

Innovative Medical Technology Overview: *Number 006/2016*

This IMTO review document describes an impartial review of the strengths and weaknesses surrounding the submission by **infirst HEALTHCARE** regarding the following medical technology.

Granulox[®] haemoglobin spray

Overview of technology

Granulox[®] haemoglobin spray is a [class III](#)¹ medical device indicated for the treatment of chronic wounds, such as venous leg ulcers, arterial leg ulcers, mixed leg ulcers, diabetic foot ulcers, secondary healing of surgical wounds and pressure ulcers.

Granulox[®] haemoglobin spray is intended to increase oxygen supply to the wound.

Comparator(s) and use in pathway of care

Granulox[®] is a patent-protected first in class medical device. Granulox[®] is positioned for use as an add-on therapy to standard care for the treatment of chronic wounds including venous leg ulcers, pressure ulcers and diabetic foot ulcers which have failed to heal after a period of standard care. Beyond administration of the spray, Granulox[®] is not expected to impact upon the standard wound care procedure.

Product performance

The main sources of evidence relating to product performance come from three retrospectively controlled cohort studies and a randomised controlled trial (RCT).

The RCT was a single-blind, single-centre study that investigated the effect of a haemoglobin solution on wound healing of venous leg ulcers (Arenbergerova et al, 2013). In the study, 72 patients with non-infected, non-healing chronic venous leg ulcers were treated in the Czech Republic and randomised to treatment with standard compression wound care plus Granulox[®] or standard compression wound care plus a sham saline solution without haemoglobin. The study recruited patients aged > 18 years with a venous leg ulcer measuring a minimum of 1.6 cm in all directions and a maximum wound surface area of 50 cm² and persisting for > 8 weeks. Each group consisted of 36 randomly allocated patients. The patients were treated in hospital for the first two weeks, and then treated at home by the study nurses, with the authors reporting that this reflects the general pattern in hospitalisation and home care of patients with venous leg ulcers. The primary outcome measure was reduction of the wound surface area during the 13 week treatment period. The safety of Granulox[®] was investigated as the secondary outcome measure. The study reported that at 13 weeks Granulox[®] treatment was associated with a 53% average reduction in wound size versus a 21% average increase in the sham arm (p<0.0001). For the Granulox[®] arm the absolute mean reductions in wound surface area after 13 weeks according to initial wound size were 11.5 cm² for wounds larger than 25 cm², 8.5 cm² for wounds initially between 15 and 25 cm² and 5.7 cm² for wounds initially smaller than 15 cm². Data for the comparator arm were not available. Pain intensity was measured using a visual

analogue scale and a mean reduction of 68% from day 0 (VAS=5.8) to day 91 (VAS=0.1) was reported for Granulox[®] compared with a 7% reduction from day 0 (VAS=5.1) to day 91 (VAS=4.8) for patients treated with the sham saline solution without haemoglobin.

Three cohort studies conducted by the same main investigator in three different patient groups were presented. Cohorts of sequential patients were recruited prospectively from patients with diabetic foot ulcers (DFU), chronic wounds (CW), and sloughy wounds (SW). The number of patients recruited to each cohort was 20, 50 and 100 respectively. An equal number of control patients were obtained retrospectively from clinical notes from the previous 12 months. These were selected sequentially by date in the notes without reported matching to prospective cases. The setting of these studies was north east England. The DFU cohort was treated in a hospital setting and the CW/SW cohorts were treated in primary care (walk-in clinic). All three cohorts shared the inclusion criterion of a wound that failed to heal (defined as a <40% reduction in area) in the previous 4 weeks. Patients with infected wounds, patients taking systemic antibiotics and/or corticosteroids and patients who were pregnant or lactating were excluded from the studies. The DFU cohort was further restricted to patients with a Site, Ischemia, Neuropathy, Bacterial Infection, Area and Depth (SINBAD) score of 0, 1 or 2. Furthermore, in this group, patients with an ankle-brachial pressure index (ABPI) <0.5 or toe pressure <70 mmHg, or glycated haemoglobin (HbA1c) measurement over 10% (13.3 mmol/L) were excluded. Follow-up measurements were reported up to 6 months in each cohort.

Results showed improvements in wound healing in all three cohorts.

In the DFU cohort mean wound size reduction was greater in the Granulox[®] group at week 4 (-63% vs -21%), week 16 (-91% vs -43%) and week 28 (-95% vs -63%). At week 28 follow-up, 15 out of 20 patients in the Granulox[®] cohort had complete healing (epithelialisation) compared to 8 out of 20 in the control cohort.

The CW cohort reported mean wound size reductions of -73% in the Granulox[®] group compared to -12% in the control group at 4 weeks. The benefit persisted at 8 weeks (-87% vs -14%) and final 26 weeks follow-up (-89% vs -75%). 45 out of 50 patients had complete healing at final 26-week follow-up compared to 19 out of 50 in the control group.

The SW cohort results were reported in a more limited fashion. At week 8 follow-up there was a mean wound size reduction of -93% in the Granulox[®] group compared to -32% in the control group. At week 6 complete wound closure was observed for 65 out of 100 patients in the Granulox[®] group and 37 out of 100 patients in the control group.

In addition to these studies, to support the efficacy and safety of haemoglobin spray when added to standard care for the treatment of chronic wounds, further evidence was presented from another small clinical trial and a number of single patient case studies.

The clinical trial (Arenberger et al, 2011) was a prospective, longitudinal, open label, single centre study comparing Granulox[®] with moist wound treatment. In the study, 28 patients in Mexico with wounds persisting for at least 8 weeks and unsuccessfully treated were randomised to treatment with Granulox[®] or moist wound treatment. The study recruited patients aged > 20 years with wounds localised in the distal lower leg region (ankle region), adequate therapy of causative diseases, a wound surface of less than 35 cm², local restriction of an inflammation, and depth of wound not deeper than the subcutis. The primary endpoint was the time at which the chronic wounds healed completely. The study was closed after six months following an unplanned intermediary evaluation and reported that

after six months 13/14 (93%) patients' chronic wounds in the Granulox[®] group healed compared to 1/14 (7%) in the standard 'moist' care group.

A series of ten patient case studies in NHS Lothian, Scotland, (Wakenshaw & Ropper 2016) were presented. Patients had chronic wounds of various aetiologies. The treatment protocol was treatment with Granulox[®] for 8-15 weeks. Two patients were excluded because they did not follow the treatment protocol. Of the remaining eight patients, one healed completely, five progressed towards healing and two stopped treatment following an infection. The authors estimate an average reduction in weekly treatment costs of -34% compared to the pre-treatment period. Reductions in pain were reported by patients and some patients were able to apply the treatment themselves.

Safety

Within the study by Arenbergerova et al, safety was assessed as a secondary endpoint. One subject treated with Granulox[®] was admitted to hospital with liver disease. However this was reported to be unrelated to treatment.

Arenberger et al (2011) also reported that there were no undesirable treatment related events identified within their study.

Granulox[®] should not be used by patients who are pregnant as no data are available to assess the impact of Granulox[®] within this group.

Strengths and limitations of the evidence

The main evidence comes from a RCT and three cohort studies.

RCTs are generally considered to provide a high level of evidence. The strengths of the Arenbergerova et al RCT include the following; the performance of a sample size calculation that helped ensure the study was powered to detect a difference between the treatment arms, the demographics of the patients in each treatment group were similar, and the size of the wounds in both groups was appropriately analysed to determine whether any differences before and after treatment were significant.

However, it is worth noting the following weaknesses; the nurses involved in treatment were not blinded which may be a source of bias, the randomisation allocation method used was not clear therefore it is uncertain whether the randomisation process was robust and - although it is acknowledged that a sham treatment is required for patient-blinding in the study - standard of care in Scotland does not include a saline solution and therefore the relevance to NHSScotland of the comparator arm is undermined.

Several strengths of the DFU, CW and SW cohort studies should be noted. In total 170 patients were included in the active treatment cohorts with an equal number of controls. The studies are well powered to detect clinically significant differences in outcomes. Across the three studies a variety of patients were included strengthening the evidence base for the broad proposed indication.

The three cohort studies are limited in general by their observational design and specifically by the retrospective recruitment of controls. A study with this design can only identify the treatment effect in an unbiased manner if the control group are selected carefully so that they are equivalent to the treatment group in all respects other than receiving the treatment

of interest. Important baseline differences in the DFU and CW cohorts were reported across the studies. Mean wound size at baseline was 5.1 cm³ in the Granulox[®] group compared to 6.6 cm³ in the control group for the DFU cohort. In the CW cohort the corresponding mean wound sizes at baseline were 7.9 cm³ and 9.4 cm³ respectively. Mean wound duration was also longer in the control group in the CW cohort (3.2 compared to 2.3 months). Other characteristics including age, gender and diabetic markers were well balanced between the treatment and control groups. However, sub-group analyses demonstrated that the treatment effect estimates were consistent when the sample was restricted in order to balance the cohorts with respect to wound size or wound duration.

Overall, Arenbergerova et al's RCT and the three reported cohort studies offer very promising results in terms of the product performance of Granulox[®]. However, continued data collection is encouraged to ensure accurate and unbiased estimates of the relative effectiveness of Granulox[®] in a variety of healthcare settings.

Economic considerations

An economic analysis was provided by the manufacturer based on resource use data collected in the reported DFU and CW cohort studies. This was a cost-analysis comparing health service costs for DFU and CW patients treated with Granulox[®] in addition to standard care compared to patients receiving standard care alone. The analysis was limited to 6 months duration based on the trial data collection period. The setting was the NHS in England.

Resource use data was collected for all patients in the DFU and CW cohort studies for the duration of follow-up using a standard form. Dressing materials and nurse time were recorded for each visit. In addition, surgical procedures related to chronic wounds including surgical debridement and amputation were recorded. Appropriate unit costs were applied for the UK NHS.

Cost differences were observed between active treatment and control cohorts. The key driver of the differences in costs was the duration of treatment because this determines the number of dressing changes. Each change of dressing requires an additional nurse visit and dressing materials. The faster average time to complete wound healing in the Granulox[®] cohorts and consequent shorter average durations of treatment resulted in substantially less resource use compared to the control cohorts.

Granulox was found to be more effective and less costly than standard care.

In DFU patients the addition of Granulox[®] to standard wound care was reported as resource saving with a mean saving of £2,330 per patient at 6 months.

In chronic wound patients the addition of Granulox[®] to standard wound care is resource saving with a mean saving of £1,469 per patient at 6 months.

Note these estimates do not include surgical procedure costs. All procedures occurred in control group. Therefore savings would be greater in both indications if these were included.

The limitation of the cost-analysis is that it uses observational data from DFU and CW cohorts. As previously noted the selection of retrospective controls and lack of details in the reporting of the control selection process raises concerns of selection bias. This could lead to an overestimation of potential savings. Sensitivity analysis provided by the manufacturer (summarised in table 1) demonstrated that the findings were robust to potential

overestimation of the treatment effect. For example, the difference in wound healing times between Granulox[®] and control patients would need to be overestimated by approximately 50% for the technology to no longer be resource-saving. Furthermore, increased savings would be expected if the time horizon of the analysis was extended from 6 to 12 months.

Table 1 – Sensitivity Analysis

| Sensitivity analysis | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---------------------------------|----------------------|--------------------|
| | DFU | Chronic wounds | Sloughy wounds |
| 1. Required percentage reduction in wound healing time in control group for Granulox [®] to no longer be resource saving | -57% | -53% | -48% |
| 2. Granulox [®] resource saving with a 50% reduction in unit costs of nursing visits | £-1,136 [base case: £-2,330] | £-715 [£-1,469] | £-412 [£-849] |
| 3. Granulox [®] resource saving with time horizon extended to 12 months | £-3,964 [£-2,330] | £-2,236 [£-1,469] | £-1,688 [£-849] |

The cost of Granulox[®] is £100-125 per can, which corresponds to an estimated cost per treatment of £4.20 based on the recommended 30 applications per container.

Organisational and patient issues

Granulox[®] is included in the NHS drug tariff part IX.

Granulox[®] is available for use in both community and hospital settings, in specialist wound care clinics and in podiatry clinics. Granulox[®] treatment is most likely to be initiated by tissue viability nurses as part of integrated wound care teams within NHSScotland.

Beyond administration of the spray, Granulox[®] is not expected to impact upon the standard wound care procedure.

Qualitative evidence presented within Healthcare Improvement Scotland's Antimicrobial Wound Dressings for Chronic Wounds HTA highlights the significant burden of a wound on patients' daily lives; from the physical impact, the psychological impact, to the restrictions on lifestyle.

Summary

RCT and observational study evidence has been presented to support the use of Granulox[®], with further supporting evidence provided from case series data. Within both RCTs, the primary endpoint was met and no treatment related adverse events were reported. However, limitations surrounding the studies should be acknowledged, particularly potential methodological weaknesses in the observational studies.

The economic evaluation presented provides evidence that Granulox[®] is likely to be effective and produce resource savings within NHSScotland.