NICE advice

EpiFix for chronic wounds

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is EpiFix, an amniotic membrane allograft comprised of dehydrated human amniotic membrane. This briefing focuses on its use in treating chronic wounds such as diabetic foot ulcers and venous leg ulcers.
- The **innovative aspect** is that it is an allograft of human amniotic membrane. It therefore differs from most wound-care products in being regulated as a human tissue product.
- The intended **place in therapy** would be as an alternative to other advanced wound dressings for chronic, difficult-to-heal wounds in addition to standard treatments.
- The **main points from the evidence** summarised in this briefing are from 5 studies, including 3 studies in people with difficult-to-heal diabetic foot ulcers and 2 studies in people with venous leg ulcers. The total number of people in the studies is not clear because the trials include overlapping populations. The studies suggest that EpiFix may be an effective addition to standard care and compression therapy in people with chronic wounds.

- **Key uncertainties** around the evidence or technology are that all studies took place in the US and so comparisons and patient selection may not be generalisable to the NHS. In particular, there are no comparisons of EpiFix with standard NHS care for any indication. Two of the 5 studies included were written by the same group of authors (Zelen et al.) and 4 studies were funded by the company. Four other studies are ongoing, and 5 studies have been completed but not published.
- The **cost** of EpiFix is £1,018.39 per unit (2 cm × 3 cm; excluding VAT) for 1 treatment. Multiple treatments are usually needed. The **resource impact** would be a significant additional cost to standard care, which might be offset if the technology allows faster wound healing. There is no published economic evidence on using EpiFix.

The technology

EpiFix (MiMedx) amniotic membrane allograft is made of dehydrated human amnion/chorion membrane tissue (dHACM). The tissue is derived from amniotic membranes donated with informed consent in the US. EpiFix is terminally sterilised to reduce virus transmission. It is promoted to enhance wound healing, reduce scar tissue formation and modulate inflammation.

EpiFix is indicated for a wide range of wounds; the scope of this briefing is chronic difficult-to-heal wounds including diabetic foot ulcers, venous leg ulcers, arterial ulcers and pressure ulcers.

The company's instructions for use recommend weekly administration. After wound cleaning and debridement in a non-infected wound, EpiFix is removed from the packaging and cut to fit the size of the wound. After EpiFix is applied, a non-adherent contact layer should be placed on top and the wound dressed as usual. EpiFix can be used alongside compression, offloading, negative pressure and hyperbaric oxygen therapy.

Innovations

The innovative aspect of EpiFix is that it is an allograft of human amniotic membrane that has been processed and purified for use (using the MiMedx proprietary PURION process). This is designed to preserve bioactive components and deliver non-viable cells, multiple extracellular matrix (ECM) proteins, active growth factors, cytokines, chemokines and other specialty proteins present in amniotic tissue with the aim of helping to regenerate

soft tissue.

Current NHS pathway or current care pathway

Chronic difficult-to-heal wounds such as diabetic foot ulcers, venous leg ulcers, arterial ulcers and pressure ulcers, are typically assessed by a health professional and categorised. Information from this is then used to guide treatment options. Different treatments are offered depending on the type of wound, and its assessment and categorisation. Wound dressings are used as the basis for treating most wounds, and will be used alongside other options such as compression bandaging, offloading, wound debridement, and control of any underlying problems such as wound ischaemia, and nutritional support. For chronic non-healing wounds, most simple conventional dressings (such as basic wound contact or gauze dressings) are not useful. The wound may progress onto needing more advanced dressings (such as hydrocolloids, alginates and hydrofibre dressings) and other treatment, such as negative pressure wound therapy, dermal or skin substitutes.

The following guidelines and advice have been identified as being relevant to this care pathway.

NICE guidance

- Diabetic foot problems
- Pressure ulcers
- Surgical site infections

SIGN guidelines

- Management of venous leg ulcers

NICE advice

- Wound care products
- Advanced antimicrobial dressing for chronic wounds

NICE advice also states that the least costly dressings that meet the required clinical performance characteristics should be used, because there is not enough evidence to determine whether advanced dressings (such as hydrocolloids, alginates and hydrofibre dressings) are more clinically effective than conventional dressings.

Population, setting and intended user

EpiFix would most likely be used in place of other advanced wound dressings including dermal substitutes in people with chronic wounds that are not healing at the expected rate, alongside standard interventions such as compression bandaging.

EpiFix is intended for use by a health professional, and may be used in a community or hospital setting. EpiFix is applied by the same clinical staff that would usually choose, apply and change the person's dressings. This would typically be a nurse, but may also include other staff such as GPs and podiatrists.

Costs

Technology costs

EpiFix is available in a number of different sizes; costs range from £348.50 for a 16 mm diameter disc to £1,018.39 for a 2 cm × 3 cm sheet.

The company estimates that 5 weekly treatments (2 cm × 3 cm) will heal a wound leading to a total cost of £5,091.95 for EpiFix. Smaller sheets of EpiFix may be used if the wound heals or gets smaller, reducing costs as treatment progresses.

EpiFix is used as an adjunct to standard care. Total care costs would also include debridement, cleaning, dressing and compression. The total treatment cost will be governed by the frequency of dressing changes, total treatment length and any additional treatment needs.

Costs of standard care

There is no standard agreed list of dressings used in chronic wound care; however, the costs described below are given for a selection of dressings in the NHS Supply Chain Catalogue.

Table 1 NHS Supply Chain Catalogue, cost of dressings for chronic wounds

Contact layers	Cost of dressing	Size of dressing
Urgotul	£3.20	10 cm × 10 cm
Atrauman AG (silver layer)	£1.37	10 cm × 10 cm
Bactigras (antimicrobial)	£0.54	10 cm × 10 cm
Activon Tulle Advancis (antimicrobial, honey)	£3.03	10 cm × 10 cm
Solvaline N (knitted viscose)	£0.20	10 cm × 10 cm
Jelonet (paraffin)	£0.30	10 cm × 10 cm
Mepitel One	£3.51	9 cm × 10 cm
Acticoat Flex 3 (antimicrobial, silver)	£8.89	10 cm × 10 cm
Other foam dressings		
Tegaderm Foam	£1.99	10 cm × 10 cm
Advazorb	£1.15	10 cm × 10 cm
Mepilex foam silicone	£2.94	10 cm × 11 cm

Resource consequences

EpiFix would be a significant additional cost to standard care. If treatment resulted in higher healing rates, the additional costs could be offset by reduced use of dressings and chronic wound-care services and by avoiding future complications such as lower limb amputation. Staff may need training on the correct application of EpiFix. EpiFix is currently used in 1 NHS wound-care centre.

Regulatory information

EpiFix is regulated under the European Union Tissue and Cells Directives (2004/23/EC, 2006/17/EC, 2006/86/EC and 2012/39/EU) and the Human Tissue (Quality and Safety for Human Application) Regulations 2007 in the UK. EpiFix was launched in the UK in January 2016, under HTA licence #22,512 (granted in February 2012).

No safety-related alerts were identified in the preparation of this briefing.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to: promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Older people, people with diabetes and those with restricted mobility are more likely to have chronic or non-healing wounds. Age and disability are protected characteristics under the Equality Act. Some people may refuse treatment with EpiFix because of religious or personal beliefs because it contains tissue of human origin.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Five studies are included in this briefing. These studies were selected because they were the highest-quality evidence and included the largest patient populations. They suggest that EpiFix may offer improved healing over standard wound-care dressings and bio-engineered living cellular constructs such as Apligraf.

Table 2 summarises the clinical studies and their individual strengths and limitations.

Overall assessment of the evidence

Two studies included in the table were written by the same group of authors (Zelen et al.). Four of the studies were funded by the company. A total of 571 people are recorded in the studies, but the total number of people in the studies is not clear because the trials include overlapping populations. Two studies included people with venous leg ulcers and the other 3 included people with diabetic foot ulcers. Most studies used time-to-total healing as an outcome, which is a valid outcome, and there is sufficient follow-up. The comparisons of EpiFix and bio-engineered living cellular constructs are less helpful in judging effectiveness in NHS practice because these technologies are not in widespread use. All studies took place in centres in the US and so this may also limit the generalisability of findings to UK practice. Four other studies are ongoing and 5 have been completed but not published.

Table 2 Summary of clinical evidence

Bianchi et al. (2017)	
Study size, design and location	Randomised controlled multicentre clinical trial in 109 people with non-healing full-thickness venous leg ulcers in 15 centres in the US.
Intervention and comparator(s)	52 people had EpiFix and multilayer compression and 57 had standard dressings with multilayer compression therapy.

Key outcomes	12-week outcomes: 31/52 (60%) VLUs treated with EpiFix had completely healed compared with 20/57 (35%) for those treated with standard care (p=0.0128). Mean percentage wound reduction was 66% for EpiFix and 40% for standard care. Mean wound size was adjusted for baseline wound size, adjusted mean wound size for EpiFix was 2.82 cm^2 compared with 4.81 cm^2 for standard care (p=0.0435). 16-week outcomes: Mean percentage wound reduction was 72% for EpiFix and 39% for standard care. Adjusted mean wound size was 2.38 cm^2 for EpiFix and 4.90 cm^2 for standard care p=0.0098.
Strengths and limitations	Wide inclusion criteria including comorbidities such as diabetes. Randomised controlled trial. This study was sponsored and funded by MiMedx.
Serena et al. (2014)	
Study size, design and location	Multicentre randomised controlled trial in 84 people with venous leg ulcers in 8 centres in the US.
Intervention and comparator(s)	53 people had EpiFix and multilayer compression and 31 had standard dressings with multilayer compression therapy.
Key outcomes	40% wound closure at 4 weeks was used as a surrogate end point for complete healing and was the primary outcome of the study. At 4 weeks, 62% of ulcers in the EpiFix group and 32% of ulcers in the control group had reduced in size by more than 40% (p=0.005). In the EpiFix group the mean reduction in wound size was 48.1% compared with 19% in the control arm.

Strengths and limitations	This study uses a surrogate end point for complete healing at 4 weeks. The suitability of this was tested at 24-month follow-up (Serena et al. 2015) using the records of 44 people in the study. In this group, 20 people (45.4%) met the primary outcome of the initial study (wound size reduction ≥40% at 4 weeks) and 24 (55%) had not. Complete healing occurred in 80% (16/20) of people in the first group and in 33.3% (8/24) of the second group (p=0.0023). This study was sponsored and funded by MiMedx.
Zelen et al. (2014)	
Study size, design and location	Prospective randomised controlled trial in 60 people with DFUs, in 3 centres in the US.
Intervention and comparator(s)	Participants were randomised to have treatment with EpiFix+SC (20), Apligraf+SC (20) or SC only with a collagen-alginate dressing (20). EpiFix and Apligraf were applied once a week. SC was as previously described.
Key outcomes	Complete healing %: • EpiFix: 85% (4 weeks); 95% (6 weeks) • Apligraf: 35% (4 weeks); 45% (6 weeks) • SC: 30% (4 weeks); 35% (6 weeks) The estimated median healing time was 13 days for EpiFix, 49 days for Apligraf and 49 days for SC only. During the study period, the mean number of Apligraf used was 6.2 per person (total cost: $9,276 per person), compared with 2.15 per person ($1,669) for EpiFix.
Strengths and limitations	The authors state that the study population was not large enough to perform any subgroup analyses. The study was sponsored and funded by MiMedx.
Zelen et al. (2015)	

Study size, design and location	Prospective, randomised, controlled trial in 100 people with DFUs in 4 centres in the US.
Intervention and comparator(s)	32 people had treatment with EpiFix+SC, 33 with Apligraf+SC and 35 with SC only.
Key outcomes	Complete healing in the 12-week study period in 97% (31/32) of DFUs treated with EpiFix, 73% (24/33) with Apligraf and 51 (18/35) with SC only. Mean time to heal was 23.6 days for the EpiFix group, 47.9 days for Apligraf and 57.4 days for SC only. Median number of applications used per healed wound was 2.5 (range 1 to 12) for EpiFix and 6 (range 1 to 13) for Apligraf.
Strengths and limitations	The authors did analyses based on the cost of treatment for EpiFix and Apligraf. These results are of limited use because the costs for SC have not been considered. The study was sponsored and funded by MiMedx.
Kirsner et al. (2015)	
Study size, design and location	Retrospective analysis of wound-care-specific data from 218 people with diabetic ulcers from 99 centres in the US.
Intervention and comparator(s)	63 people were treated with EpiFix and 163 people were treated with BLCC.
Key outcomes	The data were compared between the 2 groups. The average number of applications was significantly higher for EpiFix (3.5) than for BLCC (2.5). Analyses also showed that median time to wound closure is significantly shorter with BLCC, 93 days compared with 182 days.
Strengths and limitations	Median time to wound closure was much higher in this study than in those reported by Zelen and colleagues. It should also be noted that this study had a much larger population and appears to have included a wider morphology of diabetic foot ulcers.

Abbreviations: BLCC, bio-engineered living cellular constructs; DFU, diabetic foot ulcer; SC, standard care; VLU, venous leg ulcer.

Recent and ongoing studies

Ongoing studies

- NCT01693133: Trial of dHACM in the management of diabetic foot ulcers. Status: Recruiting participants. Primary comparator: Standard of care – moist wound therapy and offloading. Expected enrolment: 130. Estimated primary completion date: December 2016. Location: US; Alabama, California, Massachusetts, Ohio, Oregon, South Carolina, Texas, Utah, Virginia.
- NCT02322554: Cellular and tissue-based therapy registry. Status: Recruiting participants. Primary comparator: Other cellular and tissue-based products. Expected enrolment: 50,000. Estimated primary completion date: January 2020. Location: US; Texas.
- NCT02813161: The diabetic foot ulcer registry. Status: Recruiting participants. Primary comparator: Other cellular and tissue-based products, negative pressure wound therapy, debridement, dietary supplement, offloading, hyperbaric oxygen therapy. Expected enrolment: 10,000. Estimated primary completion date: January 2025. Location: US; Texas.
- NCT02813187: Venous leg ulcer registry. Status: This study is enrolling participants by invitation only. Primary comparator: Other cellular and tissue-based products, debridement. Expected enrolment: 10,000. Estimated primary completion date: May 2025. Location: US; Texas.

Completed studies with no results available

- NCT02587104: dHACM in the treatment of diabetic foot ulcers. Primary comparator: None. Enrolment: 16. Completion date: June 2016. Location: Canada; Ontario. Publications: No study results posted.
- NCT02589210: dHACM mesh in the treatment of diabetic foot ulcers. Primary Comparator: None. Enrolment: 10. Completion Date: March 2016. Location: US; Virginia. Publications: No study results posted.

- NCT01657474: Comparative study of two application regimens of amniotic membrane wound graft in the management of diabetic foot ulcers. Primary comparator: Weekly versus biweekly application of EpiFix. Enrolment: 40. Completion date: November 2013. Location: US; Virginia. Publications: No study results posted.
- NCT01552447: Human amniotic membrane grafting and standard of care versus standard of care alone in the treatment of venous leg ulcers. Primary comparator: Standard care – compression therapy/bandage. Enrolment: 98. Completion date: May 2014. Location: US; Virginia, Massachusetts, Oklahoma, Pennsylvania. Publications: No study results posted.
- NCT01552499: Comparative study of amniotic membrane wound graft In the management of diabetic foot ulcers. Primary comparator: Standard care. Enrolment: 25. Completion date: August 2012. Location: US; Virginia. Publications: No study results posted.

Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

Two of the 3 specialist commentators were familiar with this technology. None of the commentators had used EpiFix in people. One commentator stated that they had not had the opportunity to do research involving the device and another stated that the cost of EpiFix had prevented them from using it.

Level of innovation

Two specialist commentators stated that EpiFix was a minor variation on current technologies. One commentator noted that these types of dressings were usually used in ophthalmology. The third specialist commentator stated that EpiFix appeared to be novel.

Potential patient impact

Two specialist commentators agreed that EpiFix might lead to improved outcomes for people with chronic and difficult-to-heal wounds. One noted that it may be of particular

benefit in reducing the risk of deep infection. Improved healing would lead to fewer hospital visits for people with chronic wounds and reduced risk of infection and limb amputation leading to significant quality-of-life improvements. Both commentators stated that there was currently not enough evidence to support these claims. One commentator noted that there was a high level of overlap and potential for reporting bias in the current studies and that more, independent studies would be needed to confirm these benefits. The third specialist commentator stated that there was not enough evidence to show any potential patient benefit and that the technology needs to be formally evaluated in a well-designed, powered, blinded randomised controlled trial.

Potential system impact

Two specialist commentators stated that users of EpiFix would need a short training session with a product specialist. No change to the way services are delivered would be needed. Two specialist commentators noted that using EpiFix could lead to a decreased burden and cost on wound-care services but that more evidence is needed to confirm this. One commentator noted that if the initial study results were replicated in a well-powered, randomised controlled trial and compared with standard NHS treatments, EpiFix could have the potential to significantly change wound care. The third specialist commentator stated that there was not enough evidence to imply any potential system benefit.

General comments

One specialist commentator pointed out limitations in the evidence presented. They stated that most of studies were done by the same investigators and were sponsored by the manufacturer. They state that these trials took place in the US and are not representative of practice in the UK. The commentator also stated that the inclusion and exclusion criteria used in the studies were narrow and did not adequately reflect the population with diabetic foot ulcer. They pointed out that, in the 1 study where the criteria were widened (Kirsner et al. 2015), similar healing rates were not seen.

Specialist commentators

The following clinicians contributed to this briefing:

- Mr David Russell, consultant vascular surgeon, Leeds General Infirmary. No conflicts of interest.
- Ms Catherine Gooday, principal podiatrist, Norfolk and Norwich University Hospitals NHS Trust. No conflicts of interest.
- Dr Alyson M Bryden, consultant dermatologist, Ninewells Hospital, Dundee. No conflicts of interest.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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