Innovative Medical Technology Overview: Number 001/2014

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 III¹ 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 sores.

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 venous leg ulcers which have failed standard care. Beyond administration of the spray, Granulox® is not expected to impact upon the standard wound care procedure.

Product performance

The main source of evidence relating to product performance was a randomised, 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.

In addition to the Arenbergerova et al study, 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.

The single patient case studies were carried out in a German university and the dermatology department of a university in Prague. In Germany, the study population comprised of eight patients (three male, five female) with varying wound types including chronic wounds in the foot and ulcers of the foot/ankle. All wounds were classified as therapy resistant or un treatable. Following administration of the haemoglobin spray, the results showed that the wounds healed in six (75%) of all the patients after an average 16.6 weeks treatment. In Prague, the study population comprised of five male patients aged 65 years and over, with diabetes mellitus and chronic wounds in the lower leg. In all patients the wounds had existed for at least 9 months, and in one patient, the wound had existed for 3 years. The result showed that complete wound closure was observed in all five patients treated with the haemoglobin spray within a period of 8 to 12 weeks.

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 on infected wounds or by patients who are pregnant as no data is available to assess the impact of Granulox® within these indications. Granulox® should also not be used concomitantly with locally effective medicines including antibiotics, as interactions have not yet been studied sufficiently.

Strengths and limitations of the evidence

The main source of evidence comes from two small randomised controlled trials (RCT). RCTs are generally considered to provide a high level of evidence. However, the first (Arenbergerova et al), was a single blind study within which the nurses involved in treatment were not blinded to the treatment allocation and the other RCT (Arenberger et al) was open
As such this may be a source of bias in both studies. Although the assignment of patients to treatment groups was randomised in both RCTs, the allocation method used was not clear therefore it is uncertain whether the randomisation process was robust. Furthermore, the patient numbers were relatively small across both studies, and the settings in which they were undertaken may limit the generalisability to the Scottish population. Following on from this final point, although it is acknowledged that a sham treatment is required for patient-blinding in the Arenbergerova et al study, standard care in Scotland does not include a saline solution and therefore the relevance to NHSScotland of the comparator arm is undermined.

That said, it is worth noting the strengths of the Arenbergerova et al RCT: a sample size calculation was performed and 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.

The prospective trial by Arenberger et al had other weaknesses worth noting, including the absence of a power calculation and demographic data for each group to ascertain whether the intervention and control groups were similar - which increases the risk of bias.

Overall, Arenbergerova et al’s RCT offers promising results in terms of the product performance of Granulox® in a clinical trial setting. However, further research is encouraged to help evaluate the relative effectiveness of Granulox® in a variety of other healthcare settings and systems.

**Economic considerations**

The economic analysis presented by the manufacturer was not considered to be of sufficient quality to inform decision making within NHSScotland.

With reference to the analysis provided, the manufacturer presented a cost-utility analysis that had been undertaken by von Eiff (2013). Here, Granulox® as add on to standard wound care was compared to conventional dry therapy and hydroactive therapy, using a risk-weighted process analysis (RPA). The analysis compared the total average cost of care episode within each treatment arm and presented the cost per quality adjusted life year (QALY) gain in the Granulox® arm compared to the conventional dry therapy arm.

The analysis is conducted from the perspective of the healthcare system of Germany and the company justified the relevance of the analysis to NHSScotland on the basis that the demographic features are considered to be comparable to Scotland. The economic evaluation was based upon the assumption that Granulox® reduces the average time to healing compared with both conventional dry therapy and hydroactive therapy. However, the source of the data used in the analysis was not presented.

The reporting of the results was inconsistent. An incremental cost per QALY was presented, but Granulox® was also said to be cost saving versus conventional dry therapy. In addition, it is not possible to ascertain how the economic data were analysed, and therefore the economic evaluation provides insufficient evidence to determine whether or not Granulox® would be considered cost effective within NHSScotland.

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 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.

Summary

RCT 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, there are limitations surrounding the studies, particularly the generalisability to NHSScotland.

The economic evaluation presented provides insufficient evidence to determine whether or not Granulox® would be considered cost effective within NHSScotland.