NICE advice

Granulox for managing chronic non-healing wounds

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is Granulox. Granulox is a topical sterile haemoglobin spray for managing chronic non-healing wounds.
- The **innovative aspects** are that, unlike other oxygen delivery technologies, it is designed to allow oxygen to diffuse through wound exudate. It can also be used in various settings without costly consumables, electrical power or full or partial body coverage in a chamber.
- The intended **place in therapy** would be alongside standard care for people with chronic non-healing wounds.
- The **main points from the evidence** summarised in this briefing are from 8 studies (1 meta-analysis, 2 randomised controlled trials and 5 observational studies) including a total of 530 people. Seven studies were based in the UK and are generalisable to the NHS. The evidence suggests that Granulox may improve the management of chronic non-healing wounds.

- **Key uncertainties** around the evidence are that sample sizes are small, and most studies were not randomised and had a short follow-up period.
- **Experts advised** that Granulox could improve wound healing outcomes by increasing oxygenation of the wound bed. However, 1 expert felt that there is insufficient evidence to determine if Granulox could impact wound healing. Larger scale, controlled, comparative studies are needed to support the efficacy of the technology and provide cost-effectiveness data.
- The **cost** of Granulox is £125 per canister (excluding VAT) for up to 30 applications, depending on the size of the wound. The cost of standard care varies depending on the wound, the extent of the intervention and the costs of the local provider.

The technology

Granulox (Mölnlycke Health Care) is a topical sterile haemoglobin spray for treating chronic non-healing wounds, such as diabetic foot ulcers, venous leg ulcers and pressure ulcers. The company claims that the spray can transport oxygen to the base of non-healing wounds to support wound healing. It is sprayed onto the wound bed after debridement and before the relevant dressing is applied. The company claims that 1 canister of Granulox (12 ml) is sufficient for up to 30 applications, depending on the size of the wound.

Innovations

The company claims that Granulox is innovative over other oxygen therapies because it is designed to allow oxygen to diffuse through wound exudate, which could improve healing. It can be applied in various settings such as in the person's home, a GP surgery or hospital setting. Unlike other oxygen delivery technologies, Granulox does not need costly consumables, electrical power or full or partial body coverage in a chamber.

Current care pathway

Granulox is intended to be used alongside standard care for chronic non-healing wounds. Wound care depends on the type of wound and can vary between centres. Standard care typically involves cleaning and dressing it.

Complex wounds, for example diabetic foot ulcers, venous leg ulcers and pressure ulcers, can result in chronic non-healing wounds and need more advanced care. For diabetic foot or venous leg ulcers, healthcare professionals record the depth and position of the ulcer and offload or apply compression therapy. The wound is cleansed and debrided regularly and dressed with the most appropriate dressing to manage exudate and promote wound healing. More advanced dressings, such as dermal or skin substitutes, may be needed alongside standard care for chronic non-healing wounds.

If a non-healing wound is thought to be infected, healthcare professionals typically take a microbiological sample and prescribe an antibiotic to treat the infection. People may be referred to a specialist for multidisciplinary care, depending on the cause of the wound. Tissue viability nurses generally assess wounds if they are seriously infected, if there is a differential diagnosis, or if the person has complex comorbidities.

The following publications have been identified as relevant to this care pathway:

- NICE's clinical knowledge summary on venous leg ulcers
- NICE's guideline on diabetic foot problems: prevention and management
- NICE's guideline on pressure ulcers: prevention and management.

Population, setting and intended user

Granulox is intended to be used alongside current treatment for people with chronic non-healing wounds that have not responded to standard care. The technology should not be used if a person is pregnant.

Granulox can be used in primary care, secondary care or in a community setting. It can be applied by different healthcare professionals, including tissue viability nurses, podiatrists, GPs and hospital-based clinicians, as well as people or their carers at home. Healthcare professionals and other people using the technology do not need specialised training before use.

Costs

Technology costs

Granulox costs £125 for up to 30 applications per canister, depending on the size of the wound. The company states that 1 canister is sufficient for up to 10 weeks of treatment based on 3 dressing changes per week. The cost of the technology is in addition to standard care, but the company claims that the technology improves healing outcomes and so reduces the resource burden of chronic non-healing wounds.

Costs of standard care

The company states that the costs for treating chronic non-healing wounds with standard care are:

- 30 minutes of nursing time £18.50 (per dressing change)
- primary dressing £3.13 (per dressing change)
- secondary dressing £1.19 (per dressing change)
- laboratory tests £7.00 (weekly)
- antibiotics £3.04 (monthly)
- analgesics £1.94 (monthly).

Chronic wound treatment is not a single treatment. It is a treatment process over time. Total wound care costs over a year are reported as £358 to £4,684 per person for a healed wound, and £831 to £7,886 per person for an unhealed wound (Guest et al. 2020).

Unit costs and 12-month costs vary depending on the wound, the extent of the intervention and the costs of the local provider.

Resource consequences

The company states that the technology is used in at least 8 NHS Trusts.

Granulox is to be used alongside standard care and so costs more than standard care

alone. The company claims that the technology could result in cost savings later because of a reduction in time to wound healing, a reduction in resource use for treating chronic non-healing wounds in community care, a reduction in resource use associated with healed wounds compared with open or infected wounds, a reduction in infected wounds, a reduction in secondary care admissions and a reduction in amputations. There is limited published evidence to support these claims.

Because the technology is used alongside standard care, organisational changes are unlikely to be needed. The company states that Granulox can be incorporated into existing care pathways by including it on local formularies.

Regulatory information

Granulox is a CE-marked class III medical device.

Equality considerations

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Granulox is intended to be used by people with chronic non-healing wounds such as diabetic foot ulcers, venous leg ulcers and pressure ulcers. Older people, people with heart conditions and people with diabetes are more likely to have diabetic foot ulcers and other chronic non-healing wounds and may benefit from this technology. Granulox is contraindicated for use in people who are pregnant. Age, disability and pregnancy are protected characteristics under the Equality Act 2010.

The production of Granulox uses haemoglobin taken from pigs. People with certain religious or philosophical beliefs may not use products derived from pigs. The company has a letter from the Muslim Council of Britain that states that porcine products may be acceptable for medical use when no other alternative is found. Religious and philosophical beliefs are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement for medtech innovation briefings. 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

There are 8 studies summarised in this briefing, including a total of 530 people.

The included studies are 1 meta-analysis, 2 randomised controlled trials and 5 non-comparative observational studies (case series). The meta-analysis includes 3 retrospective cohort control studies across various wound types (Hunt et al. 2018, Hunt and Elg 2017 and Hunt and Elg 2016). Hunt et al. (2016) is an extension to the Haycocks et al. (2016) study. There are over 25 further published studies evaluating the technology across multiple indications.

The clinical evidence and its strengths and limitations is summarised in the overall assessment of the evidence.

Overall assessment of the evidence

The evidence base for the technology is of low to good methodological quality and most studies have small sample sizes. Seven studies were based in the UK and are generalisable to clinical practice in the NHS. In general, the evidence suggests that Granulox may lead to a reduction in wound size and pain across various wound types. One randomised controlled trial suggests that Granulox has no effect on wound healing outcomes in foot ulcers. However, this study was small and insufficiently powered. Further evidence would benefit from sufficiently powered sample sizes and randomised controlled trials focusing on complete wound healing and long-term follow up.

Elg and Hunt (2018)

Study size, design and location

Meta-analysis of pooled data from 340 people with diabetic foot ulcers, chronic wounds and sloughy wounds in the UK.

Intervention and comparator

Standard care plus Granulox compared with standard care.

Key outcomes

The meta-analysis included 340 people, of whom 170 had Granulox therapy. Five wound subtypes were identified from the 3 studies with 10 or more people in both groups: trauma (n=110), diabetic foot ulcer (n=60), venous leg ulcer (n=33), burn (n=30), post-surgery (n=24). Other wound types with less than 10 people in each group were included in the analysis (n=83). The Granulox group showed a significantly higher weekly chance of healing in the following wound types (beta, 95% range, sample and p value); trauma 1.55 (1.23 to 1.96, n=110, p<0.001), diabetic foot ulcer 2.39 (1.52 to 3.75, n=60, p<0.01), burns 1.82 (1.11 to 2.99, n=30, p=0.02) and post-surgical wounds 2.75 (1.53 to 4.96, n=24, p=0.001). Kaplan–Meier analysis for venous leg ulcers also suggested a statistically significant benefit in the Granulox group, p<0.001 (n=33). Across the 5 wound types, the overall beta (95% range, sample and p value) was 1.86 (1.58 to 2.19, n=257, p<0.001). Average reported pain scores were significantly lower within 2 weeks for the Granulox group compared with the control group (all p<0.01, t-test) with a 49% to 78% greater reduction in pain scores. The difference in wound size reduction between the groups after 4 weeks showed an average 49% to 102% greater reduction in wound size in the Granulox group (all p=0.02 or lower).

Strengths and limitations

This study suggests that Granulox may improve wound healing outcomes across various wound types. The study evaluated the Granulox groups by comparing them with retrospective standard care cohorts from the same clinics and time period. The main limitations of this study are the lack of prospective randomisation and blinding. Without this, wound healing cannot be definitively attributed to Granulox. This study was funded by SastoMed GmbH, a company owned by Mölnlycke Health Care.

Arenbergerova et al. (2013)

Study size, design and location

Single-centre randomised trial in 72 people with venous leg ulcers in Germany.

Intervention and comparator

Granulox compared with 0.9% saline solution.

Key outcomes

There were 65 out of 72 people who completed the study. After 13 weeks, 33 people in the Granulox group had a reduction in wound surface area and 1 person had an increased wound surface area. The average reduction in the wound surface area for the Granulox group was 53.4% ($p<0001$ compared with the beginning of the study). In the control group, 14 out of 31 people had a reduction in wound surface area and 17 people had an increase in wound surface area. After 13 weeks, the average wound surface area of the control group had increased from 17.5 cm^2 to 20.2 cm^2.

Strengths and limitations

This study is the only randomised trial for Granulox in people with venous leg ulcers and suggests that the application of Granulox may improve wound healing. The study was completed in Germany and so may not be generalisable to the NHS.

Jonker et al. (2021)

Study size, design and location

Single-centre randomised controlled trial in 38 people with foot ulcers in the UK.

Intervention and comparator

Standard care plus twice weekly Granulox therapy compared with standard care (once weekly podiatric medical clinic visits).

Key outcomes

There were 29 out of 38 people who completed the study. One person withdrew and 2 were lost to follow up in the control group. Five people withdrew and 1 was lost to follow up in the Granulox group. After 6 weeks, 4 out of 16 foot ulcers had healed in the control group, and 3 out of 16 had healed in the Granulox group ($p>0.99$, Fisher exact test). After 12 weeks, 8 out of 14 foot ulcers had healed in the control group, and 3 out of 13 had healed in the Granulox group ($p=0.12$, Fisher exact test). The median healing rate for the control group was 100% compared with 48% in the Granulox group. One serious adverse event happened in the Granulox group compared with 2 in the control group; none were related to the treatment.

Strengths and limitations

This study is the only randomised controlled trial for Granulox in people with foot ulcers but it has several limitations. The study was not blinded, there was no sham treatment for the control group and randomisation was not stratified by wound chronicity. The study was not adequately powered to show statistical significance between the groups.

Bateman (2015a)

Study size, design and location

A case series of 25 people with sloughy healing and non-healing wounds in the UK.

Intervention and comparator

Standard care plus Granulox, no comparator.

Key outcomes

After 4 weeks of treatment and a 5-week follow-up period, all 25 wounds had reduced in size, and 76% (n=19) of wounds had completely healed. Slough levels had reduced in 68% (n=17) of people after 2 weeks, and 100% of people after 3 weeks.

Strengths and limitations

The main limitation of this study is the non-comparative design. Without a control, wound

healing cannot be attributed to Granulox. The study also has a small sample size and short follow-up period.

Bateman (2015b)

Study size, design and location

A single centre case series of 20 people with diabetic foot ulcers in the UK.

Intervention and comparator

Standard care plus Granulox, no comparator.

Key outcomes

After 4 weeks, the average reduction in wound size was 62.3%. Five out of 20 diabetic foot ulcers had healed. The remaining 15 out of 20 diabetic foot ulcers showed a reduction in wound size.

Strengths and limitations

The main limitation of this study is the non-comparative design. Without a control, wound healing cannot be attributed to Granulox.

Tickle (2015)

Study size, design and location

A case series of 18 people with pressure ulcers in the UK.

Intervention and comparator

Standard care plus Granulox, no comparator.

Key outcomes

After 4 weeks, 17 out of 18 wounds had reduced in size. The average wound size was

3.39 cm^2 compared to 11.23 cm^2 at the beginning of the study. All 18 people reported an improvement in their pain severity score during the study, with an average score of 2.5 compared with 6.2 (on a scale of 0 to 10) at the beginning of the study.

Strengths and limitations

This study has restricted value because of the small sample size and lack of control. Granulox application varied between people because of the variation in wound size and exudate levels.

Haycocks et al. (2016)

Study size, design and location

A multi-centre case series of 17 people with non-healing diabetic foot ulcers in the UK.

Intervention and comparator

Standard care plus Granulox, no comparator.

Key outcomes

There were 16 out of 17 people who completed the study. One person with 2 wounds was withdrawn because of infection. After 4 weeks, 14 out of 18 wounds showed a positive reduction in wound size. There was an average reduction in wound size of 53.8% (standard deviation 26.6; range 11.9% to 100%) over 4 weeks. Two wounds showed no reduction in size during the study. The remaining 4 wounds showed an increase in size or did not change.

Strengths and limitations

The main limitation of this study is the non-comparative design. Without a control, wound healing cannot be attributed to Granulox. Local guidelines on standard care between the 6 participating centres may have varied. The method of wound measurement was subjective and may have resulted in overestimation of wound area.

Hunt et al. (2016)

Study size, design and location

A multi-centre case series of 13 people with non-healing diabetic foot ulcers in the UK.

Intervention and comparator

Standard care plus Granulox, no comparator.

Key outcomes

All 13 people (with 15 wounds) completed the study. After 12 weeks, 3 wounds had healed, and 8 wounds had shown a reduction in wound size. Three wounds had increased in size.

Strengths and limitations

The main limitation of this study is the non-comparative design and small sample size. Without a control, wound healing cannot be attributed to Granulox. Local guidelines on standard care between the participating centres may have varied.

Sustainability

The company claims that the technology could reduce the number of dressing changes meaning that community vehicle journeys will be reduced. The company also claims that the technology could lower infection rates, reducing the need for antibiotic medicine. There is no published evidence to support these claims.

Recent and ongoing studies

A multicentre European study to evaluate Granulox used in the treatment pathway of predominantly chronic venous leg ulcers (VLUs). ClinicalTrials.gov identifier: NCT04181320. Status: recruiting. Indication: venous leg ulcer. Devices: venous leg ulcer standard of care with Granulox. Estimated study completion date: 31 December 2022. Countries: France, Germany, Hungary, UK, Poland, Croatia and Czech Republic.

Expert 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.

All 5 experts were familiar with the technology and 4 out of 5 had used this technology before.

Level of innovation

Four experts stated that Granulox is a novel treatment, 2 of which agreed it is easy to use and more transportable than other technologies. Three experts acknowledged that other oxygen wound therapies are available, for example topical pressurised oxygen therapy, wound dressings releasing oxygen and oxygen diffusion enhancers. One expert felt that Granulox was a variation on existing treatments and was no longer new.

Potential patient impact

Three experts stated that Granulox could promote quicker wound healing by improving oxygenation of the wound bed. One expert said that it could also lower infection rates and improve quality of life. Another stated that it could reduce wound pain. Three experts said that Granulox could be beneficial for people with chronic non-healing wounds and people with microvascular disease. One expert felt that no target group has been established by current research, which could lead to the technology being used inappropriately. Two experts felt that further large-scale studies are needed to determine the efficacy and patient impact of Granulox.

Potential system impact

All 5 experts agreed that Granulox should be used in addition to standard care. Two experts felt that adopting Granulox would not need changes to the existing care pathway. One expert said that applying the product every 3 days may increase the need for podiatry or nursing visits. All experts said that there would be an initial cost to purchase the technology, but 3 experts felt that there could be long-term cost savings because of a reduced number of clinic visits, reduced dressing changes and improved healing outcomes. Two experts felt that there was not enough evidence to determine if Granulox

improved wound healing outcomes. All experts thought minimal product training would be needed for staff and people with chronic non-healing wounds before using the technology.

General comments

Four out of the 5 experts said that there were gaps in the research for this technology. Two said that they would like to see studies with larger sample sizes. Two experts stated that they would like to see more controlled comparative studies in specific target populations of wound types, for example diabetic foot ulcers or venous leg ulcers. Two experts said that outcomes in future research should include length of time to wound healing, pain score, quality of life, long-term outcomes and signs of skin deterioration and allergy. Two experts felt that the adoption of Granulox was likely to be slow without a larger evidence base with supporting cost-effectiveness data.

Patient organisation comments

Diabetes UK stated that clinicians need options to treat a varied range of conditions. It said that it would welcome the consideration of a treatment, such as Granulox, that could provide another option for clinicians to use.

Expert commentators

The following clinicians contributed to this briefing:

- Kimberly Kirkwood, principal podiatrist, Epsom and St Helier University Trust. Did not declare any interests.
- Krishna Gohil, clinical lead lower limb workstream, National Wound Care Strategy Programme. Did not declare any interests.
- Luxmi Dhoonmoon, nurse consultant tissue viability, Central and North West London NHS Foundation Trust. Did not declare any interests.
- Mark Collier, nurse consultant and associate lecturer – tissue viability, Independent. Did not declare any interests.
- Richard Leigh, consultant podiatrist, Royal Free London NHS Foundation Trust. Did not declare any interests.

Representatives from Diabetes UK contributed to this briefing.

Development of this briefing

This briefing was developed by NICE. The interim process and methods statement for medtech innovation briefings 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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