NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

UrgoStart for the treatment of leg ulcers and diabetic foot ulcers

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 overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patients
- Appendix D: Claimed benefits and decision problem from the scope

1 The technology

UrgoStart (Urgo Medical) is a dressing intended for treating chronic wounds. The indications addressed in this evaluation are leg ulcers and diabetic foot ulcers. There are 5 different formats of the dressing: UrgoStart Contact Layer, UrgoStart Non-Adhesive, UrgoStart Plus Pad, UrgoStart Border and UrgoStart Plus Border. All UrgoStart products are CE marked as class IIb devices. The CE marks for the different UrgoStart dressings were awarded between 2006 and 2016.

The UrgoStart dressings contain a layer of open weave polyester mesh, impregnated with hydrocolloid polymers, within a petroleum jelly. This is called technology lipido-colloid (TLC) and it is intended to create a moist, protective, wound healing environment. The innovative element of UrgoStart is that it contains nano-oligosaccharide factor (NOSF) which inhibits protease activity, specifically matrix metalloproteinases. There is evidence that high levels of proteases (enzymes) in wounds are linked to slower wound healing.

2 Proposed use of the technology

2.1 Disease or condition

A leg ulcer is a long-lasting sore that takes more than 4 to 6 weeks to heal. There are 3 different types: venous, arterial and mixed aetiology. 70-80% of ulcers are venous. The symptoms of a venous leg ulcer include pain, itching and swelling in the affected leg.

Foot ulcers can affect people with both type 1 and type 2 diabetes. They are a patch of broken down skin usually on the lower leg or feet. There are 2 types of diabetic foot ulcers: neuropathic ulcers and neuroischaemic ulcers. The crucial difference between the two types is the absence or presence of ischaemia. Around 50% of foot ulcers are neuroischaemic.

2.2 Patient group

Leg ulcers affect around 1 in 50 people over the age of 80. There is no difference in prevalence between socio-economic classes but they take longer to heal in people from lower social classes. Venous leg ulcers are estimated to affect around 1 in 500 people in the UK. In people under 40 years of age, men are more likely to have a venous leg ulcer but overall women are 2 times more likely. In 2001, it was estimated that the cost of treating one venous leg ulcer was between £1,298 and £1,526 per year.

Around 3 million people have diabetes. It is estimated that 1 in 20 people with diabetes will develop a foot ulcer each year, and of these, more than 1 in 10 will ultimately require amputation. Mortality rates after diabetic foot ulceration and amputation are high, with up to 70% of people dying within 5 years of having an amputation and around 50% dying within 5 years of developing a diabetic foot ulcer. £1 in every £150 the NHS spends is spent on managing foot ulcers or undertaking amputations each year.

2.3 Current management

The Scottish Intercollegiate Guideline Network (SIGN) guideline on the management of venous leg ulcers recommends simple non-adherent dressings and compression therapy. NICE has published a Clinical Knowledge Summary on venous leg ulcers. It recommends that low-adherent dressings are applied and replaced weekly. Alternative dressings to consider are hydrocolloid for pain, alginate for heavy exudate and hydrogels for slough. Most patients with leg ulcers are treated in a community setting.

NICE has published a guideline on the prevention and management of foot problems in people with diabetes . It states that clinical assessment and patient preference should inform dressing choices but that healthcare professionals should chose the lowest cost dressing that is likely to achieve the desired results. Most people with diabetic foot ulcers are treated in secondary care.

2.4 Proposed management with new technology

No specific new pathway proposed by the company. The company suggest the technology is included in formulary listings to ensure availability of the product.

3 Company claimed benefits and the decision problem

Details of the company's claimed benefits and the decision problem are described in Appendix D. In its submission, the company proposes variations to the scope as described in table 1.

Table 1: Details of variation from scope

Decision problem	Variation proposed by company	EAC view of the variation
Subgroups	To remove pressure ulcers as a subgroup as there is not enough data in this patient population.	The EAC identified 1 non-comparative study (Munter et al. 2017) which provided evidence on pressure ulcers, however, no information on the location of the ulcers was provided so the EAC felt that it was appropriate to exclude pressure ulcers as a subgroup.
	To perform sub-analysis on the following: • Poor wound healing prognosis factors (size and duration) • Age • Sex • BMI • ABPI/TBPI • History of amputation • History of revascularisation	The EAC felt that because of the inherent heterogeneity of the population defined in the scope and the limited data on patient characteristics in the studies identified, sub-analysis would not contribute to the decision problem.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company presented 8 published studies and 1 unpublished study in its clinical evidence submission. The EAC conducted a literature review and identified 6 studies which it judged most relevant to the decision problem all of which were published and had also been presented by the company: 3 RCTs in people with leg ulcers (LUs); 1 RCT and 1 non-comparative study in people with diabetic foot ulcers (DFUs) and 1 pooled data analysis which included both patient groups. Summary information on the included and excluded studies is in table 2; further details can be found in section 3 of the assessment report. ***Table 2: Included studies by the company and EAC

Study	Type of publication	Type of study	Comment
Studies included by both EAC and company			
6 studies included by both	Full text papers	4 RCTs, 1 non-comparative study and 1 pooled data analysis	RCTs in LUs: Meaume et al. 2012 Meaume et al. 2017 Schmutz et al. 2008 RCT in DFU: Edmonds et al. 2018 Non-comparative study in DFU: Richard et al. 2012 Pooled data analysis in LUs and DFUs: Munter et al. 2017
Studies in submission excluded by EAC			
Veves et al. 2002	Full text paper	RCT	Did not include UrgoStart as an intervention.
Vin et al. 2002	Full text paper	RCT	Did not include UrgoStart as an intervention
Urgo PRO study 2018	Unpublished study	Cross sectionalstudy	Did not include UrgoStart as an intervention

All primary outcomes in the assessed evidence related to wound healing with slightly different definitions. The most common definition, adopted by 3 studies (Meaume et al. 2012, Richard et al. 2012, Schmutz et al. 2008), was the relative wound area reduction.

The pivotal study for people with venous leg ulcers was the multi-centre double-blind international CHALLENGE (n = 187) RCT, which compared UrgoStart with UrgoTul Absorb, a simple non-adherent dressing with an 8

weeks follow up (Meaume et al. 2012, Meaume et al. 2017). The results reported a statistically significant increase in relative wound area reduction, in favour of UrgoStart (p=0.002). Use of UrgoStart also resulted in improved quality of life (p=0.022). The 2 groups performed equally in terms of safety and tolerance. The EAC judged that the pivotal study for people with neuro-ischaemic DFUs was the multi-centre double-blind international EXPLORER (n = 240) RCT, which compared UrgoStart with UrgoTul, a simple non-adherent dressing with a 20 week follow up (Edmonds et al. 2018). The results reported a statistically significant increase in wound closure, in favour of UrgoStart (p=0.002). The two groups performed equally in terms of safety and quality of life.

The level of benefit in terms of healing rates for venous leg ulcers and diabetic foot ulcers was also broadly supported by evidence from a pooled analysis of non-comparative data (Munter et al. 2017).

The company did not include a meta-analysis in their clinical evidence submission because they said the studies were too heterogeneous. The EAC agreed with this conclusion.

EAC's quality appraisal of the clinical evidence

The EAC carried out a quality appraisal of the 6 full text publications included in the assessment report. According to the clinical expert advisers the best primary outcome would ideally be complete wound closure (CWC) or time to reach CWC, because that is the key objective. Complete wound closure at 20 weeks follow-up was reported by Edmonds et al. (2018) while Munter et al. (2017) reported time to reach CWC. The other studies included in the assessment report used wound area reduction (WAR) as the primary outcome. The clinical experts advised that the methods of measurement of WAR are potentially subject to a large margin of error and this needs to be taken into consideration in the interpretation of the results. Regarding follow-up time, the clinical experts noted that healing rates vary depending on patient and wound characteristics. The National Diabetic Foot Care Audit suggests a

12 week follow-up for diabetic foot ulcers and 16-24 weeks for venous leg ulcers.

A qualitative quality appraisal for each included study can be found in section 3.3 of the assessment report. Tables 3 and 4 provide a summary of the EAC's quality assessment. The EAC noted the high dropout rate reported in the RCT by Schmutz and also considered the study underpowered.

Table 3: Results of methodological assessment for RCTs (reproduced from table 6 in the assessment report)

Study	Schmutz 2008 VLU	Meaume 2012* VLU	Edmonds 2018 DFU
Selection Bias	Unclear/ unknown risk	Low risk of bias	Low risk of bias
Performance Bias	Unclear/ unknown risk	Low risk of bias	Low risk of bias
Attrition Bias	Low risk of bias	Low risk of bias	Low risk of bias
Detection Bias	Low risk of bias	Low risk of bias	Low risk of bias
Other (conflicts of interest, power, endpoint)	Unclear/ unknown risk	Low risk of bias	Low risk of bias
*Meaume 2017 is a re-analysis of the same cohort used in Meaume 2012. The EAC assessed the risk of biases as the same with the exception of the 'Other' category where it was judge 'unclear/unknown risk' because the 2017 study was not powered for its primary endpoint.			

Table 4: Results of the methodological assessment for observational studies (reproduced from table 7 in the assessment report)

Study	Richard 2012 DFU	Munter 2017 DFU/VLU
Is the study based on a representative sample selected from a relevant population?	Yes	Yes
Are criteria for inclusion explicit?	Yes	No
Did all individuals enter the study at a similar point in their disease progression?	Yes	No
Was follow up long enough for important events to occur?	No	No/unclear*

Were outcomes assessed using objective criteria or was blinding used?	Yes (no blinding)	Yes (no blinding)
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	N/A	Yes
* Follow-up varied between 4-20 weeks		

EAC's conclusions about the clinical evidence

The EAC confirmed that the company had provided a submission that included all available clinical evidence on UrgoStart. They considered the main evidence for diabetic foot ulcers to be based on Edmonds et al. (2018) and for venous leg ulcers to be based on Meaume et al. (2012). The findings of these 2 pivotal studies was also broadly supported by evidence from a pooled analysis of non-comparative data (Munter et al. 2017). The EAC concluded that using UrgoStart improved wound healing in both venous leg ulcers and diabetic foot ulcers. The EAC noted there was no evidence to support improved quality of life with the intervention, however none of the included studies were powered to detect differences in secondary outcomes such as quality of life.

Table 5: Pivotal studies identified by the EAC (reproduced from table 5 in the assessment report)

Study and design and funding	Participants/ population	Intervention & comparator	Outcome measures and follow up	Withdrawals	EAC comments
Edmonds et al. 2018 Explorer study. A prospective, two-arm, multicentre, double-blind RCT. Company funded.	240 people with diabetes (hospitalised or outpatients) and a non-infected neuroischaemic DFU from France, Spain, Italy, Germany and the UK. Patients were included if DFU was greater than 1 cm² and of grade IC or IIC (University of Texas Diabetic Wound Classification system).	126 were randomised to receive UrgoStart and 114 to UrgoTul (neutral foam dressing)	20 week follow-up Proportion of patients with wound closure at week 20 Estimated mean time to reach wound closure Median WAR Median %RR UrgoStart versus UrgoTul adjusted odds ratio to wound closure	37 (15%) withdrew before the 20 week period was finished: 19 in the control group and 18 from the treatment group.	Good methodological quality. Powered to detect a statistically significant endpoint at 20 weeks. This study showed significantly more patients with DFUs achieved wound closure when treated by UrgoStart. Small number of patients treated per centre, median 3 patients. Long follow-up period (relative to other included studies).

	BMI >30 kg/m² = 44.6% Ulcer > 5cm² = 18%.		WAR of at least 50% at week 4 Adverse events HR-QoL - mean EuroQol-5D-5L index.		
Meaume et al. 2012 Challenge study. A prospective, multi-centre, double-blind RCT. Company funded.	187 people with a VLU being managed either as an inpatient or an outpatient from 45 centres in France. Selection was based on a VLU area of between 5 and 50 cm^2 and duration of 6 to 36 months. ABPI had to be between 0.8 and 1.3 and at	93 were randomised to receive UrgoStart and 94 to UrgoTul (neutral foam dressing)	8 week follow-up WAR (absolute and percentage) Wound edge progression Wound healing rate Median time to reach WAR ≥ 40% Perilesional skin Acceptability	5.4% of patients withdrew, including 2 deaths (1 from each group) and 3 withdrawals of consent.	Good methodological quality. Powered to detect a statistically significant endpoint at 8 weeks. Small number of patients treated per centre. The follow-up of 8 weeks is potentially too short to assess healing in complex wounds.

	least 50% of the ulcer covered by granulation tissue without any black necrotic tissue. BMI > 30kg/m^2 = 43.0% Ulcer area > 10cm^2 = 58.1%		Adverse events		
Munter et al. 2017. A pooled data analysis of 8 non-comparative, observational studies. All included studies were funded by Urgo.	Data obtained from 10,220 people with 7903 leg ulcers (LUs), 1306 DFUs and 1011 pressure ulcers (PUs) in France and Germany. <u>Total population</u> Mean age = 72.9 ± 12.4 Mean BMI = 27.9 ± 5.9	UrgoStart was used by all participants. There was no comparator.	Follow up ranged from 4 to 20 weeks Overall closure rate Time to wound closure Time to 50% PUSH score reduction Subgroup analysis on 1st or 2nd line	NA	Non-comparative study. The included studies varied in methodology and study outcomes. The follow-up periods of the studies varied greatly from 4 weeks to 20 weeks. The subgroup analysis was conducted with a considerably large sample size (n=4215).

	Mean PUSH score = 11.1 ± 3.2. <u>LUs</u> BMI >35 kg/m² = 10.6% Duration >6 months and/or wound area > 8cm² = 48.6% PUSH score = 11 ± 3. <u>DFUs</u> BMI >35 kg/m² = 13.4% Duration >6 months and/or wound area > 8cm² = 35.2% PUSH score = 9 ± 3. <u>PUs</u> Men = 46.9% BMI >35 kg/m² = 6.2% Diabetic = 34.9%		treatment with UrgoStart– days to closure		

	Duration >6 months = 15.6% Duration >6 months and/or wound area > 8cm² = 45.0% PUSH score = 11 ± 3 Patients with healthy periwound skin = 19.3%.				

Table 6: Outcomes associated with wound healing in pivotal studies identified by the EAC (reproduced from table 8 in the assessment report)

References, trial name & patient group.	Mean relative WAR (%)	Wound closure (%)	Mean time to CWC (days)	Mean absolute WAR (cm^2)
Meaume 2012 CHALLENGE RCT VLUs	UrgoStart: 45.2 ± 47.9 UrgoTul 21.4 ± 81.0 (p=0.002)	NR	NR	UrgoStart: 6.9 ± 11.4 UrgoTul: 2.5 ± 11.9 (p=0.003)
Edmonds 2018 EXPLORER RCT DFUs	UrgoStart: 72 ± 47 UrgoTul: 42 ± 115 (mean p value not reported. Median p= 0.024)	UrgoStart: 48% UrgoTul: 30% Adjusted odds ratio: 2.60 (p=0.002)	UrgoStart: 120 UrgoTul: 180 (p=0.029)	UrgoStart: 3.2 ± 5.2 UrgoTul: 2.3 ± 5.5 (mean p value not reported. Median p= 0.022))
Munter 2017 VLUs	NR	UrgoStart: 29.8% [95 % CI: 28.8–30.9 %]	UrgoStart: 112.5 days [95%CI: 105.8–119.3]	NR
Munter 2017 DFUs	NR	UrgoStart: 37.4% [95 % CI: 34.8–40.1 %]	UrgoStart: 98.1 days [95 %CI: 88.8–107.5]	NR

Table 7: Secondary outcomes in pivotal RCTs identified by the EAC (reproduced from table 9 in the assessment report)

References, trial name & patient group.	Tolerance and acceptability	Patient compliance	Adverse events	Infection (%)	Amputation (%)	EQ5D	VAS
Meaume 2012 CHALLENGE RCT VLUs	Easy or very easy UrgoStart: 97.1% UrgoTul: 98% Totally painless UrgoStart: 84.7% UrgoTul: 86.8% Periwound maceration UrgoStart: 15.3% UrgoTul: 16.9% (P values not reported)	Week 2: 98.9% Week 4: 96.6% Week 6: 96.4%	UrgoStart: 29 (10 dressing-related) UrgoTul: 27 (13 dressing-related) (P value not reported)	UrgoStart: 7.53 UrgoTul: 6.38 (P value not reported)	NR	Pain–discomfort: 1.53 ± 0.53 vs. 1.74 ± 0.65(p = 0.022) Anxiety– depression: 1.35 ± 0.53 vs. 1.54 ± 0.60(p= 0.037)	UrgoStart: 72.1 ± 17.5 UrgoTul: 67.3 ± 18.7 (p = 0.072)
Edmonds 2018 EXPLORER RCT DFUs	NR	NR	UrgoStart: 40 (2 dressing-related) UrgoTul: 47 (6 dressing-related) (P value not reported)	UrgoStart: 20 UrgoTul: 28 (P value not reported)	UrgoStart: 1 UrgoTul: 2 (P value not reported)	UrgoStart: 0.63 ± 0.30 UrgoTul: 0.69 ± 0.32(p=0.245)	NR
NR= not reported EQ5D not fully reported; these were the only reported scales							

4.2 Summary of economic evidence

The company submitted 6 studies as economic evidence for UrgoStart. Of these, the EAC accepted 1 full peer-reviewed paper (Augustin et al. 2016) and 1 internal company report (Taylor et al. 2011) as relevant to the decision problem (for more information, see section 4.1 of the assessment report). Augustin et al. (2016) constructed a decision tree model using clinical data from the CHALLENGE study (Meaume et al. 2012) taking the perspective of the German statutory health care system for a time horizon of 8 weeks. It showed a cost advantage of €486 for UrgoStart per patient. The EAC noted that the short duration of 8 weeks would not, for most patients, be long enough to reach wound healing. Taylor et al. (2011) constructed a one-year Markov model, also using the CHALLENGE study results (adapted to a UK setting) comparing UrgoStart with neutral foam dressing in patients with chronic leg ulcers. [redacted].

De novo analysis

The company presented separate de novo cost effectiveness models for diabetic foot ulcers and leg ulcers: 2 Markov models, each with 1 week cycle length. The technology used as the intervention is the UrgoStart dressing and the comparator is the UrgoTul dressing. Results are presented for a time horizon of 1 year.

The structure of the models is shown in Figures 1 and 2 and the assumptions are described in section 4.2 of the assessment report (pages 60-61). The EAC considers that both the model structures adequately capture all the relevant health states and the assumptions are valid and reasonable. The EAC calibrated the models based on an assumption that a proportion of the population would not see sufficient wound progression with either the technology or the comparator and would be switched to a different product after a period of time.

Figure 1: Leg ulcer model

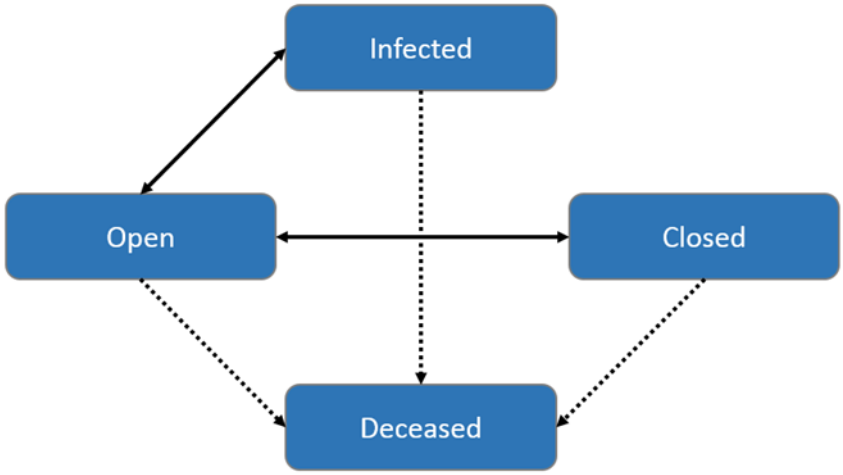
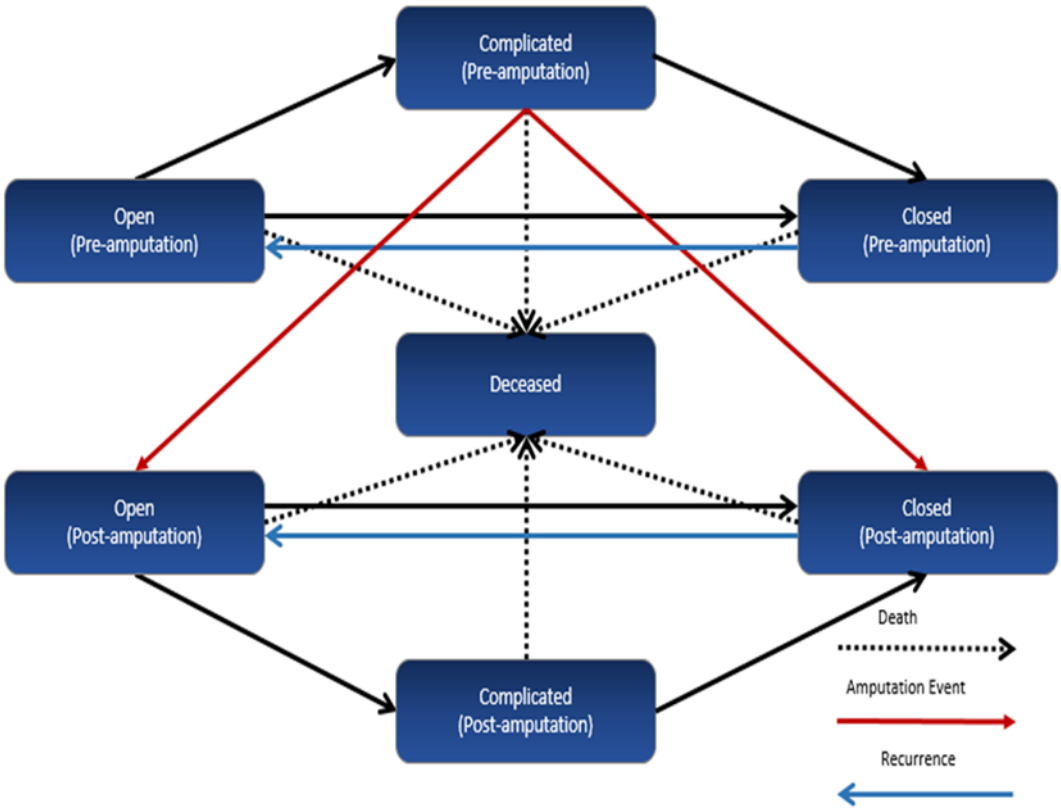


Figure 2: Diabetic foot ulcer model



Model parameters

Parameters for the leg ulcer model are mainly based on trial data from the CHALLENGE study (Meaume et al. 2012) and for diabetic foot ulcers, the EXPLORER study (Edmunds et al. 2018). Some additional sources including the National Diabetes Foot Care Audit and the Eurodial were also used. Full details of the clinical parameters and variables used in the leg ulcer and diabetic foot ulcer models and the EAC's opinion on the appropriateness of these can be found in section 4.2 of the assessment report.

The EAC did not agree with the company values for some parameters. It re-estimated the transition probabilities for some states in the diabetic foot ulcer model.

Costs and resource use

In the company's models UrgoStart has a price of £4.28 and the comparator (UrgoTul 10cmx10cm dressing) has a price of £3.13. The EAC revised the cost of the comparator to the BNF price (£2.38). The EAC also noted that other neutral dressings are available which are cheaper and may be clinically equivalent. The EAC also changed some other costs in the models including the cost of a practice nurse visit (from £50 to £18) and in the venous leg ulcer model the cost of a hospital admission (from £452 to £1,586).

Only two studies (Guest et al. 2018a for diabetic foot ulcers and Guest et al. 2018b for venous leg ulcers) included relevant resource use data. The EAC agreed that these studies are appropriate sources for resource use data but revised some of the company values. It also used the data from these studies to calibrate the models. The models were calibrated to match the proportion of patients healing with UrgoTul in the model after 1 year to the proportion of patients reported to heal after 1 year in the relevant Guest et al. study. The EAC did this by assuming that a fixed proportion of those patients treated would not heal. It assumed that treatment for these patients would proceed for a number of weeks before the dressing was changed to a different product and during this time patients treated with UrgoStart would accrue additional costs (£32.69 for people with diabetic foot ulcer and £31.81 for people with venous leg ulcers) to those treated with UrgoTul reflecting purely the additional dressing costs £31.81 (£3.85 per week for 8.26 weeks)

Results

The company's base case analysis showed UrgoStart to be cost saving by £274.25 per patient per year for leg ulcers and £666.51 per patient per year for diabetic foot ulcers when compared to a neutral dressing. As a result of changes to parameters and calibration, the final base case cost savings estimated by the EAC differed from those estimated by the company for leg ulcers (Table 8) and diabetic foot ulcers (Table 9).

Table 8: Leg ulcer model base case results (reproduced from table 17 in the assessment report)

	Company's estimates			EAC's estimates (before calibration)		
	UrgoStart	Neutral dressing	Difference	UrgoStart	Neutral dressing	Difference
Technology	£157.77	£151.94	-£5.83	£86.64	£98.27	£11.63
Inpatient	£4.60	£4.53	-£0.07	£12.19	£24.87	£12.68
Outpatient	£1140.25	£1370.58	£230.33	£627.06	£1279.29	£652.23
Medication	£8.19	£9.78	£1.59	£5.20	£10.60	£5.40
Devices*	£271.78	£320.00	£48.22	£196.17	£400.20	£204.03
Total	£1582.58	£1856.83	£274.25	£927.26	£1813.23	£885.97

*excluding primary dressing

Table 8a: Impact of calibration on the savings (reproduced from table 17 assessment report)

	EAC's model	Company's model	Difference
Saving before calibration	£886	£274	£612
Saving after calibration	£541	£274	£267

Table 9: Diabetic foot ulcer model base case results (reproduced from table 16 in the assessment report)

	Company's estimates			EAC's estimates (before calibration)		
	UrgoStart	Neutral dressing	Difference	UrgoStart	Neutral dressing	Difference
Technology	£390.72	£359.63	-£31.09	£348.47	£251.32	-£97.15
Inpatient	£597.61	£811.94	£214.33	£0	£0	£0
Outpatient	£1280.27	£1564.24	£283.97	£1052.29	£1365.09	£312.80
Medication	£37.95	£44.69	£6.74	£46.39	£60.18	£13.79
Devices*	£734.94	£802.96	£68.02	£220.44	£278.50	£58.06
Amputation event	£142.86	£267.40	£124.54	£137.24	£272.14	£134.09
Post amputation care	£0	£0	£0	£862.32	£875.11	£12.79
Total	£3184.35	£3850.86	£666.51	£2667.15	£3102.34	£434.38

*excluding primary dressing

Table 9a: Impact of calibration on the savings (reproduced from table 16 in the assessment report)

	EAC's model	Sponsor's model	Difference
Saving before calibration	£435	£667	-£232
Saving after calibration	£342	£667	-£325

The EAC estimates lower costs of treatment than those estimated by the company. This is driven primarily by the changes the EAC has made to the resource use associated with treating unhealed and healed ulcers. The costs associated with unhealed leg ulcers have risen; in contrast the costs associated with healed leg ulcers and infected leg ulcers have fallen. The costs associated with diabetic foot ulcers have generally fallen although the cost of treating unhealed diabetic foot ulcers prior to amputation has risen modestly. The changes have had the biggest impact on the estimates for leg ulcers where the EAC estimates much lower costs attributable to treatment with UrgoStart than those in the company's submission. However, the impact of calibration is greater for the leg ulcer model. After calibration, the EAC estimates cost savings of roughly twice those estimated by the company for leg ulcers and half of those estimated by the company for diabetic foot ulcers.

The EAC's base case analysis showed UrgoStart to be cost saving by £342 in diabetic foot ulcers and £541 in leg ulcers over a 1 year period. Key cost drivers are the cost of dressings, the transition parameter for healing and infection/complications and the resource use with regards to community nursing and hospital visits. The increased likelihood of healing drives the cost savings for UrgoStart.

The company performed deterministic sensitivity analysis for the key model parameters for diabetic foot ulcer and leg ulcer models. The EAC thought that this analysis was appropriate. The company's probability sensitivity analysis excluded parameters whose variation generated less than 5% change in the incremental cost in the deterministic analysis. The EAC noted that as standard practice, it is better to include all the parameters in the PSA, however, they did

not think the company's exclusions were a major concern. For the diabetic foot ulcer model, UrgoStart was cost saving in all sensitivity analyses with the exception of the analysis in which healing rates with UrgoStart estimated from the EXPLORER trial were reduced by 50%. In this scenario UrgoStart generated a modest cost increase compared to UrgoTul. For the leg ulcer model, UrgoStart was cost saving in all sensitivity analyses. The EAC performed their own sensitivity analyses and even with their changes to the parameters and their calibration of the model they also found that UrgoStart was always cost saving for leg ulcers and only a higher cost when the true healing rates with UrgoStart are half of those reported in the EXPLORER trial.

5 Ongoing research

The company referred to 2 ongoing studies ("Retrospective Study of Clinical Outcomes and Resource Use in Chronic Leg Wound Management in the UK" and "Patient Reported Quality of Life Cross-Sectional Study", but the EAC was unable to locate a record of either.

6 Issues for consideration by the Committee

Clinical evidence

According to experts, the best primary outcome would ideally be complete wound closure or time to reach complete wound closure, because that is the key objective. Complete wound closure at 20 weeks follow-up was reported by Edmonds et al. (2018) for diabetic foot ulcers and Munter et al. (2017) reported time to reach complete wound closure for leg ulcers and diabetic foot ulcers. Is there sufficient evidence to demonstrate improved healing in leg ulcers?

Experts say that leg ulcers are mainly treated in primary care and diabetic foot ulcers in secondary care. All the included leg ulcer studies are only in or mostly in a secondary care setting. Are the results generalisable to a primary care setting?

The majority of the included evidence refers to venous leg ulcers, however, the clinical experts consulted during the development of the assessment report, were of the opinion that findings on the efficacy of UrgoStart in venous leg ulcers are generalisable to the broader category of leg ulcers.

Cost evidence

Does the committee agree with the EAC's approach to calibrating the model?

What is the level of certainty for drivers of the cost savings, especially those based on expert opinion or indirect data?

7 Authors

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

A Details of assessment report:

- Chalkidou A et al., UrgoStart for the treatment of leg ulcers and diabetic foot ulcers, June 2018

B Submissions from the following sponsors:

- Urgo Medical

C Related NICE guidance

- Diabetic foot problems: prevention and management. NICE clinical guideline 19 (2016). Available from www.nice.org.uk/guidance/ng19
- Leg ulcer – venous. Clinical Knowledge Summary (2015). Available from https://cks.nice.org.uk/leg-ulcer-venous

D References

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Appendix B: Comments from professional bodies

Expert advice during topic selection 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.

Dr Chris Manu
consultant diabetologist in diabetic foot medicine

Mr David Russell
consultant vascular surgeon, ratified by the Vascular Society

Mrs Gail Powell
clinical nurse specialist wound care

Mrs Jo-anne Beresford
wounds clinical nurse specialist, ratified by the Tissue Viability Society

Dr Leanne Atkin
lecturer practitioner, nominated by the Vascular Society

Dr Louise Mitchell
clinical lead podiatrist, ratified by The Society of Chiropodists and Podiatrists/ The College of Podiatry

Mrs Nicci Aylward-Wotton
tissue viability nurse consultant

Sarah Gardner
clinical lead tissue viability service, ratified by the Tissue Viability Society.

- The majority of expert advisers had had experience of using UrgoStart with people who had venous leg ulcers, particularly those with hard to heal ulcers. At least two experts had used it for people with diabetic foot ulcers.

- Experts who had used UrgoStart for treating leg ulcers thought that a key benefit of using it was faster wound healing. Other benefits mentioned included a reduction in dressing changes, less nurse contact, improved quality of life.
- Experts who had used UrgoStart for treating diabetic foot ulcers also thought that a key benefit was faster wound healing. They said that faster healing would reduce the risk of infection and the risk of amputation and decrease mortality. One expert highlighted that it is important that patients continued to receive optimum standard care, for example debridement and off-loading, and that the dressing is not seen as a treatment in isolation.
- All experts thought that UrgoStart could be cost saving if it did lead to faster healing as the majority of costs for wound care are associated with staff time. Most experts thought that UrgoStart would particularly benefit people with hard to heal ulcers.

  Please see the expert adviser questionnaires included in the pack for full details.

Appendix C: Comments from patients

A questionnaire was designed to capture user experiences of UrgoStart. The following patient and carer organisations were contacted and asked to share the questionnaire:

- Age Related Diseases and Health Trust
- Diabetes Research & Wellness Foundation
- Diabetes UK
- Foot in Diabetes UK (FDUK)
- InDependent Diabetes Trust
- Juvenile Diabetes Research Foundation (JDRF)
- Leg Ulcer Charity
- Limbless Association
- Lindsay Leg Club Foundation
- Pressure Ulcers UK
- The Circulation Foundation
- The Relatives and Residents Association
- Vascular Society of Great Britain and Ireland
- Vasculitis UK
- Your Turn

One patient completed the survey. Additionally, the clinical experts were asked to forward the questionnaire to some of their patients. Three further patients responded to the questionnaire.

- Three of the respondents had a diabetic foot ulcer and 1 a leg ulcer. Three had been using the dressing for 2 to 5 weeks and one for over 2 years. Dressing changes ranged from 1 to 3 times a week. One patient reported that UrgoStart was the best dressing they had ever used. Another said that their foot ulcer seemed to be healing quicker. Another said that it reduced maceration and less debridement was needed. None of the respondents

reported any negative effects and all 4 said they would recommend UrgoStart to others with the same condition.

Appendix D: Claimed benefits and decision problem from scope

The company claims that the benefits to patients compared with standard care are:

- Reduced wound healing time
- Higher wound healing rate
- Increased wound area reduction
- Increased wound closure rate
- Lower risk of complications including amputation
- Improved quality of life.

The company claims that the benefits to the healthcare system compared with standard care are:

- Reduced cost because of fewer nurse, GP and outpatient visits
- Reduced total number of dressings needed
- As wounds heal faster, there may be fewer wound-related complications that need additional treatment and healthcare professional resources and cost.

	Scope issued by NICE
Population	Patients with leg ulcers in any setting Patients with diabetic foot ulcers in any setting
Intervention	UrgoStart dressing formats which contain the TLC-NOSF technology
Comparator(s)	Other wound dressing including conventional wound dressings and advanced wound dressings. Standard care is likely to vary with the different types of wounds and stage of healing.
Outcomes	The outcome measures to consider include: •time to complete wound healing •time to wound closure •wound area reduction (WAR) •wound area progression •wound healing rate •health related quality of life (HRQoL) •patient tolerance •patient acceptability •device-related adverse events •nurse, GP and outpatient visits •amputation rates •wound-related complications •total dressings used
Cost analysis	Costs will be considered from an NHS and personal social services perspective. Settings to be considered should include primary care, community and hospital. The time horizon for the cost analysis will be sufficiently long to reflect any 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	•Patients with venous leg ulcers •Patients with arterial leg ulcers •Patients with leg ulcers of mixed aetiology •Patients with diabetic foot ulcers •Patients with chronic ulcers •Patients with non-healing ulcers •Pressure ulcers

Special considerations, including those related to equality	Leg ulcers are more common in older people. Women are 2 times more likely to have a leg ulcer than men. 1 in 10 people with diabetic foot ulcers will have an amputation. Leg ulcers, and diabetic foot ulcers may be associated with other disabilities. People with leg ulcers or diabetic foot ulcers may meet the criteria for being disabled under the Equality Act 2010. Age, sex and disability are all protected characteristics under the 2010 Equality Act.	
Special considerations, specifically related to equality issues	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 characteristics?	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 MTAC will have relevant information to consider equality issues when developing guidance?	No*