2022) NICE medical technologies guidance 20

3C Patch for treating diabetic foot ulcers (2022) NICE medical technologies guidance 66

Prontosan for treating acute and chronic wounds (2022) NICE medical technologies guidance 67

The VAC Veraflo Therapy system for acute infected or chronic wounds that are failing to heal (2021) NICE medical technologies guidance 54

SEM Scanner 200 for preventing pressure ulcers (2020) NICE medical technologies guidance 51

Mepilex Border Heel and Sacrum dressings for preventing pressure ulcers (2019) NICE medical technologies guidance 40

PICO negative pressure wound dressings for closed surgical incisions (2019) NICE medical technologies guidance 43

UrgoStart for treating diabetic foot ulcers and leg ulcers (2019) NICE medical technologies guidance 42

The Debrisoft monofilament debridement pad for use in acute or chronic wounds (2014, updated 2019) NICE medical technologies guidance 17

Negative pressure wound therapy for the open abdomen (2013) NICE interventional procedures guidance 467

The MIST Therapy system for the promotion of wound healing (2011) NICE medical technologies guidance 5

All other NICE guidance and advice products - MedTech, ESNM / Evidence Summary, ESUOM, Key Therapeutic Topic, QOF Indicator, and NICE CKS

Granulox for managing chronic non-healing wounds (2022) NICE Medtech innovation briefing 296

Leg ulcer-venous (2021) NICE CKS

Palliative care – malignant skin ulcer (2021) NICE CKS

WoundExpress to manage lower leg wounds (2021) NICE Medtech innovation briefing 261

NATROX oxygen wound therapy for managing diabetic foot ulcers and complex or chronic non-healing wounds (2020) NICE MedTech innovation briefing 208

LQD Spray for treating acute and chronic wounds (2019) NICE MedTech innovation briefing 202

Coban 2 for venous leg ulcers (2018) NICE MedTech innovation briefing 140

EpiFix for chronic wounds (2018) NICE MedTech innovation briefing 139

TopClosure Tension Relief System for wound closure (2017) NICE Medtech innovation briefing 97

Chronic wounds: advanced wound dressings and antimicrobial dressings (2016) NICE evidence summary ESMPB2

The Juxta CURES adjustable compression system for treating venous leg ulcers (2015) NICE MedTech innovation briefing 25

NICE guidance – in development

NICE guidelines

Diabetic foot problems: prevention and management NICE guideline. Publication expected January 2023

Diabetes (type 1 and type 2) in children and young people: diagnosis and management - medicines for type 2 diabetes (update) NICE guideline. Publication expected April 2023

Type 2 diabetes in adults: management (medicines update) NICE guideline. Publication expected December 2024

Diabetes update NICE guideline. Publication date to be confirmed

NICE quality standards

Diabetes in pregnancy (update) NICE quality standard. Publication expected January 2023

Diabetes in adults update - Type 1 and Type 2 NICE quality standard. Publication expected February 2023

NICE technology appraisals and highly specialised technologies

Birch bark extract for treating skin wounds associated with dystrophic and junctional epidermolysis bullosa NICE technology appraisal guidance. Publication expected October 2023

NICE interventional procedures, medical technologies or diagnostics guidance

None found

All other NICE guidance and advice products - MedTech, ESNM / Evidence Summary, ESUOM, Key Therapeutic Topic, QOF Indicator, and NICE CKS

None found

Guidance from other professional bodies

Scottish Intercollegiate Guideline Network (SIGN) – Management of chronic venous leg ulcers: a national guideline (2010).

Appendix B – Details of studies and ongoing trials

Study characteristics of clinical studies

Authors	Study name	Design	Population	Interventions	Comparator	Outcomes	Statistics
Alhumaidi et al, 2022	Not stated	Real-life observational pilot study	Kuwait, 7 male patients, diabetic foot ulcers	UrgoStart Plus	Single arm study	Wound area, wound healing	Descriptive
Augustin et al, 2021	Not stated	Prospective real-life observational study	Germany, 961 patients, various wounds (leg ulcers, diabetic foot ulcers, pressure ulcers and other wounds)	UrgoStart Plus, UrgoStart Plus Pad, UrgoStart Plus Border	Single arm study	Overall wound healing progression, relative reduction in wound area, reduction in sloughy tissue in the wound bed, change in exudate level, change in periwound skin condition, change in HRQoL using Wound-QoL, overall acceptability of dressing, physician opinion on dressing performance	Descriptive, T-test, Wilcoxon signed rank test

Conde-Montero et al, 2020	Not stated	Prospective single-arm interventional study	Spain, 42 patients, hard-to-heal venous leg ulcers	UrgoStart Contact	Single arm study	Percentage of wounds with complete epitheliation, time to reach complete epitheliation, wound area reduction, treatment acceptability, safety	Descriptive
Dissemond et al, 2020a	Not stated	Systematic review	International, 1355 patients from 16 studies, chronic wounds	A range of matrix metalloproteinase inhibiting wound dressings, including UrgoStart Contact, UrgoStart	Various comparator dressings	Wound size reduction, complete wound closure, healing time and rate	Narrative synthesis
Dissemond et al, 2020b	Not stated	Prospective observational study	Germany, 1140 patients, chronic wounds of various aetiologies (including leg ulcers and diabetic foot ulcers)	UrgoStart Plus Pad, UrgoStart Plus Border	Single arm study	Wound healing, reduction in sloughy tissue, change in exudate level, change in periwound skin condition, acceptability of the dressing, health professional overall opinion on dressing performance	Descriptive

Dowsett & Nichols, 2021	Not stated	Narrative review with case study	UK, 1 patient with diabetes, leg ulcer	UrgoStart Plus	No comparator, case study	No structured outcomes	Narrative case study
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lázaro-Martinez et al, 2019	EXPLORER	Post-hoc analysis of RCT	International, 240 patients, diabetic foot ulcers	UrgoStart Contact	Control dressing (without sucrose octosulphate)	Wound closure	Descriptive
Lázaro-Martinez et al, 2020	Not stated	Prospective pilot study	Spain, 11 patients, neuroischaemic diabetic foot ulcers	UrgoStart Contact	Single arm study	Change in TcPO2 values in dressing over healing process	Shapiro-Wilk test
Lobmann et al, 2020	EXPLORER	Post-hoc analysis of RCT	International, 240 patients, diabetic foot ulcers	UrgoStart Contact	Control dressing (without sucrose octosulphate)	Wound healing	Descriptive (for input into an economic model)
Meloni et al, 2022	Not stated	Retrospective single-arm study	Italy, 30 patients, neuroischaemic diabetic foot heel ulcers	TLC-NOSF dressing supplied by Urgo – does not say which	Single-arm study	Wound healing, healing time, wound regression, re-ulceration and safety	Descriptive
Milne & Jones, 2018	Not stated	Pathway-driven patient evaluation	UK, 10 patients, leg ulcers	UrgoStart	No comparator	Wound size reduction, wound healing, slough reduction, patient feedback	Descriptive
Milne & Nichols, 2021	Not stated	Evidence-based pathway analysis	UK, 24 patients, various chronic wounds,	UrgoStart product range	No comparator	Wound type, wound progression	Descriptive

			including leg ulcers				
Mullings & Merlin-Manton, 2018	Not stated	Implementation study	UK, 76 patients, leg ulcers	UrgoStart Contact	No comparator	Ulcer time-to-healing	Descriptive
Murray & Norrie, 2020	Not stated	Implementation study	UK, 13 patients, leg ulcers	UrgoStart Plus	No comparator	Wound healing, pain VAS, changes in surrounding skin condition, exudate level	Descriptive
Nair et al, 2021	Not stated	Systematic review	International, 14 unique studies, over 12,000 patients, chronic wounds including venous leg ulcers and neuroischaemic foot ulcers	UrgoStart product range	No specific comparator stated	Reduction in healing time	Narrative synthesis
Nair, 2022	Not stated	Real life case series	Various countries, 18 patients, various chronic wounds	UrgoStart product range	No comparator	No structured outcomes	Descriptive
Richard et al, 2021	No stated	Pilot prospective non-controlled open-label clinical trial	France, 33 patients, neuropathic diabetic foot ulcers	UrgoStart Contact	Single arm study	Wound healing, time-to-healing, adverse events, tolerance and acceptability	Descriptive
Sigal et al, 2019	NEIREDES	Single-arm prospective open label trial	France, 37 patients, leg ulcers	UrgoStart Plus	Single arm study	Wound area reduction, wound closure, time to reach	Descriptive

						wound closure, wound bed condition, periwound skin condition, safety, acceptability, Global Performance Score	
Sigal et al, 2019	CASSIOPEE	Single-arm prospective open label trial	France, 51 patients, leg ulcers	UrgoStart Plus	Single arm study	Wound area reduction, wound closure, time to reach wound closure, wound bed condition, periwound skin condition, safety, acceptability, Global Performance Score	Descriptive
Tickle, 2021	Not stated	Implementation study	UK, 33 patients, various chronic wounds	UrgoStart product range	No comparator	Wound healing, wound area reduction, exudate level, periwound skin condition, Tickle Quality of Life tool	Descriptive
Vas et al, 2020	Not stated	Systematic review	International, 97 studies, diabetic	Sucrose octosulfate	No specified comparator	Clinical effectiveness	Narrative synthesis and

			foot ulcers, not all on UrgoStart	dressing, product not stated			GRADE analysis
Wounds UK, 2020	Not stated	Case series and expert opinions	UK, 4 patients, various chronic wounds	UrgoStart Plus	No comparator	No structured outcomes	Descriptive

Results of clinical studies

Authors	Results
Alhumaidi et al, 2022	Mean wound area reduced from 42.2 cm^2 (range 4.5, 195) at initial visit to 6.92 cm^2 (range not reported) at final visit. All wounds decreased in area, 71.4% were completely healed.
Augustin et al, 2021	By the final visit, wound closure or improvement was reported in 92.0% of treated wounds. Wound closure was achieved in 57.6% of diabetic foot ulcers, 45.6% of leg ulcers, 45.7% of pressure ulcers and 55.0% of other wounds. Median times to heal were 59 (IQR 38-84) days for leg ulcers, 56.5 (IQR 43-82) days for diabetic foot ulcers, 56 (IQR 35-84) days for pressure ulcers and 46 (IQR 32-70) days for other wounds. The highest wound healing rates were found in wounds with shorter duration. There was an 87.5% reduction in sloughy tissue by the final visit. Exudate decreased in 68.9% of wounds. There was a reduction in wounds with macerated periwound skin from 36.5% to 8.8%. Periwound skin condition improved in 66.4% of patients. Proportion of patients reporting spontaneous pain and pain at touch fell by 81.7% and 55.7% respectively from the initial visit. No adverse events led to discontinuation of UrgoStart dressings. Dressing tolerance was very good in 84.7% of patients and in no cases was rated as poor. The vast majority of investigators had positive or very positive views on UrgoStart and to have superior performance across a range of clinical indicators. Only 35.1% of patients completed WoundQoL at both initial and final visit but these patients were generally representative of the wider cohort. Significant improvements ($p<0.001$) were found from baseline to the final visit in overall WoundQoL score as well as physical, psychological and everyday life-related dimensions. There was a 53.4% reduction in the number of patients requiring intervention with regard to their HRQoL.
Conde-Montero et al, 2020	All patients completed the study, except one who had psychosocial problems that hindered treatment adherence. No adverse events were registered. Complete epithelialisation was achieved in 92% of wounds, after a mean of 25 +- 13 (median 21, range 5-65) days. For the 3 remaining wounds that did not heal by week 12, there was a relative wound area reduction of >75%. Evaluation of the handling characteristics of the dressing showed a high level of acceptance by patients and clinicians. Each of the nine items on the Global Performance Score was scored between 4 (very good) and 3 (good) on a 0-4 point scale.
Dissemond et	Of a total of 16 included studies, 3 assessed UrgoStart. All were included in the previous MTG42 guidance and as such are not relevant to the current appraisal.

al, 2020a	
Dissemond et al, 2020b	Wound closure or improvement by the final visit was observed in 93.3% of treated wounds. Wound closure rates were 43.6% in diabetic foot ulcers, 47.1% in leg ulcers, 48.3% in pressure ulcers and 55.2% in other wounds. For all wound types, there was a continuous reduction in wound area over the course of treatment. All wound types showed a reduction in sloughy tissue, with a global reduction from 45+-30% at baseline to 15+24% at the final visit. Duration of wound at baseline had a negative effect on wound healing. Levels of exudate decreased in 67.7% of wound by the final visit. The proportion of wounds with macerated periwound skin fell from 26.2% to 3.9%. The proportion of patients with healthy skin condition rose from 5.7% to 40.6%. Tolerance was assessed as very good by 81.4% of clinicians, with poor tolerance reported in only 0.6% of cases. There were no adverse events deemed to be associated with the investigative dressing. The UrgoStart Plus dressings were judged by investigators to be extremely useful or useful in 94.6% of patients. The dressings were very well accepted or well accepted by 98.1% of patients. Clinicians had an overall favourable opinion on the UrgoStart dressings.
Dowsett & Nichols, 2021	In a case study of 1 UK patient with a venous leg ulcer, a 76-year old man with type 2 diabetes, the wound increased in size and became wetter by week 2, but the patient reported a decrease in pain and leg swelling had reduced. Subsequently, by week 3, infection had resolved and the wound had improved significantly. UrgoStart Plus dressing was initiated following resolution of infection. By week 7, the wound had fully healed.
[redacted]	[redacted]
Lázaro-Martinez et al, 2019	In the UrgoStart specific cohort, wound closure rates were 71% for wounds with duration <= 2 months, 59% for wounds with duration 3 to <= 5 months, 29% for wounds with duration 6 to <= 11 months, and 22 % for wounds with duration >11 months. Greater wound age was significantly associated with lower closure rate.
Lázaro-Martinez et al, 2020	TcPO2 values showed a significant increase between day 0 (29.45 ± 7.38 mm Hg) and wound closure (46.54 ± 11.45 mm Hg, p = .016) after UrgoStart Contact dressing application.
Lobmann et al, 2020	Patients with wound closure is not reported correctly in Table 1 (says 126% in both arms). Mean absolute (3.2 vs 2.3cm) and relative (72% vs 42%) wound size reduction was greater on UrgoStart Contact than the control dressing.
Meloni et al, 2022	73.3% of patients healed by week 24. Mean time of healing was 84 +- 32 days. 6.7% of patients had ulcer relapse after healing. 93.3% of patients had wound regression. 7% reported mild infection, 3% (1 patient) reported major amputation due to severe infection. The paper states that no serious adverse events or local reactions related to the technology were reported during the course of the study.

Milne & Jones, 2018	Across venous and mixed aetiology leg ulcers, 70% of patients had >40% slough reduction at 4 weeks. 40% of patients had healed at the end of investigation, both venous and mixed aetiology patients. 80% of patients had >75% wound reduction at the end of the investigation period compared to baseline. Patient feedback was positive regarding comfort and no patients exited the study by choice.
Milne & Nichols, 2021	For venous and mixed aetiology leg ulcers, healing times ranged from 2 to 26 weeks and 90.5% of leg ulcers healed within 10 weeks. Healing times for other types of wounds ranged from 2 to 12 weeks (mean 7.2 weeks). An example case study is presented of a 76 year-old man with type 2 diabetes with a leg ulcer. Considerable progress was noted over a 7-week period.
Mullings & Merlin-Manton, 2018	Mean time-to-healing was 123.7 days (median 84 days) for the initial period, whereas after implementation it was 69.1 days (median 46 days).
Murray & Norrie, 2020	12 out of 13 patients experienced wound healing within 12 weeks of pathway commencement (mean healing time 6.8 weeks). Mean pain VAS reduced from 4.1 on initial assessment to 0 at final assessment. Exudate levels fell generally from low or moderate to none. Half of patients had macerated surrounding skin at initial assessment, which was resolved in most patients by week 6 and all but one patient by week 8.
Nair et al, 2021	21 studies ranging from case reports to RCTs were included that addressed sucrose octosulfate (I.e. within the UrgoStart product range). Some of the included studies were cost effectiveness studies, case reports from other countries, or older clinical studies preceding the original MTG43 guidance. There were no new clinical studies since the MTG43 guidance that are not already included in the review.
Nair, 2022	Substantial clinical improvement was observed for all wound types following UrgoStart treatment.
Richard et al, 2021	30% of diabetic foot ulcers had healed by the end of the study. Median and mean (+-SD) healing times were 58 days and 58.9 (+-25.7) days, respectively. In 73% of cases, there was wound improvement by 12 weeks. At week 12, the median and mean wound surface area were 0.47cm^2 and 0.92±1.47cm^2, respectively. Median reduction of the wound surface area was 82.7% at week 12, compared with baseline surface area, with a mean reduction of 62.7±49.9%. Seven local adverse events were observed, two of which (maceration) were assessed as possibly or probably related to the dressing. There were 13 general adverse events, of which nine were assessed to be serious, but none were considered to be related to the wound management or dressing by the study investigators. Three patients were withdrawn by investigators and switched to another dressing due to non-response. Overall, eight patients (24%) discontinued prematurely. Nurses considered dressing application to be easy or very easy in 95.6% of cases and its removal in 99.1%. Absence of bleeding or pain on removal was found in 95.0% and 95.7% respectively. Conformability on application was good or very good in 85.0% of cases.
Sigal et al, 2019	In NEREIDES, there was 60% reduction in median wound area by 12 weeks. Wound closure by week 12 occurred in 18% of patients (median time 58 (+-23) days, first event 28 days). Improvement or stabilisation occurred for 91% of patients. There was an 83% reduction in sloughy tissue by 12 weeks. There was a slight improvement in periwound skin condition. 6 patients (16%) had at least one dressing-related adverse

	event. None were considered serious. There was a high level of acceptance from clinicians and patients. On a scale of 0-36, the Global Performance of the dressing was rated as 29.
Sigal et al, 2019	In CASSIOPEE, there was 81% reduction in median wound area by 12 weeks. Wound closure by week 12 occurred in 20% of patients (median time 55 (+- 23) days, first event 23 days). Improvement or stabilisation occurred for 90% of patients. There was a 71% reduction in sloughy tissue by 12 weeks. There was a slight improvement in periwound skin condition. 9 patients (18%) had at least one dressing-related adverse event. None were considered serious. There was a high level of acceptance from clinicians and patients. On a scale of 0-36, the Global Performance of the dressing was rated as 32.
Tickle, 2021	33 out of 34 wounds healed completely within 12 weeks. There was a 45% reduction in average surface area between weeks 2 and 4 and a 57% reduction between weeks 4 and 6. After 6 weeks, there were no wounds with high exudate, after 12 weeks there were no wounds with moderate exudate and after 16 weeks all wounds were free of exudate. By week 6, there were no reports of macerated skin. There was an 85% improvement in Tickle QoL from admission to discharge.
Vas et al, 2020	One study (an RCT) was included that addressed sucrose octosulphate (I.e. within the UrgoStart product range) – this is already included in the review (Edmonds et al, 2018)
Wounds UK, 2020	Clinical opinion reflected that UrgoStart products were used in practice, there were some CHALLENGEs such as with reluctance to change practice, but implementation and outcomes have been successful. The four patients had lower leg ulcers, diabetic foot ulcers or pressure heel ulcers. In all cases, considerable improvement was noted following use of UrgoStart Plus.

No ongoing trials were identified by the NICE search or by clinical trial searches undertaken by the EAG.

Study characteristics of Economic studies

Authors	Study name/Trial used	Design/Model structure	Time Horizon	Population	Interventions	Comparator	Outcomes
Augustin et al, 2016	CHALLENGE	Decision tree	8 weeks	187 patients with Venous Leg Ulcers	UrgoStart	Neutral Dressing without NOSF - UrgoCell	40% wound healing
Betts et al, 2018a	CHALLENGE	Markov Model – Four health states (open, infected,	1 year	Cohort of 1000 patients with Diabetic foot ulcers	UrgoStart	Neutral comparator dressing	Relative wound area reduction at 8 weeks

		closed, deceased)					
Betts et al, 2018b	-	Budget Impact Model	5 years	130 patients with diabetic foot ulcers	UrgoStart	Neutral comparator dressing	Patient Eligibility for UrgoStart
Lobmann et al, 2019	EXPLORER	2-stage decision tree/Markov model with 5 states (healed, remain without AEs, infected wound, infection leading to inpatient stay or amputation, death)	20 weeks/100 weeks	240 diabetic patients with diabetic foot ulcers. Mean age 64.5, 84.1% male.	UrgoStart Contact	Neutral Dressing without sucrose octasulfate potassium salt - UrgoTul	Rate of wound closure at week 20, estimated healing time, reduction In wound area
Lobmann et al, 2020	EXPLORER	2-stage decision tree/Markov model with 5 states (healed, remain without AEs, infected wound, infection leading to inpatient stay or amputation, death)	20 weeks/100 weeks	240 diabetic patients with diabetic foot ulcers. Mean age 64.5, 84.1% male.	UrgoStart Contact	Neutral Dressing without sucrose octasulfate potassium salt - UrgoTul	Total direct cost of wound dressing, wound healing rates
Maunoury et al, 2021	EXPLORER	Markov with five states, uninfected,	Lifetime (40 years)	240 diabetic patients with diabetic foot	UrgoStart Contact	Neutral Dressing without	Life expectancy without

		closed, infection, amputation, death		ulcers. Mean age 64.5, 84.1% male.		sucrose octasulfate potassium salt - UrgoTul	Ulcers, expressed in life years without ULCER.
Mloch et al, 2019	EXPLORER and CHALLENGE	Decision Tree with two health states, treatment success and treatment failure	1 year	Venous Leg Ulcers	UrgoStart	Control dressing – UrgoTul	

Results of economic studies

Authors	Results
Augustin et al, 2016	After 8 weeks of treatment, costs were estimated to be €849.86 for UrgoStart and €1335.51 for the comparator, resulting in an effect-adjusted advantage of €485.64 for UrgoStart. Prices of UrgoStart were varied in €5 increments up to €45, and the resulting break-even point was €27.29. The basic start price of UrgoStart is €9.98. Indicates the results are very robust. The probability of treatment success was also varied between 25% and 75%, based on a real starting value of 65.6% The break-even response rate was 43.15% confirming the robustness of the model.
Betts et al, 2018a	Urgostart was a dominant strategy; cost-saving of £274.25 and QALY gain of 0.03 per patient. At 1 year, 949 wounds had healed using UrgoStart compared to 854 wounds using a neutral dressing. The cost of healed wounds were £1666.80 and £2174.89 respectively. Scenario analysis showed that at a comparator cost of £0, in 1000 model runs, UrgoStart was dominant in approximately 90% of cases.
Betts et al, 2018b	Over 5 year-period, 1.3 million patients were eligible for Urgostart . Cost per patients was £1445.90 v £1638.64 using a neutral dressing. Using UrgoStart could save £251.7 million for the NHS whilst avoiding 26.1 million days with ulceration for patients.

Lobmann et al, 2019	At 20 weeks, estimated total treatment costs were €2,864.21 for the treatment group and €2,958.69 for the control group, resulting in a cost-effectiveness estimate of €6,017.25 compared to €9,928.49 for the control group due to the higher healing rates. Resulting ICERs were -€530.80 at 20 weeks and -€20,905.16, highlighting the dominance of the treatment over the comparator. Sensitivity analysis was performed by adjusting parameters an arbitrary 20% in a one-way sensitivity analysis, highlighting that the number of dressing changes per week was most impactful.
Lobmann et al, 2020	Results show wound healing rates between 71% and 14.8% and direct costs of €2482-€3278 for the treatment group and €2768 - €3194 for the control group. The longer timer period increased these differences further.
Maunoury et al, 2021	Treatment with TLC-NOSF lead to a cost-saving of €35 489 with QALY gains of 0.50 LYw/DFU, and was the dominant strategy in base-case and all sensitivity analysis. For every 100 patients treated with TLC-NOSF, two amputations could be avoided. Subgroup analysis highlighted that the sooner the treatment was used, the better the outcomes with the largest effect seen when ulcers are present for two-months or less. Potential savings show €3345 per patient per year, or up to €4771 when TLC-NOSF is used as a first line treatment. UrgoStart dressings lead to an increase health benefits and decrease in associated treatment costs.
Mloch et al, 2019	UrgoStart was a dominant treatment strategy, at 0.03 and 0.05 QALY gain for NDFU and VLU respectively, and incremental costs were -€5 and €143. Sensitivity analysis showed that even with UrgoStart being 10 times higher than UrgoTul, the ICER remained well below the threshold, at €21,777 for NDFU and €£2,888 for VLU.

Appendix C – Literature search strategy

Medline search strategy

1 (urgostart* or urgo-start* or urgo start*).tw. (15)
2 (urgo adj2 medical).tw. (11)
3 (nano-oligosaccharide factor or nanooligosaccharide factor or NOSF).tw. (35)
4 (technology adj2 (lipido-colloid or lipido colloid or lipidocolloid)).tw. (15)
5 TLC-NOSF.tw. (20)
6 or/1-5 (54)
7 Bandages, Hydrocolloid/ (975)
8 ((hydrocolloid or hydrogel or matrixins or matrix metalloproteinase* or matrix metallopeptidase* or mmp or mmps or protease* or sucrosofate* or sucrose octasulfate* or sucrose octasulphate*) adj4 (bandage* or dressing* or gauze* or mesh*)).tw. (1617)
9 or/7-8 (2226)
10 ulcer/ or skin ulcer/ or pressure ulcer/ (37127)
11 exp Leg Ulcer/ (24909)
12 Diabetic Foot/ (10688)
13 ((acruris or crural or cruris or decubitus or diabet* or foot or feet or heel* or leg* or limb* or plantar* or pressure or skin or sole* or stasis or toe* or varicose* or venous) adj3 ulc*).tw. (36190)
14 ((pressure or bed) adj4 (sore or sores)).tw. (3455)
15 bedsore*.tw. (557)
16 Wound Healing/ (103409)
17 ((chronic or clos* or heal* or non-healing or nonhealing or progress* or reduct* or repair*) adj2 (ulc* or wound*)).tw. (118690)
18 or/10-17 (236163)
19 9 and 18 (1542)
20 6 or 19 (1575)
21 limit 20 to ed=20180301-20220930 (466)
22 limit 20 to dt=20180301-20220930 (525)
23 21 or 22 (587)
24 limit 23 to english language (577)
25 limit 24 to (letter or historical article or comment or editorial or news or case reports) (25)
26 24 not 25 (552)
27 animals/ not humans/ (5010113)
28 26 not 27 (417)

Appendix D – References

List of included clinical papers

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