Granulox® Health Technology Assessment
- The case for haemoglobin spray in South Africa

– A summary of the mode of action, clinical, cost-effectiveness, and health-economic evidence for haemoglobin spray in chronic wound care
- **Chronic wound care** – Summary introduction to a major health burden with large unmet medical needs

- **Mode of action** – Addressing the chronic hypoxia common to all chronic wounds

- **Clinical evidence** – Prospective randomised and retrospectively controlled data

- **Cost effectiveness** – Estimates of cost effectiveness for reimbursement in South Africa

- **Sensitivity analysis** – Assessment of robustness of cost-effectiveness across patient sub-populations
The cost of care for patients with chronic wounds is high.

Cost of care burden for major disease areas, UK data

Chronic wounds are estimated to cost 3% of the total UK NHS budget and has been estimated to cost £3.1bn\(^1\) annually.

The quality of life impact is also substantial.

A patient with a chronic ulcer has substantially reduced quality of life (-40%) and when the ulceration leads to a major amputation reduced by more than half (-58%).

Standard care doesn’t suffice for many patients

Persistency, % venous leg ulcers remaining unclosed

30% of venous leg ulcers do not heal within 6 months despite standard care

Persistency, % diabetic foot ulcers remaining unclosed

25% of diabetic foot ulcers do not heal within 6 months despite standard care

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Healing requires addressing key elements for success

Oxygen is important for successful healing

- Cell proliferation
- Bacterial defence
- Angiogenesis
- Collagen synthesis

In the absence of oxygen several crucial processes stop working.

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No oxygen – No healing

Oxygen concentration in the tissue

**Regional perfusion index**

- **Normal** (1.00)
  - Normal healing
- **-40%** (0.60)
  - Healing delayed
- **-60%** (0.40)
  - Healing fails

Relation between Regional perfusion index and Healing outcomes, % of wounds:

- **Healed**
  - 95% (n=64)
  - 58% (n=38)
  - 3% (n=64)

**Healing outcomes, % of wounds**

1Regional perfusion index – oxygen levels in wound vs oxygen levels in upper-body skin; 2 Hauser CJ. Tissue salvage by mapping of skin surface transcutaneous oxygen tension index. Arch Surg 1987; 122: 1128-30. Copyright infirst HEALTHCARE, reproduced with permission.
Yes oxygen – Yes healing

No oxygen – No healing...

All non-healing ulcers

97% of Non-healing ulcers

- Very low: 70%
- Low/Impaired: 27%
- Near normal: 3%

98% of Healed ulcers

- Very low: 0%
- Low/Impaired: 28%
- Near normal: 70%

1 Hauser (1987) Tissue salvage by mapping of skin surface transcutaneous oxygen tension index. Arch Surg; 122: 1128-30; *Transcutaneous oxygen pressure; ** Regional perfusion index – oxygen levels near wound vs oxygen levels in upper-body skin; Runagsetakit Chinsakchai Mahawongkajit et al (2010) Transcutaneous Oxygen tension predictor of ulcer healing in limb ischemia. JWC 19; Copyright infirst HEALTHCARE, reproduced with permission.
Despite plenty of oxygen in air, it is not available to the wound

A liquid film of as little as 0.1mm blocks 99% of oxygen diffusion vs one micrometre\(^1\)

\(1\) Einstein-Smoluchowski-relation for water, infirst HEALTHCARE, Data on File March 2015; Pictures used with permission; Copyright infirst HEALTHCARE, reproduced with permission.
Three options for improved oxygen delivery

**Topical oxygen therapy**
- High concentration of oxygen delivered topically as gas or chemically
- Positive results but a systematic review and a recent NICE review of a new oxygen dressing found little proven benefit

**Hyperbaric oxygen therapy**
- Improves amount of oxygen in air and in blood plasma while in the chamber
- But most of the oxygen in blood is not carried in the plasma
- Positive results but systematic review suggest data is weak

**Facilitated diffusion**
- Haemoglobin, a natural oxygen transporter which increases oxygen in the wound bed
- Applied with dressing changes it keeps working for days
- Few studies but highly positive, up to 2x standard care response rate and pain scores <50%

Sources:
3. MIB11 Oxyzyme and Iodozyme 2-layer hydrogel wound dressings with iodine for treating non-healing wounds  
- Hälsa Pharma GmbH. Granulox® Instructions for Use. April 2014
In vitro research shows diffusion rates increases by over 800%

- Transports more than eight times more oxygen at low oxygen tension\(^1\)
- Proven to work continuously for 5 days in vitro\(^2\)
- Apply when changing dressing, at least every three days\(^3\)

Granulox® - Oxygen delivered within 20 minutes

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<table>
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<tr>
<th>Design</th>
<th>Tamaulipas study&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Prague study&lt;sup&gt;2,3&lt;/sup&gt;</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Prospective randomised single centre study in chronic lower leg ulcers</td>
<td>Prospective randomised single centre study in chronic venous leg ulcers (ABI&gt;0.8)</td>
</tr>
<tr>
<td></td>
<td>2x14 pts; Standard care vs Granulox treatment, 6 months plus switch-over follow-up</td>
<td>2x36 pts standard care plus sham product vs standard care plus Granulox, 13 weeks</td>
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<tr>
<td></td>
<td>Un-blinded</td>
<td>Assessor blinded.</td>
</tr>
</tbody>
</table>

Sources: 
<sup>1</sup>Arenberger, Engels, Arenbergerova, Gkalpakiotis, García, Martínez, Anaya, Fernandez (2011). Clinical results of the application of a hemoglobin spray to promote healing of chronic wounds. GMS Krankenhaushygiene Interdisziplinär 2011, Vol. 6(1), ISSN 1863-5245; 
<sup>3</sup>Arenbergerova et al (2013) Effect of topical haemoglobin on venous leg ulcer healing. EWMA JOURNAL VOL 13. NO 2., n=72;
Tamaulipas: Granulox® 93% healed vs 7% at 6 months*

Wound persistency, % remaining unclosed\(^1\) and the results from the Gobierno de Tamaulipas study\(^2\)


Representative chronic wound population receiving standard care\(^1\)

overlaid with healing outcomes (93% vs 7%) from Tamaulipas chronic lower leg ulcer study at 6 months\(^2\)

26% better
### Tamaulipas study¹

**Design**

- Prospective randomised single centre study in chronic lower leg ulcers
- 2x14 pts; Standard care vs Granulox treatment, 6 months plus switch-over follow-up
- Un-blinded

### Prague study²,³

**Design**

- Prospective randomised single centre study in chronic venous leg ulcers (ABI>0.8)
- 2x36 pts standard care plus sham product vs standard care plus Granulox, 13 weeks
- Assessor blinded.

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Patient quality of life significantly better by week two

Mean pain scores, 10 cm VAS\(^1\)

<table>
<thead>
<tr>
<th>Week</th>
<th>Standard care plus Granulox</th>
<th>Standard care alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.00</td>
<td>5.00</td>
</tr>
<tr>
<td>2</td>
<td>5.00</td>
<td>4.00</td>
</tr>
<tr>
<td>6</td>
<td>4.00</td>
<td>3.00</td>
</tr>
<tr>
<td>13</td>
<td>3.00</td>
<td>2.00</td>
</tr>
</tbody>
</table>

Mean pain score reduction %\(^1\)

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<th>Week</th>
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<th>Standard care alone</th>
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<tbody>
<tr>
<td>Week 2</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>-4%</td>
<td></td>
</tr>
<tr>
<td>Week 13*</td>
<td>-7%</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Adapted from Arenbergerova et al (2013) Effect of topical haemoglobin on venous leg ulcer healing. EWMA JOURNAL VOL 13. NO 2., n=72 ; *-68% and -7% reported in the paper, slightly different results compared to those extracted from reading scores from the graphics in the paper. Copyright infirst HEALTHCARE, reproduced with permission.
100% response rate, 0% worsening, by week four

100% of patients in the Granulox arm responding and showing a wound size reduction at 4 weeks, vs 48% under standard care

Avoiding risk of deterioration, no Granulox patient worsening, 52% of standard care patients continuing to deteriorate

1 Adapted from Arenbergerova et al (2013) Effect of topical haemoglobin on venous leg ulcer healing. EWMA JOURNAL VOL 13. NO 2., n=72, responder data provided courtesy of Dr Peter Arenberger, post hoc analysis. Infirst HEALTHCARE Data on File March 2015 (unpublished, submitted for publication to Journal of Wound Care). Copyright infirst HEALTHCARE, reproduced with permission.
53% average size reduction and 97% improved by week 13

### Percent wound size change vs baseline

- **Standard care**
  - Baseline adjusted wound size change
  - 95% Confidence intervals

- **Standard care plus Granulox**
  - Baseline adjusted wound size change
  - 95% Confidence intervals

- **74% difference in average baseline adjusted wound size change**

### Improved vs worsened at week 13

- **Standard care**
  - 97% improved
  - 35% worsened

- **Standard care plus Granulox**
  - 21.3% improved
  - -53.4% worsened

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1 Adapted from Arenbergerova et al (2013) Effect of topical haemoglobin on venous leg ulcer healing. EWMA JOURNAL VOL 13. NO 2., n=72. 2 Responder data provided courtesy of Dr Peter Arenberger, post hoc analysis. Infirst HEALTHCARE Data on File March 2015 (unpublished, submitted for publication to Journal of Wound Care). Copyright infirst HEALTHCARE, reproduced with permission.
### Three retrospectively controlled studies

**Study designs**

<table>
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<th>Chronic Wounds&lt;sup&gt;2&lt;/sup&gt;</th>
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<td>• Sloughy Wounds</td>
</tr>
<tr>
<td>• 20 Standard Care</td>
<td>• 50 Standard Care</td>
<td>• 100 Standard Care</td>
</tr>
<tr>
<td>• 20 As above + Granulox®</td>
<td>• 50 As above + Granulox®</td>
<td>• 100 As above + Granulox®</td>
</tr>
</tbody>
</table>

- Retrospectively controlled single centre study in UK
- 2x20 pts; Granulox prospective treatment, vs Standard care retrospective from same clinic and period the year before
- SINGBAD ≤2, Chronic for min 12 weeks, 6 months follow-up. First 20 patients seen meeting inclusions, exclusions at baseline as per Granulox labelling
- Un-blinded

- Retrospectively controlled single centre study in UK
- 2x50 pts; Granulox prospective treatment, vs Standard care retrospective from same clinic and period the year before
- All wounds with <40% wound-size reduction over last 4 weeks, first 50 patients seen meeting inclusions, 6 months follow-up, exclusions as per labelling
- Un-blinded

- Retrospectively controlled single centre study in UK
- 2x100 pts; Granulox prospective treatment, vs Standard care retrospective from same clinic and period the year before
- All wounds ≥10% slough coverage at baseline, first 100 patients seen meeting inclusion, 6 months follow-up, exclusions as per label
- Un-blinded.

<sup>1</sup> Data shared by Sharon Hunt ahead of publication, data on file, preliminary pending publication, July 2016;  <sup>2</sup> Data shared by Sharon Hunt ahead of publication, data on file, preliminary pending publication, July 2016;  <sup>3</sup> Data shared by Sharon Hunt ahead of publication, data on file, preliminary pending publication, July 2016.
Substantially faster and greater wound size reduction

Average percent wound-size reduction vs baseline, by week

**Chronic Diabetic Foot Ulcers**

- Control
- Granulox

- Three wounds stopping treatment with Granulox and subsequently stagnated or worsened (Pt6, Pt17, Pt11)

**Chronic Wounds – Any**

- Control
- Granulox

- Three patients stopped Granulox early at week 12 (G34), week 16 (G27) and week 20 (G17) and all three deteriorated, two patients G20 and G45 stopped just before healed

**Slough Wounds**

- Control
- Granulox

- Reduction contributed from two wounds that stopped Granulox and started to deteriorate (S91 Week 10; S83 Week 16, E19 Week 20)

*Source: Sharon Hunt, Data on File, Preliminary pending data validation and publication*
Rapid and reliable elimination of Wound Slough

Average percentage of sloughy tissue coverage, % - for wound remaining open only

**Chronic Diabetic Foot Ulcers**

- Control: 50%
- Granulox: 50%

Weeks: 0, 4, 8, 12, 16, 20, 24, 28

Where Granulox is stopped early (Pt6, Pt7, Pt11), slough may return (Pt6 only)

Base: All valid data per period. Healed wounds treated as zero slough.

**Chronic Wounds – Any**

- Control: 38%
- Granulox: 47%

Weeks: 0, 4, 8, 12, 16, 20, 24, 28

Three patients stopped Granulox pre-maturely* at week 12 (G34), week 16 (G27), and 20 (G17) subsequently all three recurred with slough — with no slough returning in any other Granulox treated wounds.

Base: All valid data per period. Healed wounds treated as zero slough. * Two more patients stopped Granulox just before full healing G20 & G45 - with no slough recurrence.

**Slough Wounds**

- Control: 29%
- Granulox: 57%

Weeks: 0, 4, 8, 12, 16, 20, 24, 28

6 wounds remaining in the Granulox group, 4 with slough, with these no longer receiving Granulox. Of the 6 patients where Granulox was stopped pre-maturely, slough re-occurred in 4 patients, but in no wounds treated with Granulox.

Base: All valid data per period. Healed wounds treated as zero slough.

Source: Sharon Hunt, Data on File, Preliminary pending data validation and publication
Twice as many wounds fully closed within 8-16 weeks

Number of wound non-healed by week – Wound closure defined as complete wound epithelialisation

**Chronic Diabetic Foot Ulcers**

- **Control**
- **Granulox**
- **Max Delta**

- **n=20+20***

- A substantial difference in healing outcomes already within 8-10 weeks
- 53% fewer wounds remaining by week 16

- *One death in each of the groups, week 6 in the control group, and week 10 in the Granulox group, excluded

**Chronic Wounds – Any**

- **Control**
- **Granulox**
- **Max**

- **n=50+50**

- 66% fewer wounds remaining by week 8

- **Six deaths occurred in the Control group during the follow-up period, One death in the Granulox group, additionally four patients were lost to follow-up in the control group. To ensure conservative analysis only patients completing follow-up included.

**Sloughy Wounds**

- **Control**
- **Granulox**
- **Max**

- **n=100+100***

- 64% fewer wounds remaining by week 10

- **Five deaths occurred in the Control group during the follow-up period, no deaths occurred in the Granulox group. No patients were lost to follow-up**

Source: Sharon Hunt, Data on File, Preliminary pending data validation and publication
Quickly improved quality of life, pain reduction within a week

Average reported pain scores (10 cm VAS)

Diabetic Foot Ulcers

- n=20+20*

- Control
- Granulox

About half of DFU patients are neuropathic and therefore have no or minimal pain

Chronic Wounds

- n=50+50*

- Control
- Granulox

Average pain-scores are 73-97% lower for Granulox patients, despite starting higher

Sloughy Wounds

- n=100+100*

- Control
- Granulox

Source: Sharon Hunt, Data on File, Preliminary pending data validation and publication; * Average pain-scores across all patients, healed wounds recorded as zero pain
**Number of recorded adverse events by treatment group**

### Diabetic Foot Ulcers*

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Control</th>
<th>Granulox</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Amputation</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Surgery (theatre/bedside)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Infected/Antibiotics</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Chronic Wounds**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Control</th>
<th>Granulox</th>
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<tbody>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Amputation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surgery (theatre/bedside)</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Infected/Antibiotics</td>
<td>0</td>
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### Sloughy Wounds***

<table>
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<tr>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Amputation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surgery (theatre/bedside)</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Infected/Antibiotics</td>
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<td>0</td>
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*Control: Death (A08), Amputation (A20, A11 awaiting amputation but not within 28 week follow-up), Theatre Surgery (A10, A18, A20), Bedside surgery (A04, A08, A15), Infection/Anti-biotics (A04,A11,A14,A15,A18); Granulox; Death (Pt10) ; **Control; 6 Deaths (C04, C09, C18,C20,C27, C46); 8 surgery (C05,C12,C13,C14,C20,C25,C36,C44); 8 infection/Anti-biotics (C11,C12,C20,C21,C23,C30,C41,C50), 5 lost to follow-up (C22,C23,C24, C25); Granulox, One death (G07).  *** Control; 5 deaths (R20,R33,66,68,78); 14 surgery (R09, R28, R31, R41, R51, 55, 60, 70, 73, 74, 82, 90, 92, 94), 3 infected/Antibiotics (R10, R12, 92); Granulox One surgery (S91), and one infection (S90).
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“In fifteen years as a health economist at the Centre for Health Economics at York, as a director of Pharmerit Ltd UK and as an NICE Scientific Advice Programme expert and having analysed, constructed or reviewed over 100 cost-effectiveness / economic evaluation studies I cannot recall a single technology that demonstrates as much cost-effectiveness potential as Granulox”*

- Chris Bojke, Senior Research Fellow, Centre for Health Economics, University of York

* Bold emphasis added; reproduced with permission.
“From an economic point of view, the Granulox® combination treatment is superior to all other alternative treatments tested”

- Professor Wilfred van Eiff

Centre for Hospital Management
Westphalian Wilhelms University of Munster

1 Infirst Healthcare Data on File. Treatment utility per unit cost calculated based on treatment utility / total cost of treatment per episode. Treatment utility per unit cost calculated from the utility scores and total episode treatment costs for each treatment type and normalised based on standard care utility as reported by von Eiff (2013). Health economic evaluation. The economic efficiency of Granulox. Centre for Hospital Management. Westphalian Wilhelms University of Munster.
Simulated cost savings may add up to more than R1Bn per year

**Simulated wound persistency**¹

- **Percent chronic VLU wounds remaining un-healed**
- **Weeks of wound care (open wound weeks)**
- **Cost of wound care (ZAR)**

**When projected to 15,000 chronic VLUs**¹

- **At six months**
  - Standard (6 mo)
  - Plus Granulox (6 mo)
  - Saving (at 6 mo)
- **At twelve months**
  - Standard (12 mo)
  - Plus Granulox (12 mo)
  - Saving (at 12 mo)

**Percent chronic VLU wounds remaining un-healed**

- Granulox
- Non-Granulox
- 26 weeks (6 months)

**Cost of wound care (ZAR)**

- Standard (6 mo)
- Plus Granulox (6 mo)
- Saving (at 6 mo)
- Standard (12 mo)
- Plus Granulox (12 mo)
- Saving (at 12 mo)

—

¹ Adopted from Arenberger Elg Petyt Cutting (2014). Expected outcomes from topical haemoglobin spray in non-healing and worsening venous leg ulcers, J Wound Care 24(5), projected to estimated chronic VLU population of 15,000 in south Africa; ²Applying average weekly cost of care from Harding, Posnett and Vowden (2013) and projected to YE2014 using PSSRU Unit Costs HCHS pay and prices index and converted to South African Rand at 20:1; Costs: Healed R137pw, Improving/progressing R1999pw, Static/stagnant R2282pw, Deteriorating R3629pw (No patients assumed severe at R14,500pw). Costs of Granulox® assuming R153.5 per application, 30 applications/can and mean of 2.33 applications per week per patient for an additional weekly cost of R357.7/week.
Three retrospectively controlled datasets with activity level data

### Study designs

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<td>• 100 As above + Granulox&lt;sup&gt;®&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Data available

- Dressings used
- Wound rinse used, if any
- Debriding agents used, if any
- Weekly dressing frequency
- Number of nurse visits by type
- Surgical procedures at tariff prices
- Prescription items specific for wound care, i.e., antibiotics, pain relievers.
- Offloading devices not included unless fitted during the follow-up period.

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<sup>1</sup> Persistent for min 12 weeks, SINBAD ≤ 2, exclusions as per label; <sup>2</sup> < 40% wound size reduction over last 4 weeks, exclusions as per label; <sup>3</sup> ≥ 10% slough coverage at baseline, exclusions as per the label.
The method used to convert to South African technology impact

Steps taken to convert international data to cost effectiveness data for use in South Africa

1. - Actual dressings and health care resources used in each of the evaluations from case records

2. - Costs of dressings, nurse visits and surgical procedures extracted from UK Tariff

3. - Prices converted to South African Rand based on long-term exchange rate and South African usage*

* All prices for dressings and healthcare resources assumed at current UK tariff prices and GBP/Rand FX rate of £1 = R20.0. The price of Granulox® is assumed at R153.5 per application (30 applications net per 12ml spray can (R4,605 equivalent) all net VAT. Graphics used with permission / Under permissible use.
Granulox® consistently reduce total cost of care by half

Average total cost of care from baseline including costs of surgical procedures for the first 26/28 weeks, but no costs of surgery from week 26/28 onwards

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<tbody>
<tr>
<td>Costs of care, 52 weeks, R/patient (n=40)</td>
<td>Costs of care, 52 weeks, R/patient (n=100)</td>
<td>Costs of care, 52 weeks, R/patient (n=200)</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td><strong>Granulox</strong></td>
<td><strong>Savings</strong></td>
</tr>
<tr>
<td>$35,747$</td>
<td>$62,903$</td>
<td>$27,156$</td>
</tr>
<tr>
<td>$98,931$</td>
<td>$25,728$</td>
<td>$73,203$</td>
</tr>
<tr>
<td>$61%$ reduction in total cost of care</td>
<td>$71%$ reduction in total cost of care</td>
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</tbody>
</table>

3 Method to predict time to wound closure used as per Arenberger, Cutting, Elg, Petyt (2015) Expected outcomes from topical haemoglobin spray in non-healing and worsening venous leg ulcers. J Wound Care. May;24(5):228, 230-2, 236. Costs include wound rinse, primary and secondary dressings, nursing, prescriptions relating to the wound, and the cost of any wound-related surgical procedures during the follow-up period. Same wound care regimen as last observed assumed continued for extension. No cost of prescriptions or surgery assumed for the period from week 27/29-52. 3 In DFUs, data for patients who died or were lost to follow up included up to the date of amputation, loss of follow up or death with no cost assumed from amputation or death. In the control cohort, one death week 6 and one amputation week 7 with the cost of the amputation included for cost of surgery. 3 In the Chronic control cohort, there were 6 deaths, wk 2, 8, 9, 3×10, and 4 patients lost to follow-up (All in wk8, records no longer available, C22, C23, C24, C25). Data for patients who died or were lost to follow-up included up to the date of amputation, loss of follow up or death with no cost assumed from amputation or death. 4 In the Slough dataset control group, there were 5 deaths (wks 3,5,10,11,12). There were no deaths in the Granulox group. For patients who died, healing rate to date of last observation used as basis to predict time to wound closure should the patient have not died. No procedure or prescription costs assumed for the period 27/29-52. Data by Sharon Hunt / South Tees NHS Foundation Trust. Preliminary pending validation and publication.
The fair price per can of Granulox® is R73-106k per can

Fair price per can analysis - Average total cost of care savings per can of Granulox used – as estimate of cost neutral price of a can of Granulox®

### Diabetic Foot Ulcers

**Savings per can – Value realised per can**

- **R106,155**

  - The actual justified price of Granulox® is at least 23 times higher than the current price at a 96% discount vs fair price.

### Chronic Wounds

**Savings per can – Value realised per can**

- **R89,968**

  - The actual justified price of Granulox® is at least 20 times higher than the current price at a 95% discount vs fair price.

### Sloughy wounds

**Savings per can – Value realised per can**

- **R75,112**

  - The actual justified price of Granulox® is at least 16 times higher than the current price at a 94% discount vs fair price.

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1. Total savings in patient care divided by the number of cans based on per spray basis, i.e. the same can is used on multiple patients. Time to healing method used as per Arenberger, Cutting, Elg, Petyt (2015) Expected outcomes from topical haemoglobin spray in non-healing and worsening venous leg ulcers. J Wound Care. May;24(5):228, 230-2, 236. Costs include wound rinse used, primary and secondary dressings, nursing, prescriptions relating to the wound, and the cost of any wound-related surgical procedures during the follow-up period based on UK tariff prices and a Rand/GBP exchange rate of 20. Same wound care regimen as last observed assumed continued for wounds remaining unhealed at 6 months and also from death onwards in slough dataset. No cost of prescriptions or surgery assumed for the period from week 27/29 to 52.

2. In DFUs, data for patients who died or were lost to follow-up are included up to the date of amputation, loss of follow up or death with no cost assumed from amputation or death. In the control cohort, one death week 6 and one amputation week 7 with the cost of the amputation included for cost of surgery. In the Chronic control cohort, there were 6 deaths, wks 2, 8, 9, 3x10, and 5 patients lost to follow up. There were no deaths in the Granulox group. For patients who died, healing rate to date of last observation used as basis to predict time to wound closure should the patient have not died. Note: Preliminary pending validation and publication. Data by Sharon Hunt / South Tees NHS Foundation Trust.
- **Chronic wound care** – Summary introduction to a major health burden with large unmet medical needs

- **Mode of action** – Addressing the chronic hypoxia common to all chronic wounds

- **Clinical evidence** – Prospective randomised and retrospectively controlled data

- **Cost effectiveness** – Estimates of cost effectiveness for reimbursement in South Africa

- **Sensitivity analysis** – Assessment of robustness of effectiveness across patient sub-populations
Few baseline differences can have influenced results

Tests for difference in baseline patient and wound attributes between control and Granulox® groups by evaluation dataset

**DFU wounds** – p-values from t-tests or chi-square tests between groups (n=40), note small samples

- Wound size
- Vascular
- Ulcer type
- SINBAD
- Off-loading
- Neuropathy
- History
- Healing rate
- HbA1c
- Age

**Chronic wounds** – p-values t-test/chi-square (n=100), note small counts for some ulcer sub-types

- Wound size
- Vascular
- Ulcer type
- SINBAD
- Off-loading
- Neuropathy
- History
- Healing rate
- Age

**Slough study** – p-values t-test for parametric variables and chi-square for nominal data (n=200)

- Wound size
- Vascular
- Ulcer type
- SINBAD
- Off-loading
- Neuropathy
- History
- Age

Source: Data on File, shared by Sharon Hunt / South Tees NHS Trust ahead of publication. All categorical data analysis using Chi-square, and all parametric data analysed using two-tail, different variance t-tests. Data included for all patients regardless of death or drop-out on intention to treat basis.
Wound healing effectiveness at 4 weeks selected for analysis

While any other measures for estimating impact on wound healing from variations in baseline attributes would be possible, wound size reduction from baseline to week 4 was selected².

Healing at 4-Weeks - suggested as the period for review of effectiveness in the Granulox® consensus guidelines¹

Substantial and consistent supportive data - culminating in international guidance

- Sheehan, Jones, Caselli et al (2003). Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of healing in a 12-week prospective trial. Diabetes Care. 26(6):1879-82

²"if a reduction [in wound size] of at least 40% following 4 weeks of standard therapy is not seen, then treatment re-evaluation should ensue"

2. Analysis of additional outcome variables can be conducted on request, e.g. wound closed at 6 months, total cost of care excluding surgical procedures, total cost of care including surgery, 12 months predicted costs.
1. Differences in baseline wound size; Chronic and Sloughy wounds

2. The impact of wound ischemia; Sloughy wounds

3. The impact of wound neuropathy; Sloughy wounds

4. The impact of wound persistency prior to baseline; Chronic wounds

5. The impact of healing rate prior to baseline; Chronic wounds
Substantial healing benefit regardless of baseline wound size

Analysis of impact of difference in baseline wound size on healing outcomes – Wounds size change to Week 4

Chronic wounds – p-values for group differences by variable, focus on baseline wound size

Wound size

Vascular

Ulcer type

p=0.05

Nearly significant. More very large wounds in control group and more small wounds in Granulox® group

Chronic study – number of patients by baseline wound size

0-10

10-100

>100

Wounds size in cm

0

5

10

15

20

25

30

Control

Granulox

Nearly twice as many very large wounds

Chronic wounds – Observed healing rate from baseline to week four in the Granulox® treatment group and in the retrospective control cohort

0%

-10%

-20%

-30%

-40%

-50%

-60%

-70%

-80%

-90%

-100%

-9% * -14% * -16% * -54% *

Wounds size at baseline in cm

0-10

10-100

>100

More than three times higher average healing speed regardless of wound size

Source: Data on File, shared by Sharon Hunt / South Tees NHS Trust ahead of publication. Wound size at baseline calculated as L*W*/4; 1 Excludes patient C4 in the control group, size 4.7cm² (RIP week 2); *Note: Small sample size.
Benefit regardless of wound size also for sloughy wounds

**Baseline wound size analysis – Variation in healing speed depending on baseline wound size**

**Sloughy wounds** – p-values for group differences by variable, focus on baseline wound size

- **Wound size**
  - More small wounds in the Granulox group, and more very large wounds in the control group

- **Vascular**
- **Ulcer type**

**Sloughy wounds** – number of wounds by baseline wound size area at baseline in cm²

- **Granulox**
- **Standard**

- **p=0.05**

**Source:** Data on file. Shared by Sharon Hunt / South Tees NHS Foundation Trust, preliminary pending publication. Excludes one patient in the Control group, Patient 66, who died in Week 3, who had a large wound size area of 117cm² at baseline.

**Sloughy wounds** – Analysis of baseline adjusted wound size change, in cm², week 0 to week 4 (see lower graph for percent wound size change vs baseline)

- **Granulox**
- **Standard**

- **Consistent and substantial healing-benefit regardless of baseline wound size, with 20-70% greater wound size reduction at 4 weeks vs standard care alone, increasing with wound size**

**Percent wound size change, Week 0-4**

- **Granulox**
  - 0-5: -94%
  - >5-10: -91%
  - >10-40: -82%
  - >40: -10%

- **Standard**
  - 0-5: -26%
  - >5-10: -57%
  - >10-40: -4%
  - >40: -10%
Evaluation of baseline differences

1. Differences in baseline wound size; Chronic and Sloughy wounds

2. The impact of wound ischemia; Sloughy wounds

3. The impact of wound neuropathy; Sloughy wounds

4. The impact of wound persistency prior to baseline; Chronic wounds

5. The impact of healing rate prior to baseline; Chronic wounds
Substantial benefits also in non-ischemic wounds

**Impact of ischemia analysis – Variation in healing speed depending on ischemic condition of patient**

**Sloughy wounds** – p-values for group differences by variable, focus on vascular deficiency

- More wounds with vascular deficiency in the control group

**Sloughy wounds** – number of wounds diagnosed with vascular deficiency

- More wounds with vascular deficiency in the control group

**Sloughy wounds** – Average wound size change to week 4 by vascular deficiency status

- Double the average healing speed across also non-ischemic wounds

Source: Data on File. Shared by Sharon Hunt / South Tees NHS Foundation Trust; Data missing at week 4 for six patients; One for Standard Ischemic, patient 28 (missing data for week 4, later returned to care with size increased by 56% by week 8). Four in the Standard Non-Ischemic patients with missing data at week 4 – Patient 31, 51, 66 (RIP week 3), 82, 90. No missing data in the Granulox group. *Note: Very small sample size, n=5*.

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Evaluation of baseline differences

1. Differences in baseline wound size; Chronic and Sloughy wounds

2. The impact of wound ischemia; Sloughy wounds

3. The impact of wound neuropathy; Sloughy wounds

4. The impact of wound persistency prior to baseline; Chronic wounds

5. The impact of healing rate prior to baseline; Chronic wounds
Substantial healing benefit regardless of neuropathy status

Impact of neuropathy analysis – Variation in healing speed depending on neuropathy of patients

Sloughy wounds – p-values for group differences

More patients with neuropathy in the control cohort

Sloughy wounds – number of patients diagnosed with neuropathy

Diagnosed with Neuropathy

*Note: Very small sample size, n=3.
1. Differences in baseline wound size; Chronic and Sloughy wounds

2. The impact of wound ischemia; Sloughy wounds

3. The impact of wound neuropathy; Sloughy wounds

4. **The impact of wound persistency prior to baseline; Chronic wounds**

5. The impact of healing rate prior to baseline; Chronic wounds
Healing impact is superior, regardless of wound persistency

Analysis of impact of wound persistence at baseline – Wound size change to week 4 by wound persistency at baseline

**Chronic wounds** – p-values for pre-baseline wound persistency difference

More wounds with shorter persistency in the Granulox® cohort

**Chronic wounds** – Number of wounds by wound persistency at baseline, in months

<table>
<thead>
<tr>
<th>Wound persistency at baseline, in months</th>
<th>Control</th>
<th>Granulox</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>1-2</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>2-3</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>3-4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4-6</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>6-10</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Wound persistency at baseline, in months

Wound size area change, % vs baseline at week 4; Linear regression lines by group

R² = 0.269

Substantially more wounds with greater wound size reduction on Granulox® - regardless of wound history. Also, there may be a healing speed benefit from treating with Granulox® earlier rather than later

Source: Data on File, shared by Sharon Hunt / South Tees NHS Trust ahead of publication. Wound size calculated as L*W*π/4; ¹ Excludes patient C4 in the control group, present for 1.4 months at baseline (RIP week 2).
Evaluation of baseline differences

1. Differences in baseline wound size; Chronic and Sloughy wounds

2. The impact of wound ischemia; Sloughy wounds

3. The impact of wound neuropathy; Sloughy wounds

4. The impact of wound persistency prior to baseline; Chronic wounds

5. The impact of healing rate prior to baseline; Chronic wounds
Substantial benefit regardless of baseline healing trajectory

**Healing trajectory analysis – Variation in healing speed depending on baseline healing speed (wound size change)**

**Chronic wounds** – p-values for group differences by pre-baseline wound size change

More deteriorating wounds in the Granulox group

**Chronic wounds** – wounds by healing rate in the four weeks prior to baseline

Wound healing trajectory at baseline, i.e.
- Size change < -5% Improving, +/-5% Static, >5% Deteriorating

<table>
<thead>
<tr>
<th>Improving</th>
<th>Static</th>
<th>Deteriorating</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>7</td>
</tr>
</tbody>
</table>

More than double the average healing speed regardless of prior ‘chronic’ healing trajectory

Note: * Very small sample (n=5, 5, 3 respectively). 1 Excludes patient C4 in the control group (RIP Week2), in “Static” group. Samples <5 shaded. Data on File, shared by Sharon Hunt / South Tees NHS Foundation Trust ahead of publication. Preliminary pending publication.
Thank you

Any questions, please contact Richard Straughan on ceo@redermis.com
Case series show excellent results across all indications
Instruction for use

Read all of this leaflet carefully because it contains important information for you. This medical device is available without prescription. However, you still need to use Granulox® carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Consult your doctor or pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen.
- If you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Granulox® is and what it is used for
2. What you need to know before you use Granulox®
3. What you need to know while using Granulox®
4. How to use Granulox®
5. Possible side effects
6. How to store Granulox®
7. Further information

1. What Granulox® is and what it is used for

Granulox® is a spray for use on chronic wounds. Granulox® is an innovative medical device for the treatment of chronic wounds, such as venous leg ulcer, arterial leg ulcer, mixed leg ulcer, diabetic foot ulcers, secondary healing of surgical wounds and pressure sores. Granulox® can also be used on sloughy and infected wounds.

Chronic wounds are usually characterised by a below-average oxygen supply to the affected tissue. This has a major impact on wound healing. The precondition for use is appropriate medical treatment of the primary disease. In the case of chronic arterial wounds, the possibilities for improving blood flow must already have been exhausted.

Granulox® provides the wound with the required oxygen by means of diffusion. The active substance haemoglobin supplies the base of the wound externally with oxygen. The improved oxygen supply to the base of the wound supports wound healing.

2. What you need to know before you use Granulox®

Do not use Granulox®:
- If you are pregnant.
- No data are available to allow an assessment of these cases.

3. What you need to know while using Granulox®

- Granulox® should not be used simultaneously with locally effective medicines, such as antibiotics, as interactions have not yet been studied sufficiently.
- Disinfectants are known to impair the efficacy of Granulox®. Therefore, after application of a disinfectant, the area must be subsequently flushed thoroughly with a physiological solution.
- Thorough flushing with a physiological solution is necessary after use of proteolytic (enzymatic) debridents.

If your symptoms worsen or you experience any side effects, you must stop using the medical device and consult a doctor.

4. How to use Granulox®

Before you start to use Granulox®, a doctor or medically qualified person must have explained Granulox® treatment to you.

After sufficient debridement and cleaning of the wound, spray Granulox® onto the cleaned wound. Remove the protective cap from the spray container. Hold the nozzle about 5 to 10 cm from the wound and spray until the wound is completely coated with a thin film. 1 to 2 seconds are normally sufficient to cover a wound area of 2 x 3 cm. Apply again every time the dressing is changed, but at least every three days. After use, cover the wound with a breathable wound dressing. IMPORTANT: only use breathable wound dressings and bandaging materials.

After use, replace the protective cap on the spray container. It is not necessary to clean the nozzle as the product has been preserved. If the nozzle becomes blocked after several uses, it can be re-opened by cleaning it. Use sterile materials or disinfectants for cleaning. After cleaning, the first spray should be discarded, e.g. by spraying it onto cellulose. One pack of Granulox® is sufficient for up to 30 applications depending on the size of the wound. After opening, Granulox® can be used until the expiry date.

5. Possible side effects

Side effects of Granulox® have not been reported. Hypersensitivity reactions to any one of the ingredients contained in Granulox® cannot be fully ruled out. If your symptoms worsen or you develop side effects, please stop using Granulox® and consult a doctor.

6. How to store Granulox®

Granulox® should be stored in the refrigerator at temperatures from 2 °C to 8 °C. On the days it is being used, Granulox® can be stored at room temperature (max. 25 °C). If Granulox® is used on a daily basis (e.g. in clinical practice or home visits), the spray container can be stored continuously at room temperature until it is empty. The storage time at room temperature must not exceed a maximum period of 6 weeks. Keep out of reach of children. Pressurised container: May burst if heated. Do not pierce or burn, even after use. You may not use Granulox® after the expiry date given on the product and the outer packaging.
Essential product information continued and Pack design*

**What Granulox® contains**
- The active ingredient is 10% carbonylated haemoglobin. The other ingredients are: 0.7% phenylethanol, 0.9% sodium chloride, 0.05% Naazaotyretatine, ad 100% water

**What Granulox® looks like and contents of the pack**
- Granulox® is a red, aqueous spray. One spray contains 12 ml.

*Source: *Hälsa Pharma GmbH. Granulox® Instructions for Use. April 2016