Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	**PROMOGRAN and PROMOGRAN PRISMA for the dressing of chronic venous leg ulcers or diabetic foot ulcers**
Topic exploration report number:	TER235

Introduction and aims

PROMOGRAN and PROMOGRAN PRISMA are indicated for the management of wounds healing by secondary intention, including diabetic foot ulcers (DFU) and venous leg ulcers (VLU). Chronic VLU and DFU, along with pressure ulcers, make up more than 90% of chronic wounds and are especially prone to recurrence, with recurrence rates ranging from 24-57% and 60% upwards for VLU and DFU respectively.

PROMOGRAN and PROMOGRAN PRIMSA dressings are an alternative to standard care options such as hydrocolloids, alginates, foams and hydro-fibres. They are a matrix comprised of 45% oxidized regenerated cellulose (ORC) and 55% collagen. PROMOGRAN PRISMA also contains silver to provide protection against microbial infection. When exposed to exudate from the wound, the dressings become a soft and conformable biodegradable gel. The dressings are bioabsorbable, which means that the old dressing does not need to be removed, preventing the wound bed and newly formed tissue from being disturbed.

Where wounds are 'stalled' in the inflammatory phase of healing the PROMOGRAN Matrix and PROMOGRAN PRISMA Matrix dressings have the potential to improve healing times compared to standard care and lead to a reduction in pain and risk of infection, and improve quality of life outcomes. There may also be wider organisational benefits through increased time between dressing changes, reduced inpatient length of stay, and more care being provided in primary care instead of in secondary care.

PROMOGRAN is CE mark class III (or IVDD Annex II list A, or IVDR class D).

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of ORC-collagen matrix wound dressings for chronic VLU or DFU.

Summary of evidence

General guidelines and Technology Assessments

NICE produced an evidence summary (ESMPB2) on advanced wound dressings and antimicrobial dressings in 2016. However, specialised dressings, which aid wound healing by means of physiologically active components, such as collagen, were outside of the scope. They noted a lack of good quality evidence and considered the evidence to be insufficient to distinguish between different types of advanced dressings. There was some evidence that advanced dressings are more effective than conventional dressings. However, many of the conventional dressings used as comparators are no longer routinely recommended for chronic wounds.

NICE issued guidance on preventing and managing diabetic foot problems in 2015 and this guidance was updated in 2019 (NG19). SIGN issued guidance on the management of chronic VLU in 2010. These guidelines give important recommendations about wound care but do not make recommendations on specific products or types of dressing.

Healthcare Improvement Scotland undertook a HTA of antimicrobial wound dressings (AWDs) for chronic wounds in 2015. The routine use of AWDs to heal chronic wounds was not recommended. The evidence for the use of silver in chronic VLU or DFU with wound infection was insufficient to draw conclusions on impact on wound infection. The evidence suggested there was no difference between treatment groups for either condition for most healing outcomes.

The Health Service Executive produced National Wound Management Guidelines in 2018. They recommend that, in the absence of strong clinical or cost effective evidence, clinicians should choose wound dressings that have high performance characteristics appropriate for the wound and its phase of healing; meet patient acceptability; best match their clinical experience; and have the lowest acquisition cost. They suggest that antimicrobial dressings should be avoided unless the wound is infected or there is a clinical risk of the wound becoming infected.

The International Working Group on the Diabetic Foot produced guidelines on the use of interventions to enhance healing of chronic foot ulcers in diabetes in 2019. They recommend not using dressings containing surface antimicrobial agents with the sole aim of accelerating the healing of an ulcer. For those that are difficult to heal, they recommend considering sucrose-octasulfate impregnated dressing as an adjunctive. There was no specific recommendation relating to PROMOGRAN or ORC-collagen dressings.

Technology Assessments of PROMOGRAN and related guidance

Barber et al. (2006) assessed bioengineered skin substitutes for the management of wounds. PROMOGRAN, amongst others, was comparable with standard treatment in terms of wound healing time, wound closure and decreased ulcer area in those with VLU. There was no difference found between groups for pain, recurrence or wound infection. In patients with DFU, wound healing time appeared better with PROMOGRAN but there was no difference in recurrence rates.

Wu et al. (2017) report the findings of a multidisciplinary panel convened to discuss the use of ORC-collagen dressings, which was informed by a literature search. Panel members identified

wound types where the dressings could be used and then provided recommendations for practice. They were recommended for VLU and DFU, amongst others.

Systematic reviews

Venous leg ulcers

A number of systematic reviews and meta-analyses of dressings for VLU have been published (Norman et al. 2018, Palfreyman et al. 2007, Saco et al. 2016). They typically found low or very low quality evidence and do not report subgroup analyses for ORC-collagen dressings. Westby et al. (2016) undertook a Cochrane review of protease-modulating matrix (PMM) environments for VLU. They report the findings of a comparison of two different PMM regimes which identified only one study comparing PROMOGRAN with UrgoStart. They concluded that there was too much uncertainty to determine whether there was a difference in the rates of healing, adverse events, pain and infection. It was unclear whether overall PMM dressings healed ulcers quicker than non-PMM dressings (HR 1.21 95% CI 0.74 to 1.97), or whether there was a difference in the probability of healing in the short-, medium- or long-term. It was also unclear whether there was a difference in adverse events, resource use or mean total costs.

Diabetic foot ulcers

Chicone et al. (2018) undertook a systematic review of ORC-collagen matrix dressing in chronic DFU. Three RCTs were included, one of which was at high risk of bias. A meta-analysis of the remaining two RCTs found no improvement in would healing rates compared with standard care. Chicone concluded that there is currently no evidence to suggest that ORC-collagen promotes healing rates in DFUs and that additional high-quality RCTs are required.

A number of systematic reviews and meta-analyses of dressings for DFU have been published. They typically found low or very low quality evidence and do not report subgroup analyses for ORC-collagen dressings (Wu et al. 2015, Dumville et al. 2012, Zhang et al. 2019). Wu et al. (2015) published an overview of systematic reviews of dressings for DFU in people with diabetes. They identified 13 systematic reviews containing 17 RCTs, collectively reporting findings for 11 comparisons supported by direct data and 26 comparisons supported by indirect data. Only four comparisons informed by direct data found evidence of a difference between dressing types and the evidence was low or very low quality.

Primary studies

Venous leg ulcers

Smeets et al. (2008) looked at the effect of a ORC-collagen matrix on proteases in wound exudate (N=27). A significant reduction in protease activity was found compared to control over a 12-week period. Three studies were identified which compared an ORC-collagen dressing to an alternative in patients with VLU. Vin et al. (2002) compared PROMOGRAN with a non-adherent dressing over a 12-week period (N=73). Significantly fewer patients switched to another dressing with PROMOGRAN. The proportion healed or improved was not significantly different between groups. Decrease in surface area was significantly greater with PROMOGRAN. Cullen et al. (2017) undertook an RCT comparing a ORC-collagen-silver dressing plus standard care to standard care (N=49). There was no significant difference in overall healing rates or wound area reduction between groups. Wollina et al. (2005) compared PROMOGRAN plus “good” ulcer care with “good” ulcer care alone for 2 weeks (N=40). While there was a reduction

in ulcer area, improvement in wound score, and a decrease in pain score with PROMOGRAN, no significant differences are reported between groups.

In addition, Barrett et al. (2004) report two case reports where PROMOGRAN was applied to hard-to-heal VLU and resulted in reduced exudation and stimulation of healing.

Diabetic foot ulcers

Seven studies were identified which compared an ORC-collagen matrix (with or without silver) to an alternative. A retrospective cohort study was undertaken by Griffin et al. (2019) comparing an ORC-collagen-silver dressing with ovine collagen extracellular matrix (N=844). A significantly higher proportion of ulcers in the ORC group healed or improved and significantly fewer worsened. Median time to granulation was significantly shorter in the ORC group.

Gottrup et al. (2013) undertook an RCT comparing ORC-collagen-silver therapy to standard care (N=39). Significantly more responders, and significantly fewer withdrawals due to infection, were reported in the intervention group. Protease levels were significantly higher in the standard care group at four weeks. Ulrich et al. (2011) compared an ORC-collagen matrix with hydrocolloid dressing to hydrocolloid dressing alone to assess concentration and activity of gelatinases, elastase and plasmin in wound exudate (N=32). According to the graphs presented, a significantly lower level of gelatinase was observed in the control group at day 28 and 42 (but not day 5, 14 or 56). No significant difference in MMP-2, elastase or plasmin was observed between groups. There was no significant difference in wound size between groups. However, some findings from the graphs contradict the text.

Lazaro-Martinez et al. (2007) undertook an RCT comparing an ORC-collagen dressing to standard care for neuropathic diabetic foot ulcers (N=40). At six weeks, the number of patients with healing was significantly greater, and the mean time to healing significantly less, in the intervention group. Lobmann et al. (2007) compared PROMOGRAN to standard wound care (N=33) and found no differences between groups in matrix metalloproteinases over eight days. Veves et al. (2002) undertook an RCT comparing PROMOGRAN to moistened gauze and a secondary dressing (N=276). At 12 weeks, there was no significant difference in wound closure rates. However, patients and investigators expressed a strong preference for PROMOGRAN.

One study was identified which suggests PROMOGRAN may be beneficial when used alongside autologous growth factors (AGF). Kakagia et al. (2007) compared PROMOGRAN with AGF and with both treatments together (N=51). They found significantly greater reduction in dimensions of ulcers for patients receiving both PROMOGRAN and AGF than each alone. There was no significant difference between PROMOGRAN alone and AGF alone.

In addition, Monami et al. (2002) report two case reports of patients treated with PROMOGRAN. Healing was complete within 5 and 12 weeks.

Economic evidence

Information submitted by the manufacturer gives costs of £15.75 and £5.23 for big and small PROMOGRAN Matrix dressings respectively. PROMOGRAN PRISMA is costed at £18.12 and £6.36 for big and small dressings respectively.

A cost-consequence analysis developed by the manufacturer suggests that, in comparison to standard care, PROMOGRAN/PROMOGRAN PRISMA leads to overall cost savings of £226 and £1,722 per patient with hard-to-heal VLU and unhealed DFU, respectively.

Ghatnekar et al. (2002) used a Markov model to estimate the cost-effectiveness of PROMOGAN compared with good wound care in four European countries (France, Germany, Switzerland and UK). Over three months, 26% and 21% of ulcers were healed respectively. Over 12 months, an average of 3.75 and 3.41 months were estimated to be spent in the healed state. PROMOGRAN was found to be cost-saving in all four countries.

Ongoing trials

One ongoing trial comparing a topical growth factor with and without PROMOGRAN for chronic wounds was identified (N=80). This was due to complete in September 2020 and only limited to patients where the ulcer was located between and including the knee and ankle.

Areas of uncertainty

This topic exploration suggests that there is a lack of good quality, large studies comparing ORC-collagen dressings (with or without silver) with other dressings for VLU and DFU. There are a number of small studies which suggest potential clinical benefits for DFU, while the impact on the level of proteases is less clear. There are far fewer studies of ORC-collagen dressings in VLU patients. One study has looked at the potential for combining ORC-collagen dressing with AGF and found promising results. A second study in this area was due to complete in September 2020.

A high-specificity-low-sensitivity search was used given the large amounts of literature on wound dressings. This increases the likelihood that key studies were not identified. Identifying key search terms will be important if this topic is taken forward to full appraisal.

Conclusions

There is a lack of guidance in this area, where guidance or systematic reviews have been published they highlight the lack of a good quality evidence base. Low quality primary evidence identified suggests there may be clinical benefit to using ORC-collagen dressings but this is dependent on the comparator and more likely to be demonstrated when compared to standard care, the definition of which may vary. There is also a lack of ongoing studies in this topic area which could add future clarity.

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	Healthcare Improvement Scotland (2015). Antimicrobial wound dressings (AWDs) for chronic wounds. http://www.healthcareimprovementscotland.org/our_work/technologies_and_medicines/topics_assessed/hta13_antimicrobial_dressings.aspx
Health Technology Assessment Group	HSE National Wound Management Guidelines (2018). https://healthservice.hse.ie/filelibrary/onmsd/hse-national-wound-management-guidelines-2018.pdf
Health Information and Quality Authority	None identified.
EUnetHTA	None identified.
International HTA Database	Barber C, Watt A, Pham C, et al. (2006) Bioengineered skin substitutes for the management of wounds: a systematic review. Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S). https://database.inahta.org/article/6283
UK guidelines and guidance	
SIGN	SIGN 120 (2010). Management of chronic venous leg ulcers. https://www.sign.ac.uk/our-guidelines/management-of-chronic-venous-leg-ulcers/
NICE	NICE Evidence summary [ESMPB2] 2016. Chronic wounds: advanced wound dressings and antimicrobial dressings. https://www.nice.org.uk/advice/esmpb2/chapter/Key-points-from-the-evidence NICE Key therapeutic topic [KTT14] 2019. Wound care products. https://www.nice.org.uk/advice/ktt14 NICE guideline [NG19] 2019. Diabetic foot problems: prevention and management. https://www.nice.org.uk/guidance/ng19
Secondary literature and economic evaluations	
https://www.epistemonikos.org/en/	Venous leg ulcers Norman G, Westby MJ, Rithalia AD, et al. (2018) Dressings and topical agents for treating venous leg ulcers. Cochrane Database Syst Rev. 15;6(6):CD012583. doi: 10.1002/14651858.CD012583. Palfreyman S, Nelson EA, Michaels JA. (2007) Dressings for venous leg ulcers: systematic review and meta-analysis. BMJ. 2007 Aug 4;335(7613):244. doi: 10.1136/bmj.39248.634977.AE. Diabetic foot ulcers

	Wu L, Norman G, Dumville JC, et al. (2015) Dressings for treating foot ulcers in people with diabetes: an overview of systematic reviews. Cochrane Database Syst Rev. 2015 14;(7):CD010471. doi: 10.1002/14651858.CD010471.pub2. Dumville JC, Soares MO, O'Meara S, et al. (2012) Systematic review and mixed treatment comparison: dressings to heal diabetic foot ulcers. Diabetologia. 55(7):1902-10. doi: 10.1007/s00125-012-2558-5. Zhang X, Sun D, Jiang GC. (2019) Comparative efficacy of nine different dressings in healing diabetic foot ulcer: A Bayesian network analysis. J Diabetes. 11(6):418-426. doi: 10.1111/1753-0407.12871. Chicone G, de Carvalho VF, Paggiaro AO. (2018) Use of Oxidized Regenerated Cellulose/Collagen Matrix in Chronic Diabetic Foot Ulcers: A Systematic Review. Adv Skin Wound Care. 31(2):66-71. doi: 10.1097/01.ASW.0000527297.95688.76. Both diabetic foot and venous leg ulcers Saco M, Howe N, Nathoo R, et al. (2016) Comparing the efficacies of alginate, foam, hydrocolloid, hydrofiber, and hydrogel dressings in the management of diabetic foot ulcers and venous leg ulcers: a systematic review and meta-analysis examining how to dress for success. Dermatol Online J. 15;22(8):13030/qt7ph5v17z..
https://www.tripdatabase.com/	Rayman G, Vas P, Dhatariya K, et al. (2020) International Working Group on the Diabetic Foot (IWGDF). Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 36 Suppl 1:e3283. doi: 10.1002/dmrr.3283.
Cochrane library	Westby MJ, Norman G, Dumville JC, et al. (2016). Protease-modulating matrix treatments for healing venous leg ulcers. Cochrane Database Syst Rev. 12:CD011918. doi: 10.1002/14651858.CD011918.pub2.
Medline	None identified
Primary studies	
https://www.epistemonikos.org/en/	Venous leg ulcers Smeets R, Ulrich D, Unglaub F, et al. (2018) Effect of oxidised regenerated cellulose/collagen matrix on proteases in wound exudate of patients with chronic venous ulceration. Int Wound J. 5(2):195-203. doi: 10.1111/j.1742-481X.2007.00367.x. Vin F, Teot L, Meaume S. (2002) The healing properties of Promogran in venous leg ulcers. J Wound Care. 11(9):335-41. doi: 10.12968/jowc.2002.11.9.26438. Michaels JA, Campbell B, King B, et al. (2009) Randomized controlled trial and cost-effectiveness analysis of silver-donating antimicrobial dressings for venous leg ulcers (VULCAN trial). Br J Surg. 96(10):1147-56. doi: 10.1002/bjs.6786. Diabetic foot ulcers Kakagia DD, Kazakos KJ, Xarchas KC, et al. (2007) Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial. J Diabetes Complications. 21(6):387-91. doi: 10.1016/j.jdiacomp.2007.03.006.

https://www.tripdatabase.com/	Venous leg ulcers Cullen BM, Serena TE, Gibson MC, et al. (2017) Randomized Controlled Trial Comparing Collagen/Oxidized Regenerated Cellulose/Silver to Standard of Care in the Management of Venous Leg Ulcers. Adv Skin Wound Care. 30(10):464-468. doi: 10.1097/01.ASW.0000524452.80170.d8. Wu S, Applewhite AJ, Niezgoda J, et al. (2017) Oxidized Regenerated Cellulose/Collagen Dressings: Review of Evidence and Recommendations. Adv Skin Wound Care. 30(11S Suppl 1):S1-S18. doi:10.1097/01.ASW.0000525951.20270.6c Diabetic foot ulcers Veves A, Sheehan P, Pham HT. (2002) A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Arch Surg. 137(7):822-7. doi: 10.1001/archsurg.137.7.822. Gottrup F, Cullen BM, Karlsmark T. (2013) Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. Wound Repair Regen. 21(2):216-25. doi: 10.1111/wrr.12020. Lázaro-Martínez JL, García-Morales E, Beneit-Montesinos JV. (2007) Randomized comparative trial of a collagen/oxidized regenerated cellulose dressing in the treatment of neuropathic diabetic foot ulcers. Cir Esp. 82(1):27-31. doi: 10.1016/s0009-739x(07)71657-3. Ghatnekar O, Willis M, Persson U. (2002) Cost-effectiveness of treating deep diabetic foot ulcers with Promogran in four European countries. J Wound Care. 11(2):70-4. doi: 10.12968/jowc.2002.11.2.26675.
Cochrane library	Diabetic foot ulcers Lobmann R, Zemlin C, Motzkau M. (2007) Expression of matrix metalloproteinases and growth factors in diabetic foot wounds treated with a protease absorbent dressing. J Diabetes Complications. 20(5):329-35. doi: 10.1016/j.jdiacomp.2005.08.007.
Medline	Venous leg ulcers Barrett SA, Moore K. (2004) Use of Promogran to treat venous leg ulcers. J Wound Care. 13(Sup1):2-7. doi: 10.12968/jowc.2004.13.Sup1.2. Diabetic foot ulcers Griffin L, Carter MJ, D'Agostino R Jr. (2019) Comparative Effectiveness of Two Collagen-containing Dressings: Oxidized Regenerated Cellulose (ORC)/Collagen/Silver-ORC Dressing Versus Ovine Collagen Extracellular Matrix. Wounds. 31(11):E73-E76. Monami M, Mannucci E, Giulio M. (2002) Use of an oxidized regenerated cellulose and collagen composite for healing of chronic diabetic foot ulcers: a report of two cases. Diabetes Care. 25(10):1892-3. doi: 10.2337/diacare.25.10.1892.

Ongoing primary or secondary research	
PROSPERO database	None identified
Clinicaltrials.gov	None identified
https://www.tripdatabase.com/	Study of Combined Topical Growth Factor and Protease Inhibitor in Chronic Wound Healing. ClinicalTrials.gov Identifier: NCT02845466. https://clinicaltrials.gov/ct2/show/NCT02845466
Other	
Evidence provided by the Topic Proposer	Evidence not identified by the search: Ulrich et al. (2011). Effect of oxidized regenerated cellulose/collagen matrix on proteases in wound exudate of patients with diabetic foot ulcers. https://pubmed.ncbi.nlm.nih.gov/21860331/ Wollina et al. (2005). Some effects of a topical collagen-based matrix on the microcirculation and wound healing in patients with chronic venous leg ulcers: preliminary observations. https://pubmed.ncbi.nlm.nih.gov/16286373/ Evidence also identified by the search: Lazaro-Martinez et al. (2007). [Randomized comparative trial of a collagen/oxidized regenerated cellulose dressing in the treatment of neuropathic diabetic foot ulcers] https://pubmed.ncbi.nlm.nih.gov/17580028/ Gottrup et al. (2013). Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. https://pubmed.ncbi.nlm.nih.gov/23438054/ Veves et al. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. https://jamanetwork.com/journals/jamasurgery/fullarticle/212677 Vin et al. (2002). The healing properties of Promogran in venous leg ulcers. https://pubmed.ncbi.nlm.nih.gov/12430368/

Date of search:	22nd December 2020
Concepts used:	Guidance: PROMOGRAN; wound dressing; venous leg ulcer dressing; diabetic foot ulcer dressing Primary & secondary studies: PROMOGRAN; cellulose collagen venous leg ulcer; cellulose collagen diabetic foot ulcer;