Clinical Evaluation Report

for

Revamil Product group
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**Attachments:**
1. Literature search Oncologic wounds
2. Literature search Oncologic wounds
3. Literature search Chronic ulcers
4. Literature side effects
5. Review Post Market Surveillance 2005-2010
1. INTRODUCTION
This document concerns the overall clinical evaluation of Revamil product group. The following devices fall within this group:

- Revamil wound dressing (5x5, 8x8, 10x20)
- Revamil gel (single dose)
- Revamil gel

Clinical evaluation is regarded as an ongoing process conducted throughout the life cycle of a medical device. It is first performed during the conformity assessment process leading to the marketing of a medical device and then repeated periodically as new clinical safety and performance information about the device is obtained during its use in the post market phase.

This document provides the overall results of literature review, in vitro performance testing, clinical (case)study data and Post Market Surveillance data to provide evidence for the safety and clinical performance of Revamil product group as claimed by its labeling.

The data summarized in this document is reported in more detail in underlying reports to which references are made in this document.

1.1 Names of the device
During the design and development process the following names have been used for the Revamil product group:
- Revamil

1.2 Manufacturer
Bfactory Health Products B.V.
Remmerden 58
3911 TZ Rhenen
The Netherlands

2. RELATION TO OVERALL RISK MANAGEMENT
This clinical evaluation is part of the overall risk evaluation process of Revamil product group.

3. OBJECTIVE AND SCOPE
This clinical evaluation study is performed in order to:

- Identify and discuss any literature data on wound care products aimed for a similar indication and based on similar formulations as Revamil product group, that support the safety and performance claims of Revamil product group.

- Identify and discuss any literature data on any other products based on similar formulations as the Revamil product group or based on similar principles of action; and if such products are found, discuss if these data can be extrapolated with regards to the clinical safety and performance claims of Revamil product group.

- Evaluate the results of in vitro performance test data supporting the clinical performance of Revamil product group.
- Evaluate results of clinical (case) studies and Post Market Surveillance data supporting the clinical performance and safety of Revamil product group.

- Achieve essential information for assessing clinical benefits and foreseeable risks of Revamil product group. In case risks are identified, an assessment is made if risks are acceptable when weighted against the clinical benefit and a verification is made if sufficient control measures have been taken including information provided in the Instructions for Use.

- Justify the need for a Clinical Investigation or Post Market Clinical Follow Up.

- Assess if Revamil product group is safe when used as intended and applied to indicated wounds and complies to the safety requirements of the MDD 93/42/EC.

- Assess if Revamil product group performs as claimed when used as intended and applied to indicated wounds and complies to the performance requirements of the MDD 93/42/EC.

4. APPLICABLE, REGULATION, STANDARDS AND GUIDELINES
The present evaluation was performed according to the requirements and guidance of
- MDD 93/42/EC Annex I and Annex X.
- EN ISO 14971:2009 “Medical devices - Application of risk management to medical devices”.
5. PRODUCT

5.1 Product description

The following devices fall within the Revamil product group (see figure 1):

- Revamil wound dressing (5x5, 8x8, 10x20)
- Revamil Single Dose gel (single dose)
- Revamil gel

Figure 1: Overview Revamil product group

Revamil Single Dose gel (2g)  Revamil gel (18g)  Revamil Wound dressing

For an overview of physical product descriptions see table 1.

For an overview of claims, indications, use and safety precautions/ contra-indications see section 5.2 - table 2.
Table 1: Physical description of the Revamil Product Group

<table>
<thead>
<tr>
<th></th>
<th>Revamil gel 18g</th>
<th>Revamil Single Dose 2g</th>
<th>Revamil wound dressing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device presentation</strong></td>
<td>Aluminum tube with inner coating</td>
<td>LDPE/HDPE Syringe</td>
<td>Impregnated polyacetate dressing</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>3.5 (spec: 3-6)</td>
<td>3.5 (spec: 3-6)</td>
<td>3.5 (spec: 3-6)</td>
</tr>
<tr>
<td><strong>Packaging</strong></td>
<td>Tube in carton box</td>
<td>12 syringes in carton box</td>
<td>Single dressing between LDPE sheets in sealed in pouch, 5-10 pouches packaged per carton box</td>
</tr>
<tr>
<td><strong>Sterile/ non-sterile</strong></td>
<td>Gamma-irradiation at min 25kGy, no sterility claimed</td>
<td>Gamma-irradiation at min 25kGy, no sterility claimed</td>
<td>Sterilization validated (VDmax25kGy), sterility claimed</td>
</tr>
<tr>
<td><strong>Storage</strong></td>
<td>4 -30°C</td>
<td>4 -30°C</td>
<td>10-30°C</td>
</tr>
<tr>
<td><strong>Shelf life</strong></td>
<td>2 years</td>
<td>2 years</td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Stability after opening</strong></td>
<td>3 months</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
5.2 Claims, indications, use, safety precautions/ contra-indications

Table 2 provides an overview of claims, indications, use and precautions per Revamil product type.

Table 2: Overview claims, indications, use, safety precautions/ contra-indications

<table>
<thead>
<tr>
<th></th>
<th>Revamil gel 18g</th>
<th>Revamil Single Dose 2g</th>
<th>Revamil wound dressing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Claims</strong></td>
<td>Managing the micro-environment of the wound</td>
<td>Managing the micro-environment of the wound</td>
<td>Managing the micro-environment of the wound</td>
</tr>
<tr>
<td></td>
<td>See 5.4</td>
<td>See 5.4</td>
<td>See 5.4</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>- Bed sores</td>
<td>- Bed sores</td>
<td>- Bed sores</td>
</tr>
<tr>
<td></td>
<td>- Different kinds of ulcers</td>
<td>- Different kinds of ulcers</td>
<td>- Different kinds of ulcers</td>
</tr>
<tr>
<td></td>
<td>- Infected wounds,</td>
<td>- Infected wounds,</td>
<td>- Infected wounds,</td>
</tr>
<tr>
<td></td>
<td>- Acute wounds,</td>
<td>- Acute wounds,</td>
<td>- Acute wounds,</td>
</tr>
<tr>
<td></td>
<td>- Surgery and radiation induced oncological wounds</td>
<td>- Surgery and radiation induced oncological wounds</td>
<td>- Surgery and radiation induced oncological wounds</td>
</tr>
<tr>
<td></td>
<td>- Minor (1st- and 2nd degree) burns</td>
<td>- Minor (1st- and 2nd degree) burns</td>
<td>- Minor (1st- and 2nd degree) burns</td>
</tr>
<tr>
<td><strong>Instructions for use</strong></td>
<td>See 5.2.1</td>
<td>See 5.2.1</td>
<td>See 5.2.1</td>
</tr>
<tr>
<td><strong>Single use/ reusable</strong></td>
<td>Reusable</td>
<td>Single use</td>
<td>Single use</td>
</tr>
<tr>
<td></td>
<td>Repeated use:</td>
<td>Repeated use:</td>
<td>Repeated use:</td>
</tr>
<tr>
<td></td>
<td>- Replace each 1-2d</td>
<td>- Replace each 1-2d</td>
<td>- Replace each 1-3d</td>
</tr>
<tr>
<td></td>
<td>- Max. 30d in total</td>
<td>- Max. 30d in total</td>
<td>- Max. 30d in total</td>
</tr>
<tr>
<td><strong>Used in combination with</strong></td>
<td>Semi-occlusive wound dressings that guarantee a moist wound environment and that can be attached in the normal way</td>
<td>Semi-occlusive wound dressings that guarantee a moist wound environment and that can be attached in the normal way</td>
<td>- Attach by self-adhesive, porous tape</td>
</tr>
<tr>
<td></td>
<td>See 5.3</td>
<td>See 5.3</td>
<td>- Can also be covered by a secondary dressing that is attached in the conventional way</td>
</tr>
<tr>
<td><strong>Safety precautions/ Contra-indications</strong></td>
<td>See 5.3</td>
<td>See 5.3</td>
<td>See 5.3</td>
</tr>
</tbody>
</table>

5.2.1 Instructions for use

**Revamil Wound Dressing**
1. When required first clean the wound in the conventional way
2. Open the packaging at the upper side by tearing open the seal
3. Remove the impregnated dressing from the protective sheets and spread it out over the wound surface
4. Attach the dressing in the normal way, e.g. by self-adhesive, porous tape
5. Revamil Wound Dressing can also be covered by a secondary dressing that is attached in the conventional way
6. After one to at most three days remove the dressing carefully from the wound and replace it with a new Revamil Wound Dressing

**Revamil gel**
1. Before applying Revamil gel first clean the wound.
2. (2g) Remove the closing tip from the syringe.
3. (2g) By slowly pressing the plunger of the syringe Revamil wound gel is released from the syringe.
4. Spread a thin layer of Revamil on the secondary wound dressing.
5. Revamil can also be applied directly to the wound and then covered with a secondary dressing.
6. Attach the secondary dressing in the normal way.
7. Depending on the nature of the wound, replace dressing every day or every two days.

5.3 Safety precautions/ contraindications
- Do not use if the packaging/tube/syringe is damaged
- Do not use if the packaging is not sealed tight
- Do not re-sterilize an opened packaging
- Before applying Revamil, wet the wound with 0.9% NaCl.
- Always replace the top on the tube after use.
- Do not allow the tube to come into direct contact with the surface of the wound.
- Use the contents of a tube within 3 months after opening tube.
- Do not treat different patients with the same tube/syringe.
- After removal of the packaging, do not use in case honey is present on the outside of the syringe.
- Empty syringes are disposed.
- Do not allow the syringe to come into direct contact with the surface of the wound.
- Revamil Single Dose provides only one dose per unit.
- Do not reuse an already used dressing. Reuse of a dressing can lead to loss of function of honey, contamination of the product and contamination or infection of the wound
- Do not use if the patient is known to be allergic or hypersensitive to honey
- In case of unexpected side effects after use contact doctor or distributor
- Do not treat a wound for more than 30 days consecutively

5.4 Summary clinical performance

In summary, the clinical performance of Revamil product group is based on the following primary clinical product characteristic:

Managing the micro-environment of the wound.

This micro-environment is created by the main product component, honey:

- In its initial stage honey forms on a protective layer against bacterial ingress (protection against bacteria from outside the wound) over the wound:
  - by means of its physical (osmotic, pH) characteristics
  - by means of a high sugar concentration
- In its second stage honey creates a wound moist environment
  - by means of a high sugar concentration and osmolarity which attracts wound moisture. Wound moisture on its turn facilitates (autolytic) debridement and granulation

The combination of a protective layer and a moist environment provides a micro-environment for a wound which, on its turn, enables the healing process.

With regards to the clinical performance of Revamil, management of wound micro-environment is regarded as the primary (direct) clinical product characteristic.

The wound healing process, which is enabled by the micro-environment is more a secondary (indirect) clinical product performance characteristic. The latter is not claimed for the Revamil product group, however is by Bfactory a relevant indirect parameter in order to evaluate whether or not the micro-environment is in place.

For the evaluation of the clinical performance of Revamil therefore both primary and secondary performance characteristics will be discussed by this document.
6. STRATEGY FOR OBTAINING EVIDENCE FOR CLINICAL SAFETY AND PERFORMANCE OF REVAMIL

6.1 Context of evaluation and choice of clinical data types

All Revamil products are based on 100% pure honey. Products are produced under controlled conditions which guarantees that Revamil does not contain any traces of pesticides and that the same quality can be reproduced consistently. For the description of the manufacturing process and quality control steps reference is made to the Technical File and the underlying Quality Management System according to Annex V.

The applicable Essential Requirements of MDD 93/42/EC and standards are identified in the Essential Requirements Checklist.

Product and process risks are documented in the Risk Management Report.

At the early stage of development several literature and in vitro studies have been performed for selection of the main component: honey. These data provided the first insight into the biological safety and performance aspects of the honey as candidate for further development and resulted into the final product specification. Initially Revamil products were developed based on the honey as only component (e.g. Revamil Single Dose 2g in a syringe and 18g in a tube). As a results of Post Market input the Revamil honey impregnated polyacetate dressings were developed.

Based on that specification the biological safety evaluation of Revamil was performed.

In addition, a literature review was performed according to MEDDEV 2.7.1 and EN ISO 14155 focusing on equivalent products with regard to their clinical safety and performance, in order to justify the need of a clinical investigation and to achieve essential information on the benefits and risks of Revamil.

Since the information gathered in the literature review and in vitro studies allowed to conclude that Revamil performs according to its claims when used and indicated as intended and no unacceptable risks for the patient were foreseen, it was concluded that no extensive clinical investigation was needed but that, parallel to market introduction, the clinical safety and performance should be closely followed up by means of a combination of case studies, collection of Post Market data and trend analysis of complaints.

Results of these studies are summarized in the following sections. Further details are described in the referred documents.

6.2 Literature review

6.2.1 Identification of the data

The literature study was undertaken using standard practice for the systematic review of scientific literature (see for details Attachment 1-4). A number of databases were identified, which were thought to be most suitable for conducting this specific study, including PubMed (Medline), Google and references from literature.

The following keywords were applied alone or in appropriate combinations: honey, wounds, burns, side effects, pain, ulcers, chronic ulcers, burn, oncological, review, pH, osmolarity, moist environment, microbial.
In order to avoid bias, literature with both positive and negative outcomes, in terms of supporting the claim for the Revamil, was sought. Bibliographies of the literature retrieved were also consulted for further relevant references.

The criteria for selecting the literature were:
- Data were required to be the most comprehensive and up-to-date available, and that it should preferably come from recognized, scientific, peer-reviewed journals in the field, and
- Data were gathered from the following sources:
  - Independent review papers
  - Published controlled clinical investigations
  - Reports of significant experience with similar devices
- The articles should clearly describe and evaluate the application of honey on wound management, either by describing case studies, clinical study and/or they should describe the background of its mode of action.

See for details and outcome: Attachment 1-4

6.2.2 Relevance of the data
Due regard has been paid to the extent to which the published data are relevant and applicable to the relevant characteristics of Revamil.

It was acknowledges that different types of honey have different source related compositions, but since the relevant parameters (high concentration of sugars, low pH, high osmolarity) for the evaluation of its clinical performance the different types of honey are regarded similar.

6.3 Evaluators
This clinical evaluation has been conducted and approved (see front page) by members of the Design and Development Team of Revamil product group representative for the following capabilities:
- Device technology
- Risk management
- Biological safety evaluation
- Microbiological safety and performance evaluation
- Clinical evaluation
- Diagnosis and management of the conditions and wounds intended to be treated,

These capabilities were considered relevant as the clinical performance and safety of Revamil product group is directly related to the design of the products, its composition, its initial protective layer function against bacterial ingress, its role in providing a moist environment that facilitates (autolytic) debridement and granulation and the diversity of wounds that fall under Revamil’s intended indications.

NOTE: Personal capabilities records are documented as part of Bfactory’s Human Resource and Critical suppliers/subcontractor files.
7. **CLINICAL BACKGROUND**

7.1 **Clinical background wounds**

In the absence of complicating factors, wound healing of the skin is a rapid and efficient process leading to restoration of barrier function. The process includes three phases: inflammation, proliferation and remodeling, and consists of a variety of single physiological mechanisms. When any of the components of the wound healing process is compromised, healing may be delayed\(^1\)\(^2\). Failure of a wound to heal within the expected time frame usually results in a chronic wound.

Chronic wounds are often associated with an underlying disease such as disturbed venous return in venous leg ulcers, increased mechanical pressures in decubitus, and the nervous, metabolic and/or vascular damage in diabetic foot ulcers\(^3\)\(^4\).

However, there is strong evidence that a chronic wound also fails to heal because the orderly sequence of events is disrupted at one or more of the wound healing stages and that the hostile micro-environment of the wound also plays an important role in that impaired healing process\(^5\).

This hostile micro-environment is for different wound types characterized by similar pathomechanisms including a dry wound surface, unbalanced proteases leading to breakdown of signature growth molecules, high levels of pro-inflammatory mediators, bacterial contamination, cellular damage from reactive oxygen species and tissue ischemia\(^6\)\(^7\)\(^8\)\(^9\).

Also an important factor that changes the micro-environment to the disadvantage of wound healing is colonization of the wound with micro-organisms, followed by bacterial tissue infection. The host’s immune response to the presence of bacteria prolongs inflammation, delays healing and damages tissue\(^10\)\(^11\).

Therefore, preventing the progression from colonization to infection is a major concern in wound care. However, it is acknowledged that most likely a combination of the underlying disease, hostile micro-environment and related disturbed cascade of pathomechanisms compromise a normal healing process of chronic wounds.

7.2 **Current treatments**

Standard treatment of chronic wounds focus on the normalization of the micro-environment which includes, amongst other, wound bed preparation, application of dressings that provides a moist environment to the wound, and infection control. Additional therapies are e.g. compression therapy and treatment with bioactive dressings and skin-substitutes\(^2\)\(^12\). Generally chronic wounds heal slower as healthy wounds and can have a curing period of about 3-15 weeks.

7.3 **Revamil product group**

With the knowledge of the factors that inhibit wound healing as described above Bfactory developed the Revamil product group. The clinical performance of Revamil product group is based on influencing the micro-environment of the wound by the characteristics of the main product component, honey:

- In its initial stage honey forms on a protective layer against bacterial ingress over the wound:
  - by means of its physical (osmotic, pH) characteristics
  - by means of a high sugar concentration
- In its second stage honey creates a wound moist environment
  - by means of a high sugar concentration and osmolarity which attracts wound moisture. Wound moisture on its turn facilitates (autolytic) debridement and granulation

The combination of a protective layer and a moist environment provides a micro-environment for a wound which, on its turn, indirectly enables the healing process.

In section 8 the role the product characteristics in affecting the micro-environment of the wound will be clarified by using information obtained from literature and in vitro tests.

The clinical safety and performance of Revamil was further followed up pro-actively in the Post Market phase by means of a Post Market clinical case study. Parallel, information was gathered about the product use and usability in the clinical field. In addition a trend analysis was performed on data collected so far via the Post Market Surveillance and complaint handling process in order to confirm the clinical performance and safety of Revamil. The combined information was reviewed for unforeseen risks (section 9).

Table 3 provides an overview of the clinical claims and sections that provide supportive evidence for those claims.

**Table 3: Overview clinical claims and clinical data**

<table>
<thead>
<tr>
<th>Claim</th>
<th>Validation summarized in section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Honey manages the micro-environment of the wound</td>
<td>8.1.2.1, 8.2, 9.1</td>
</tr>
<tr>
<td>Honey forms in its initial stage a protective layer over the wound by means of its physical (osmotic, pH) characteristics</td>
<td>8.1.2.2, 8.1.2.3, 8.2, 9.1</td>
</tr>
<tr>
<td>Honey forms in its initial stage a protective layer over the wound by means of a high sugar concentration</td>
<td>8.1.2.3, 8.2, 9.1</td>
</tr>
<tr>
<td>Honey creates in the second stage a wound moist environment by means of a high sugar concentration and osmolarity that attracts wound moisture. Wound moisture on its turn enables (autolytic) debridement and granulation</td>
<td>8.1.2.3, 9.1</td>
</tr>
<tr>
<td>Suitable for bed sores, different kinds of ulcers, infected wounds, acute wounds, surgery and radiation induced oncological wounds, minor (1st- and 2nd degree) burns</td>
<td>9.1, 9.1.7, 9.2</td>
</tr>
<tr>
<td>Safe for its intended use and indication</td>
<td>9.1.6.5, 9.2, 10</td>
</tr>
</tbody>
</table>

### 8. EVALUATION CLINICAL PERFORMANCE RESULTS OF REVAMIL

#### 8.1 Literature review

#### 8.1.1 Equivalent products

For the evaluation of the clinical safety and performance of Revamil product group literature data from equivalent marketed devices was collected and evaluated. For the selection of equivalent products the following characteristics were regarded relevant for the determination of “equivalency”:

- Design/composition
- Indication
- Application/intended use
- Claims/mode of action
In table 4 an overview is provided of the Revamil products and their characteristics.

**Design/composition**
With regards to the design and composition, products could be distinguished based on pure honey, delivered by a syringe or tube, and honey impregnated dressings. For all these products honey is claimed to be the component that is responsible for the clinical performance so for the clinical evaluation Bfactory concentrated on data of the safety and performance of this honey component.

**Indication**
All products are indicated for similar types of wounds and the indication for Revamil falls within the equivalent product indicated wound range: Bed sores, different kinds of ulcers, infected wounds, acute wounds, surgery and radiation induced oncological wounds, minor (1rst- and 2nd degree) burns.

**Application/intended use**
It is acknowledged that for these products the way of application of honey differs, however, this is regarded as not critical for the safety and clinical performance comparison of these products; the application and use of pure honey (from a syringe or tube) as applied by/covered by a secondary dressing to keep the honey in place and mechanically protected from the environment is regarded equivalent to the application of honey by means of impregnated Polyacetate dressings, where the function of this dressing is similar.

All products are aimed for repeated use (new application every 1-3d, depending on the wound exudate). Revamil is aimed to be used for a total of less than 30 days whereas all other products are also aimed for longer periods. For Revamil this limitation was introduced during its market introduction due to the lack of market experience with the product. (see section 9 for further discussion).

**Claims/mode of action**
The claims for Revamil product group (honey provides protective layer by means of low pH and high osmolarity and sugar concentration against bacterial growth and infection, high sugar contents provides moist environment which on its turn facilitates (autolytic) debridement and granulation) falls within the claims as indicated for the equivalent products. It is acknowledged that for some equivalent products additional claims are made (e.g. effective against more than 200 clinical strains including MRSA, MSSA, VRE, etc, promoting growth, anti-inflammatory, reducing formation of scar tissue). Such claims are not made for Revamil since Bfactory has the opinion that scientific evidence is not sufficient for such claims, specifically with regards to the presence of certain components (See 8.2.1). According to Bfactory the combination of a protective layer against bacterial ingress (protection against bacteria from outside the wound) and a moist environment provides a micro-environment for a wound which, on its turn, indirectly enables the healing process. Therefore also literature data of equivalent products have been taken into consideration that evaluates wound healing.

As honey is considered the most relevant component for the clinical performance of Revamil product group in addition to the above mentioned equivalent products also fundamental scientific studies with pure honey were taken into account for the evaluation.
### Table 4: Revamil products

<table>
<thead>
<tr>
<th>Product</th>
<th>Design/Composition</th>
<th>Indication</th>
<th>Intended use</th>
<th>Claims</th>
</tr>
</thead>
</table>
| Revamil gel              | Controlled Bfactory honey pH 3.5 Honey gel in syringe | - Bed sores  
- Different kinds of ulcers  
- Infected wounds,  
- Acute wounds,  
- Surgery and radiation induced oncological wounds  
- Minor (1st- and 2nd degree) burns | - Repeated use  
- Replace each 1-2d  
- Max. 30d in total | - Honey forms initially a protective layer over the wound by means of:  
  o a physical (osmotic, pH) barrier  
  o a high sugar concentration  
- Honey creates a wound moist environment by means of a high sugar concentration and osmolarity that attracts wound moisture. Wound moisture on its turn facilitates (autolytic) debridement and granulation |
| Revamil Wound Dressing   | Controlled Bfactory honey pH 3.5 Polyacetate impregnated dressing | - Bed sores  
- Different kinds of ulcers  
- Infected wounds,  
- Acute wounds,  
- Surgery and radiation induced oncological wounds  
- Minor (1st- and 2nd degree) burns | - Repeated use  
- Replace each 1-3d  
- Max. 30d in total | idem                                                                                                                                                                                                       |
8.1.2 Revamil product group

For Revamil product group it is claimed that in its initial stage it provides a physical barrier against bacterial ingress of bacteria by means of:
- Low pH
- High osmolarity
- High sugar concentration

Further it is claimed that in the second stage by the high sugar concentration and osmolarity of honey it attracts wound moisture. Wound moisture on its turn facilitates (autolytic) debridement and granulation.

In the following subsections this is clarified in more detail.

8.1.2.1 Honey for wound treatment

Since the ancient Egypt honey has been used for the treatment of chronic wounds. For the last ten years a renewed interest for the use of honey in wound healing has arisen and honey has been rediscovered by the medical profession13 14 15 16 17 18 19 20.

Research to support the clinical wound treatment characteristics has mainly been focused on honey's antibacterial properties. Many of these publications describe honey to rapidly clear infection of wounds with no adverse effects. Using concentrations of honey ranging from 1.8% to 11% (v/v) researches have achieved complete inhibition of the major wound-infecting species of bacteria. The antibacterial activity of honey has also been shown in vivo, with reports of infected wounds dressed with honey becoming sterile in 3-10 days21 22 23 24 25 26.

The antibacterial activity of honey has been attributed to the local high osmolarity and the acidity. The high osmolarity of honey inhibits the microbial growth, because it ‘ties up’ water molecules so that bacteria have insufficient water to support their growth. The antibacterial potency is reflected in the sensitivity results reports for wound-infecting species of bacteria21,25,26.

It has been reported that certain types of honey stop bacteria from growing, even strains such as MRSA (multi-resistant Staphylococcus aureus) being resistant to ‘last resort’ antibiotics such as vancomycin27.

Biofilms formed by Pseudomonas aeruginosa and Staphylococcus aureus have been shown to be an important factor in the pathophysiology of chronic rhinosinusitis. In an in vitro biofilm model Sidr and Manuka honeys showed to be effective in killing biofilms of these bacteria with a bacteriocidal rate up to 90%.28

In addition, the renewed interest in honey as a wound dressing has prompted research groups to try to decipher the role of different honey components in wound healing14 29 30.

Based on a thorough review of findings, Bfactory concluded that the proposed mechanism of action of additional honey compounds is speculative and not evidence-based31.

Therefore Bfactory states that the first characteristic of honey relevant for wound treatment shall be attributes to its barrier function against bacterial ingress during its initial phase after application. This barrier function is based on its high osmolarity, its high sugar concentration and low pH.

Further Bfactory states that the second characteristic of honey relevant for wound treatment shall be attributes to its ability to create a moist environment during its second phase after application. Wound moisture is attracted by the high sugar concentration and osmolarity of honey. Wound moisture on its turn facilitates (autolytic) debridement and granulation.
8.1.2.2 Low pH

Schneider et al. published a review article specifically evaluating the role of pH on wound healing\(^{32}\). Under normal circumstances an acidic milieu is found on the skin surface. This acidic milieu varies depending on the anatomical location and age of the person between a pH of 4–6; The superficial layers of the skin are naturally acidic which results from lactic acid in sweat and produced by skin bacteria. This naturally pH has always been seen as an important aspect of the skin’s barrier function. At this pH mutualistic flora such as Staphylococci, Micrococci, Corynebacterium and Propionibacteria grow but not transient (pathogenic) bacteria such as Gram negative bacteria like Escherichia and Pseudomonas or Gram positive ones such as Staphylococcus aureus or Candida albicans\(^{33,34}\).

Recently, Kwakman et al. (2010) investigated the effect of pH of Revamil honey on the killing of Bacillus subtilis\(^ {35,36} \). To assess the effect of pH on the survival of micro-organisms in honey, different dilutions (0-40%) of Revamil honey were titrated with NaOH to neutralize the pH to 7.0. Bacillus subtilis bacteria were added (10^7/ml), and after 24 hrs the numbers of surviving bacteria were determined. It was shown that neutralization of the pH from 3.5 to 7.0 reduced the bactericidal activity to that of honey-equivalent sugar solutions. The same experiment showed that a 40% (honey-equivalent) sugar solution is able to reduce the number of viable bacteria from 10^7 to 10^2/ml in 24hrs. From these experiments it can be concluded that a low pH (3.5) contributes substantially to the bactericidal effect in vitro of Bfactory honey. In addition, these experiments substantiate the role of the bactericidal effect of a high sugar concentration, in the range of 40-100% sugar.

The skin’s acidic milieu is disturbed in wounds; the pH of wounds that are contaminated by bacteria tends to shift towards an acidic milieu\(^{37}\). Chronic wound showed a more alkaline milieu, accept during wound healing of e.g. leg ulcers and pressure sores where a shift was observed towards a more acidic milieu again\(^ {32,37}\). Unless the fact that it is not clear at this stage if this shift towards an acidic milieu is part of the natural defense mechanism of the tissue or a consequence of the infection induced or wound healing related molecular cascades, it is believed by Bfactory that the addition of a topical natural acidic milieu on the wounded skin can help to “replace” on a temporary basis the acid barrier function of the skin and can provide a protective layer against (additional) bacterial ingress of pathogenic bacteria.

An interventional clinical study supported this view by showing that topical application of acidic ointments in diabetics and stroke patients significantly reduced their bacterial load on the skin surface\(^ {38}\).

Gethin summarized the results of several studies in which 1-5% acidic acid was used on acute and chronic wound by soaking to eradicate Pseudomonas aeruginosa. In principle acidic acid appeared to be effective however, the limitations of using acetic acid soaks were the short duration of effect, the lack of poly-antimicrobial effect and additional concerns regarding quality and safety\(^ {39}\). This limitation of its effectiveness is likely to be related to the fact that the treatment (soaking) is at a topical/surface level and the infection is at (lower layer) tissue level, by which wound does not maintain acidity for periods longer than about one hour and therefore soaks would require frequent replacement\(^ {40}\).

As Revamil contains pure honey with a pH of 3.5 and it is indicated by above literature that such low pH will reduce the growth of pathogenic bacteria Bfactory states that Revamil product group is able to create a protective barrier against bacterial ingress from outside, particular in the first phase after application (the phase in which the pure honey is not diluted yet by wound exudate by which the acid pH might be neutralized). Since Revamil is intended to be removed each day in case of exuding wounds and each 2-3days for dry wounds it is believed that this protective barrier can be maintained. As indicated above this barrier mechanism is not only due to the pH but will likely be a combined mechanism based on the osmotic characteristics of honey as well (see section 8.1.2.3).
The assumption that honey provides a protective barrier is supported by the clinical data described in section 9.1 of this report in which Revamil treated ulcers did not show additional or increased wound microbial contamination during their treatment period.

Based on this role of the low pH in honey for the treatment of chronic (contaminated) wounds, various wound care products have been developed and placed on the market during the last decade: Medihoney, Meldra and Honeysoft claim (a part of) their functionality to be dependent on the acidity of honey. As Revamil is a honey based product for which its pH is within the same low range as for these equivalent products (see table 4) it is stated by Bfactory that for Revamil a similar antimicrobial protection can be claimed in its function as temporary protective barrier against bacterial ingress.

8.1.2.3 High osmolarity, high sugar concentration and moist environment

An important function of sugar in the treatment of infected wounds is to create an environment of low water activity or water vapour pressure (aw) which inhibits or stresses bacterial growth\(^{41,42}\). A low aw means a high osmotic pressure (\(\pi\)) since both are thermodynamically related according to the equation \(\pi = (RT/V) \times \log (1/aw)\), where V is the partial molal volume of water. In this way, a solution of low aw has high osmotic pressure. Bacteria, like all other forms of life, require water for growth and these water requirements are best defined in terms of water activity or water vapour pressure (aw) of the substrate. When the aqueous solutions in the environment of the microorganism are concentrated by the addition of a solute such as sugar (sucrose), the consequences for microbial growth result mainly (although not only) from the change in aw. At present, numerous data are available on the relationship between aw and the ability of microorganisms to grow, and it has been reported that every microorganism has a limiting aw below which it will not grow\(^{41,42,43,44}\). Of the whole range of bacteria that infect human skin, subcutaneous tissues, and mucous membranes, the lowest aw is tolerated by S. aureus, which can proliferate with an aw as low as 0.86\(^{41,42}\).

Undiluted honey contains high levels of sugars (80-85%wt/vol) and has an extreme low aw-value (between 0.45-0.70) which is much lower than that of bacteria, fungi and moulds. When these organisms are exposed to such environment they will be inhibited. In order to evaluate the use of sugar for the treatment of infected wounds Chirife investigated in in vitro experiments the bacterial growth inhibition of bacteria relevant for wound infection, such as Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, and Staphylococcus aureus. Studies showed that solutions of appropriate sugar concentration incubated at pH 7.0 and 35°C were lethal to the bacterial species studied. On the basis of these results, it is proposed that an important function of sugar in the treatment of infected wounds is to create an environment of low water activity (aw), which inhibits or stresses bacterial growth. These finding were supported by recent studies performed by Kwakman who showed that a 40% (honey-equivalent) sugar solution is able to reduce the number of viable bacteria substantially in 24hrs. which substantiates the role of the bactericidal effect of a high sugar concentration in honey in the range of 40-100% sugar (see section 8.1.2.2).

It was however acknowledged that, when wounds are treated repetitively with sugar or sugar containing products (like the honey in Revamil and Revamil wound dressing) the actual sugar concentration (or aw) on a wound is not constant but will change as a) liquid released by the tissues will cause local dilution which increases the aw and b) removal of the diluted sugar (or honey/honey wound dressing including the exudate) and replacement by fresh concentrate of sugar (honey/honey wound dressing) will locally decrease the aw. At the beginning of every treatment, the sugar concentration should be high, approaching saturation, which for body temperature is about 225 g/100 g water and corresponds to aw about 0.83. Than water activity is progressively raised owing to the uptake of water from the surrounding tissues until more sugar is again placed in the wound and the aw drops to a low value again. In this way, bacteria at the device-wound surface interface bacteria are subjected to a series of osmotic shocks owing to the continuous change of aw of the...
environment; It is known that abrupt changes in the water activity of bacterial cultures cause injury and death, even without going beyond the conditions which are suitable for growth. Therefore it is believed that although conditions of the sugar-treated wound are such that the limiting $a_w$ for growth is temporarily surpassed, bacteria on top of the wound surface will be stressed by the repeated osmotic shock and highly likely slowed down or even inhibited in their growth.

As Revamil contains pure honey and by means of the above described mechanism BFactory believes that Revamil product group is able to create a protective barrier against bacterial ingress from outside, in particular the first phase after application (the phase in which the pure honey is not diluted yet by wound exudate). Since Revamil is intended to be removed each day in case of exuding wounds and each 2-3 days for dry wounds it is believed that this protective barrier can be maintained. Further at the device-wound surface interface remaining bacteria after device change undergo osmotic stress by which, at least temporarily, these bacteria are reduced in their growth and activity by which less ingress can be expected during that time period.

This assumption is supported by the clinical data described in section 9.1 of this report in which Revamil treated ulcers did not show additional or increased wound microbial contamination during their treatment period.

As mentioned, when used as wound contact layer, dilution by wound exudate eventually results in loss of osmotic antibacterial activity. In contrary due to its high sugar contents and therefore high osmolarity, honey also creates a moist environment by drawing exudate to the wound surface which serves another process:

Chronic wounds are often characterized by the presence of necrotic tissue and slough. Under normal conditions, dead tissue in a wound will separate spontaneously from the healthy tissue beneath. This occurs as a result of autolysis and presumably involves macrophage activity and the action of proteolytic enzymes which act at the interface of the necrotic and healthy tissue. A dry micro-environment prevents the autolytic and proteolytic actions of macrophages and enzymes, impairing wound healing. A moist wound environment promotes this autolytic debridement and facilitates granulation.

By this a non-adherent layer between the dressing and the wound bed is realized which finally also facilitates dressing changes. The ability of Revamil to create a moist creating environment, facilitating (autolytic) debridement and granulation, was supported by the clinical data described in section 9.1 of this report in which Revamil treated ulcers showed clear cleansing, granulation tissue formation and wound closure during treatment.

Based on these roles of honey for the treatment of chronic (contaminated) wounds, various wound care products have been developed and placed on the market during the last decade: Medihoney, Meldra and Honeysoft claim (a part of) their functionality to be dependent on the osmolarity of honey, antimicrobial activity, ability to create a moist environment, by which the cleansing and debridement is eased and by which wound healing is facilitated (see table 4). As Revamil is a honey based product for which its sugar contents in the honey is similar as for these equivalent products, is stated by BFactory that for Revamil the function of a) a protective barrier against bacterial ingress during its initial stage after application, and b) creating a moist creating environment, facilitating (autolytic) debridement and granulation, can be claimed.

8.2 In vitro performance studies

8.2.1 Bacterial challenge test

To investigate to what extend the honey used in the Revamil product group is suitable to reduce bacterial growth a test model was used according to the European Pharmacopoeia section 5.1.3 Efficacy of Antimicrobial Preservation. In this test model a product is
contaminated with a certain amount of viable microorganisms (bacteria, yeast and mould) and monitored how the product is able to reduce the number of viable microorganisms. A concentration range of 100%, 25% and 10% honey, both irradiated and non-irradiated, was contaminated with a certain amount of various bacteria types (P.aeruginosa, S.aureus, E.faecalis, Z.rouxil) and after 24h and 48h the log reduction was measured. Results showed that within already 48h for all concentrations a log reduction of >3.0 was measured.

From these results it can be concluded that the honey used in Revamil products is suitable to reduce bacterial growth and that it is highly likely that, even after dilution with wound exudate the honey still has the capability to reduce bacterial growth.

Further it could be concluded that irradiation of honey did not influence its antimicrobial activity. This is in alignment with the conclusion found in literature that gamma sterilisation is accepted to be the best method to sterilize honey and reducing the risk of contamination sufficiently, without deterioration of the desired properties for medical use\textsuperscript{49 50}.

This study in addition supported the claim that Revamil (containing 100% honey) is able to function as a protective barrier against bacterial ingress during its initial stage after application.

8.2.2 Antimicrobial activity: comparison with equivalent products

In order to evaluate the antimicrobial activity of Revamil product group and to compare results with marketed devices a challenge test was performed with Revamil (honey), Mesitran and Honeysoft wound dressing\textsuperscript{51}. A 20% concentration of each product was inoculated with a defined amount of microorganisms (S. aureus, P. aeruginosa). The antimicrobial activity was determined in a time range of 2, 5-7, 24, 48 and 144h. As a guideline the antimicrobial activity was defined according to the criteria used by the European Pharmacopoeia:

- not less than 2.0 log reduction from the initial count at 2 days
- not less than 3.0 log reduction from the initial count at 7 days
- no increase from the initial count at 28d

In this study a more than 1.0 log reduction (90% of the added micro-organisms is non-viable) is defined as anti-microbial activity.

Results showed that both for Revamil as Honeysoft wound dressing a reduction to undetectable levels for S. aureus, P. aeruginosa was obtained during the test period. Mesitran met only the requirements of the test for S.aureus and a contamination with B. subtilis was discovered, highly likely originating from the product itself.

Overall it could be concluded that Revamil and Honeysoft outperformed Mesitran and that there was no significant difference in the antimicrobial activity between Revamil and Honeysoft.

8.3 Conclusion

From the literature review and comparison with equivalent products it can be concluded that Revamil product group has an equivalent composition and has equivalent claims as the equivalent products: “the product contains honey with a high osmolarity/high sugar concentration and low pH and it acts as a protective barrier against bacterial ingress by the low pH and high osmolarity/high sugar concentration of the honey component.

By its high sugar concentration it prevents the growth of bacteria and therefore a layer of Revamil (containing pure honey) on the wound is able to protect the wound from bacteria ingress from outside the wound during the initial period after application. This conclusion was confirmed by literature data and the in vitro tests in which Revamil products containing 100% honey proved to be suitable to reduce bacterial growth. Further it is highly likely that,
even after dilution with wound exudate the honey still has the capability to reduce bacterial growth at the device-wound surface interface since local bacteria will be subjected to a series of osmotic shocks due to the dressing changes. In an in vitro comparison study it was shown that there was no significant difference in the antimicrobial activity between Revamil and Honeysoft.

Further it can be concluded from the literature review and comparison with equivalent products that due to the high sugar concentration (osmolarity) of the honey Revamil creates a wound moist environment which facilitates (autolytic) debridement and granulation.

Based on these results it could be overall concluded that Revamil product group performs as indicated by the instructions for use and that no extensive clinical investigation is needed. To further follow up the clinical performance, safety and usability of Revamil product group and to collect a broader market experience during use in various wound types and populations Bfactory decided to perform a Post Market case study and collect pro-actively clinical safety and performance data by Post Market Surveillance.

9. POST MARKET CASE STUDY, SURVEILLANCE AND COMPLAINTS TREND ANALYSIS

9.1 Case study

With regards to the clinical performance of Revamil management of wound micro-environment is regarded as the primary (direct) clinical product characteristic.

The wound healing process, which is enabled by the “corrected” micro-environment is more a secondary (indirect) clinical product performance characteristic. The latter is not claimed for the Revamil product group, however is by Bfactory a relevant indirect parameter in order to evaluate whether or not the micro-environment of chronic wounds is “managed” (changed) to such extend that wound healing can take place.

9.1.1 Introduction

Starting from 2004 a specialised wound department was initiated at Bronovo hospital at The Hague. Patients from surrounding regions are referred to this department to be treated for long-term existing wounds that did not show a tendency for healing. The aetiology of the wounds is often multifactorial. Many of the patients show extensive co-morbidity like diabetes mellitus, venous insufficiency, high blood pressure, low resistance etc. From February 2005 until August 2005 fifty seven (57) patients were treated with Revamil Single Dose honey. Treatments were carried out by wound care specialist O. Groenhart, who has long-standing experience with the application of honey on chronic wounds, especially with Revamil.

9.1.2 Revamil representative product

The study was initiated at the time that only the "gel" versions of the Revamil product group were developed. However, the results are regarded as representative for the whole Revamil product group (including the impregnated dressings) because honey is the main component responsible for the clinical performance. This presumption has been confirmed at a later stage by the Post Market data of the Revamil dressings. The safety aspects of the dressing have been evaluated in the Biological safety evaluation and were also confirmed by the Post Market data (see section 9.2 and 10).
9.1.3 **Representative patient target group**

The common characteristic of the patient population is the presence of very difficult to heal ulcer at the lower leg region and feet, of different aetiology. The chronic venous leg ulcer was chosen as a model indication to demonstrate efficacy in chronic wounds. The results were expected to be applicable to other indicated chronic wounds such as pressure ulcer and diabetic ulcer because there is strong evidence that in the chronic phase of these impaired healing conditions the hostile microenvironment is characterized by similar pathomechanisms including unbalanced proteases leading to breakdown of signature growth molecules, high levels of pro-inflammatory mediators, bacterial contamination, cellular damage from reactive oxygen species and tissue ischemia\(^6\)\(^-\)\(^8\). Furthermore, it is conceivable that large burn wounds grade 2, which might require several weeks before closure by secondary intent suffer from similar pathomechanisms\(^9\).

9.1.4 **Objective**

The objective of the clinical case study was the assessment of the safety and performance of Revamil honey gel for wound healing of ulcers of different aetiology.

9.1.5 **Study design**

9.1.5.1 **Study site**

Patients that were treated at Bronovo Wound Department (The Hague, the Netherlands) were included in the survey. The study was carried out from February 2005 to August 2005 at Bronovo hospital by wound care specialist O. Groenhart, under supervision of Dr. Smeets (surgeon).

9.1.5.2 **Patient population included**

The common characteristic of the patient population is the presence of very difficult to heal wounds, mainly at the lower leg region and feet, of different aetiology. Typical wounds existed for 3 to 6 months and showed no tendency for healing.

**Wound classification**

Before treatment with Revamil was started wounds were classified according to Wagner\(^52\) (see table 5). This classification is based on the assessment of the depth of the wound, presence of wound infection, presence of necrotic tissue. The classification was originally applied to classify diabetic ulcers, however, at Bronovo this classification was applied to specify the severity of wounds of different etiologies. In this study the etiology of the wounds was not assessed, although co-morbidity like diabetes mellitus was recorded. Based on the Wagner classification, the following wound types and characteristics were distinguished (Table 5).

<table>
<thead>
<tr>
<th>Wound Type</th>
<th>Wound Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Closed ulcer*</td>
</tr>
<tr>
<td>1</td>
<td>Superficial ulcer, no granulation, no infection</td>
</tr>
<tr>
<td>2</td>
<td>Deep ulcer, with involvement of e.g. ligaments, tendons</td>
</tr>
<tr>
<td>3</td>
<td>Deep ulcer, infected (e.g. abscesses, osteomyelitis, joint sepsis)</td>
</tr>
<tr>
<td>4</td>
<td>Deep ulcer, infected, tissue gangrene (necrosis)</td>
</tr>
<tr>
<td>5</td>
<td>Extensive gangrene</td>
</tr>
</tbody>
</table>

Table 5: Wounds classified according to Wagner.
*For the purpose of this study included WT0 wounds means: Wounds that initially had an intact skin but needed abrasion to “open” the skin in order to relieve entrapped infection.

In addition the following wound parameters were documented (see for details case study files):
- Wound depth, length, width (measured with ruler in mm)
- Percentage of wound yellow/red/black (observation by experience)
- Wound odor (0=no, 1=rotting, 3=sickly smell)
- Exudate (0=no, 1=very few, 2=few, 3=much, 4=very much)
- Wound edge (0=vital, 1=necrotic, 2=softened, 3=irritated)

Other characteristics recorded were e.g. (see for details case study files):
- Age
- Gender
- Type of treatment before start and during treatment with Revamil
- Duration of existence of wound before start treatment with Revamil
- Co-morbidity
- Location of the wound
- Pain before treatment (0=no pain, 1=light pain, 2=moderate pain, 3=severer pain)

9.1.5.3 Wound treatment

The secondary dressing of wounds treated with Revamil gel were replaced every day, or every two days, depending on the amount of exudate. The duration of treatment was intended to be according to the Instructions for use:<30 days.

When practically feasible, wound were observed each week for the performance variables as described above

9.1.5.4 Performance variables

The following performance variables were recorded to assess the clinical performance of Revamil:
- Number of days elapsed after start treatment with Revamil that the wound becomes clean (no necrosis, no slough)
- Number of days elapsed after start treatment with Revamil before the start of granulation is observed (visual observation by experience)
- Number of days elapsed after start treatment with Revamil before wound closure is achieved (granulation has overgrown the wound and the epithelial layer is closed, (visual observation by experience)

The following performance variables were recorded to assess the clinical safety of Revamil:
- Side effects (pain, burning sensation, itching, oedema, infection, allergic reaction or any other adverse reaction that occurred).
- Pain related to treatment with Revamil (0: no pain, 1: light pain, 2: moderate pain, 3: severe pain, 4: treatment stopped because of severe pain).

9.1.6 Results

For detailed results of the case study reference is made to the case study file. Below a summary of results is presented.

9.1.6.1 Patient population characteristics

In total 57 patients were included in the evaluation. Thirty eight percent (38%) of the patients were still under treatment when the survey ended and follow-up was not registered after study finalization.
The average age of patients in this study is very high (see figure 1): Almost 90% of the patients is older than 60 years while 45% of the patients is even older than 80 years.

**Figure 1.** Patient age distribution

40% Of the patients suffer from Diabetes mellitus, 41% suffer from venous insufficiency, while 14% suffered from neuropathy, see Figure 2.

**Figure 2: Comorbidity patients**
9.1.6.2 Wound location and treatment

Wounds treated were mainly localised at the lower extremities (Figure 3).

![Localization of the wounds](image)

**Figure 3:** Localization of the wounds

During the evaluation of data it was observed that Revamil has not been used as intended (and clearly documented in the Instruction for Use) for a maximum period of 30 days but for a longer time period: 1-30 weeks, with an average of 8 weeks uninterrupted. After communication with the clinicians it became clear that in the wound treatment field wound treatment devices (including honey containing devices) and therapies are continued for longer periods of time than 30 days in cases chronic wounds respond positive on the treatment and start to heal, and particular when they had failed to heal in the past with other treatments. In those cases where no safety hazards are expected (e.g. which could be the case particularly for systemic treatments, which is not the case for Revamil), it was then decided by the wound care specialist to continue in order not to interrupt the healing process.

9.1.6.3 Performance wound cleaning

During the assessment period wound cleaning was evaluated for 43 wounds. Depending on the wound type, the average time elapsed before wounds to become clean is 2-8 weeks (Figure 4). Superficial ulcers (Wound types WT 1) became clean within 3 weeks after the start with Revamil, while for infected and necrotic ulcers (Wound type WT 2, 3, 4) the average time for wounds to become clean was 5-8 weeks. During the assessment period of 6 months 74% of the wounds became clean. Reasons why wounds did not become clean were: Infection originates from internal infection (N=1), wound does not respond to Revamil (N=2), treatment stopped before wound was clean (patient died (N=1), patient was hospitalized (N=1), one patient stopped treatment (N=1), treatment initiated at end of assessment period (N=5). During the follow up periods, there was no report of an additional or increase of wound microbial contamination/wound infection related to the application of Revamil.
9.1.6.3 Performance granulation

During the assessment period granulation formation was evaluated for 42 wounds. Depending on the wound type, the average time elapsed before granulation starts is 2-8 weeks (Figure 5). As for wound cleaning, granulation starts earlier in superficial ulcers (2-3 weeks), than for infected and necrotic ulcers (6-8 weeks). Sixty five (65%) percent of the wounds showed healthy granulation tissue during the evaluation period. In wounds that did not become clean during the evaluation period, no granulation tissue formed.

Figure 4: The effect of treatment with Revamil on wound cleaning

Figure 5: The effect of treatment with Revamil on the start of granulation
9.1.6.4 Performance wound closure

During the assessment period wound closure was evaluated for 29 wounds. During the evaluation period 47% of the wounds had healed to closure. Superficial wounds (WT1) closed after on average 5 weeks, while more severe wounds (WT2-4) healed after on average 8-12 weeks. Reasons why wounds did not close during the treatment period were:
- Treatment was not ended yet (N=21)
- Treatment stopped because of stinging sensation (N=2)
- Long-term wounds that also under other treatments did not show a tendency to heal (N=2)
- Overall weak condition patient (e.g. >91 of age, comorbidity) (N=1)
- Wound infection that originated from other sources, osteosynthesis (N=1)
- Ill treatment of wound at home or during hospitalization (N=2)
- Patient did not return for treatment to hospital (N=1)

Mean time (wks) elapsed before wounds close

Figure 6: The effect of treatment with Revamil on wound closure

9.1.6.5 Side effects

Before the treatment with Revamil started, 27 patients (47%) experienced light to severe wound pain. After treatment with Revamil only 9 patients (16%) experienced light to severe wound pain. Two patients experienced severe pain after treatment with Revamil and the treatment was stopped. These patients already experienced moderate pain before the treatment with Revamil was initiated. No itching or allergic reactions or other side effects have been observed after application of Revamil.
9.1.7 Summary of the clinical data and appraisal

Data obtained by the case study with Revamil were compared with clinical investigation and case study data of honey based wound treatment found in literature. A summary of results is presented in table 7 and sections 9.1.6.1 to 9.1.6.4.

For the interpretation of results is shall be obvious that detailed values and figures can not be compared one to one since the case study and the studies described in literature have not been performed by using exactly the same study set up (e.g. follow up period, inclusion/exclusion criteria, parameter scoring method, amount of included patients, wound types). For example: The Revamil case studies combined the parameters of “granulation” with “reduction of ulcer size” for comparison, because in practice reduction of ulcer size initiates when granulation starts. An overview is given in the Table 6 below.

Table 6. Comparison parameters performance case series and literature

<table>
<thead>
<tr>
<th>Performance</th>
<th>Revamil case series</th>
<th>Equivalent products literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction ulcer size/ granulation tissue</td>
<td>65%</td>
<td>55,5</td>
</tr>
<tr>
<td>Wound closure</td>
<td>47%</td>
<td>52%</td>
</tr>
<tr>
<td>Side effects</td>
<td>3,5%</td>
<td>2-6%</td>
</tr>
</tbody>
</table>

This comparison is only meant to asses if safety and performance trends observed for Revamil and other honey based treatments are equivalent.

Figure 7: The effect of Revamil on pain sensation
Table 7: Overview of clinical case data and data obtained from literature

* WT1-4 are wounds classified according to Wagner, see section 9.1.4.2

<table>
<thead>
<tr>
<th>Post market surveillance case series 57 patients</th>
<th>Literature data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wound cleaning</strong></td>
<td><strong>Chronic ulcers of different types</strong> (N=130)</td>
</tr>
<tr>
<td>Closed ulcers (WT0) Superficial ulcer, no granulation, no infection (WT1)* (N=15)</td>
<td>No data</td>
</tr>
<tr>
<td>Deep ulcer, with involvement of e.g. ligaments, tendons (WT2) (N=19)</td>
<td>73% (11 of 15 wounds)</td>
</tr>
<tr>
<td>Deep ulcer, infected (e.g. abcesses, osteomyelitis, joint sepsis) (WT3) (N=14)</td>
<td>71% (10 of 14 wounds)</td>
</tr>
<tr>
<td>Deep ulcer, infected, necrosis (WT4) (N=9)</td>
<td>67% (6 of 9 wounds)</td>
</tr>
<tr>
<td><strong>Start granulation</strong></td>
<td></td>
</tr>
<tr>
<td>Closed ulcers (WT0) Superficial ulcer, no granulation, no infection (WT1)* (N=15)</td>
<td>Pain (3.5%) (2 of 57 patients)</td>
</tr>
<tr>
<td>Deep ulcer, with involvement of e.g. ligaments, tendons (WT2) (N=19)</td>
<td></td>
</tr>
<tr>
<td>Deep ulcer, infected (e.g. abcesses, osteomyelitis, joint sepsis) (WT3) (N=14)</td>
<td></td>
</tr>
<tr>
<td>Deep ulcer, infected, necrosis (WT4) (N=9)</td>
<td></td>
</tr>
<tr>
<td><strong>Wound closure</strong></td>
<td></td>
</tr>
<tr>
<td>Closed ulcers (WT0) Superficial ulcer, no granulation, no infection (WT1)* (N=15)</td>
<td>60% (9 of 15 wounds)</td>
</tr>
<tr>
<td>Deep ulcer, with involvement of e.g. ligaments, tendons (WT2) (N=19)</td>
<td>42% (8 of 19 wounds)</td>
</tr>
<tr>
<td>Deep ulcer, infected (e.g. abcesses, osteomyelitis, joint sepsis) (WT3) (N=14)</td>
<td>57% (8 of 14 wounds)</td>
</tr>
<tr>
<td>Deep ulcer, infected, necrosis (WT4) (N=9)</td>
<td>33% (3 of 9 wounds)</td>
</tr>
<tr>
<td><strong>Device-related side effects</strong></td>
<td></td>
</tr>
<tr>
<td>Pain (3.5%) (2 of 57 patients)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Device-related serious events (infection, death)</strong></td>
<td>0</td>
</tr>
</tbody>
</table>
9.1.7.1 Literature survey ulcers

For a detailed report of this search, see Attachment 3.

Summary
Totally were included 130 patients. 90 Patients were included in randomized clinical trials (chronic leg ulcers and pressure ulcers). 55,5% (N=50) of the wounds treated showed reduction of ulcer size, 52% (N=47) of the wounds healed to closure. In both trials honey treatments showed better healing compared to control treatment. In a case series with 40 patients honey treatment showed progressive healing and high patient satisfaction.

Conclusion
From the literature data assessed it can be concluded that honey is effective and safe in the treatment of chronic leg ulcers and pressure ulcers. Treatment with honey scores high in patient satisfaction; less pain, less malodor.

9.1.7.2 Literature survey oncologic wounds

For a detailed report of this search, see Attachment 1.

Summary
Totally were included 170 patients. In the different studies, different honey types were applied. The overall effects of treatment with honey is rapid clearance of infection and improved wound healing. For patients after breast surgery, followed by radiation, treatment with honey resulted in a marked reduction of total treatment period. It shall be noted however that for treatment with a combination of PTX and honey, the effect of PTX alone is already beneficial. PTX plus honey provided shorter treatment duration, however this was not considered sufficient to substantiate effectiveness in radiation induced burns by honey alone.

All 12 oncologic wounds after vulva surgery that were treated with honey healed to closure. Candida infection was reported near the wound side in 3 patients which might be the result of the presence of diluted honey in that area. Most probably the reduced effectiveness of honey was due to the fact that yeasts are less susceptible to the antimicrobial activity of honey especially in cases where the honey is diluted. The Candida infections rapidly responded to treatment with nystatin cream. Some over-granulation was reported in 1 wound.

Conclusion
From the literature data assessed it can be concluded that honey is effective and safe in the treatment of oncologic wounds and after surgery. Treatment of radiation-induced burns however was not sufficiently substantiated.

9.1.7.3 Literature survey burn wounds

For a detailed report of this search, see Attachment 2.

Summary
Totally were included 635 patients. Different honey types were applied in the different studies, e.g. local honey, acacia honey, commercial Langnese honey, Tualang honey. Several studies show that honey in the treatment of superficial and partial thickness burn wounds is superior to other treatments, e.g. compared to standard treatment with SSD (p< 0,001). Superiority concerns reduced healing time and fewer infections at the wound site. In case of graft rate fixation in full thickness wounds the treatment of Tangial excision was...
superior compared to honey as sole treatment. In none of the studies side effects of the treatment have been reported.

**Conclusion**
From the literature data assessed it can be concluded that honey is effective and safe in the treatment of superficial and partial thickness wounds. Given the fact that in the different studies included in this survey different honey types have been used, we conclude that Bfactory honey as used in Revamil Single Dose is safe for use for the treatment of superficial and partial thickness wounds.

### 9.1.7.4 Literature report side effects

For a detailed report of this search, see Attachment 4

**Summary**
Totally were included 195 patients with wounds of different aetiology. In comparative studies, there was no significant difference with respect to healing time or wound size reduction between patient groups treated with honey or the alternative wound dressing. In some studies pain sensation after dressing application was scored on a 1-10 scale, in other studies a qualitative evaluation of pain sensation was registered. In summary, the overall effect of honey treatment of wounds resulted in less wound pain. For Intrasite and Honey respectively, 0 and 10% patients experienced pain. In comparison to saline, honey treated wounds resulted in less pain.

**Conclusion**
From the literature data assessed it can be concluded that honey is as effective as other products in the treatment of wounds with different aetiology. With respect to pain it should be distinguished that many wounds are continuously painful. For this survey it can be concluded that in many cases such painful wounds benefit from treatment with honey, because these became less painful. However, the application of honey to a wound can evoke a pain sensation or itching. A pain sensation is also observed after treatment with e.g. saline or hydrocolloid. From this literature survey it is concluded that although sometimes a short stinging sensation is observed after application of honey to a wound, the benefits outweigh this discomfort, because the overall effect is positive with respect to pain reduction.

### 9.1.8 Summary and discussion clinical case series

The effectiveness of Revamil wound gel on the healing of chronic wounds of different aetiology and of different grades of severity were recorded in a case series that included 57 patients. The common feature of the wounds treated was the long-term existence of the wounds and absence of any tendency to healing at the start of treatment with Revamil.

The results show that:
- Revamil is used in the clinical field for periods up to 30 weeks (see below)
- Revamil wound gel facilitates cleaning of the wound site. After on average 2-8 weeks after start of the treatment, 74% of the treated wounds became clean.
- During the follow up periods, there was no report of an additional or increase of wound microbial contamination/wound infection related to the application of Revamil.
- Revamil wound gel facilitates, as an indirect consequence of the above mentioned effect, the formation of granulation tissue. The onset of granulation starts at the same time, or immediately after, that the wound environment has become clean.
- As a follow up indirect effect, in wounds where granulation has initiated, Revamil wound gel facilitates closure of the wound.
- The overall effect of treatment with Revamil wound gel is reduction of ulcer pain. After treatment with Revamil wound gel the percentage of patients that experienced light to severe ulcer pain before treatment, reduced from 47% to 16%. When ulcer pain increased after the treatment, patients already experienced moderate pain before the treatment started. Based on the limited amount of scored pain and the fact that pain sensation is a known side effect of wound treatment BFactory concluded that this side effect is acceptable for Revamils intended use and indications.
- During treatment, even at the longer time periods of 30 weeks, no other side effects or risks were identified.

Overall it can be concluded that Revamil manages the microenviroment to such extend that it, as an indirect effect, enables the wound healing of chronic wounds. In addition results showed that Revamil facilitates cleaning of the wound site. Both observations support the claim that Revamil facilitates (autolytic) debridement and granulation. During the follow up periods, there was no report of an additional or increase of wound microbial contamination/wound infection related to the application of Revamil. This observation supports the claim that Revamil provides (in its initial phase) a protective layer against bacterial ingress.

The case study supported the clinical safety and performance conclusions of Revamil product group derived from literature data of equivalent products and honey.

Both product safety (side effect) and performance results found in the Revamil case study are in alignment with the trends seen in clinical investigation and case studies of other honey containing products as published in literature.

The data obtained from the chronic venous leg ulcer case study with Revamil can be regarded as also applicable to other indicated chronic wounds and 2nd degree burns since there is strong evidence that in the chronic phase of these impaired wounds the hostile microenviroment is characterized by similar pathomechanisms and literature data of equivalent products provided strong trend results that honey based products are suitable for treatment of these types of wound as well.

Initially a limitation of the period of use (less than 30days) was decided upon because of the lack of clinical data at its first market introduction. Market data show that in practice these types of devices are used for longer time periods especially in those situations when chronic wounds respond positive on the treatment and start to heal, and in particular when they had failed to heal in the past with other treatments and no side effects were reported. BFactory decided to update its risk analysis and biological safety evaluation (see for details the Risk management report and Biological safety evaluation report). Since by the update of the risk analysis and biological safety evaluation no clinical safety or performance risks were identified BFactory concluded that the extended (but unintended) use period does not impair a safety risk so no additional control measures need to be taken.

9.2 Post market surveillance and complaints trend analysis
Over the period 2004-2010 post market surveillance (PMS) data was collected for the Revamil product group in order to assess if
- products perform as intended
- any side effects occur
- products are safe
- products are used/applied in the intended way
Information was obtained via
- at least 3 interviews with end-users taken by Bfactory or its distributors
- interviews with distributors
- questionnaire via Internet/send with products
- continuous “non-formal” meetings with distributors and customers

Each year an assessment of results was performed.
Over the last years a total of 25 interviews were carried out with end-users and distributors.
In summary the following was concluded:

- Revamil products are used successfully on various type of acute and chronic wounds:
  - Diabetic foot
  - Ulcus Cruris
  - Decubitis
  - Light and potential infection risk
- The products can be well used according to instructions for use and indications and are easy to apply and (Revamil dressing or secondary) dressings are easy to remove.
- Some pain complaints are apparent, more with the 18 gr and Single Dose, less or none with the dressing
- The interviews have lead to clear product innovations:
  - The wound dressing has been mentioned several times as a potential improvement, on which basis Bfactory has developed this product
  - The dressing has, based on requests expressed in the interviews, been delivered in various sizes

Based on the results it was concluded that the Revamil product perform as expected and that no new risks were identified. Therefore no specific additional PMCF study was felt needed, however, PMS is regarded as a continuous process for Bfactory to monitor clinical safety and performance of its products and to obtain new (design) market input as well.

Detailed information is available in the PMS records as summarized in the Review Report of 2011 (attachment 5)\(^3\).

10. SUMMARY BIOLOGICAL SAFETY
Detailed biological and clinical safety data are presented in the biological safety evaluation report.

In summary it could be concluded that taken into consideration
- the controlled composition of Revamil product
- absence of contaminants like heavy metals, antibiotics and pesticides
- the application of Revamil products on acute and chronic breached skin surfaces
- the use of Revamil products for 1-3d in a repeated pattern for longer term periods (<30d)

the risks with regards to irritation, (sub)acute systemic toxicity, genotoxicity are considered negligible and therefore acceptable.

With regards to the evaluation of cytotoxicity of honey containing products it is generally known that honey, due to its complete dilution in the culture medium, will raise the osmolarity of the culture medium by which cell vitality will be negatively affected. This is due
Bfactory to the limitation the test model which is considered a closed, non-draining system as compared to an in vivo situation. As the high osmolarity is one of the characteristics responsible for the functionality of the product this risk cannot be reduced. Taking its benefit into consideration (antimicrobial activity, creating a moist environment) Bfactory concludes that this risk is acceptable.

With regards to irritation it was noted that wound care products in general, including those containing honey, can cause a pain sensation, for the honey product likely to be caused by the high osmolarity and/or low pH. As the high osmolarity and low pH are characteristics responsible for the functionality of the product this risk cannot be reduced. Taking its benefit into consideration (protective layer, creating a moist environment) Bfactory concludes that this risk is acceptable. Post market data indicated that for Revamil the pain sensation is sometimes reported, however it also has been reported that Revamil reduces the pain after application. As a pain sensation is a commonly known phenomena for the wound care specialists and nurses no additional warning is needed in the Instructions for Use. However, a warning was added that in case of unexpected side effects after use of Revamil products the distributor or a specialist shall be contacted.

The risks with regards to sensitization is negligible, but since some individuals might be allergic for honey this is added as a contra-indication on the labeling;

The risks with regards to chronic exposure (e.g. carcinogenicity, chronic toxicity, immunotoxicity, reproductive/developmental toxicity) are regarded negligible because of the known and controlled composition of the final product, its known absence of chronic hazards and because honey containing wound care product are already used in a similar way (repeated use, long term) for decades.

It was concluded that Revamil products are biological safe for their intended use, indications and application time. No risks are foreseen in case of unintended extended use.

11. ASSESSMENT CLINICAL PERFORMANCE BENEFIT AND FORESEEABLE RISKS
Based on the:
- Biological safety evaluation
- In vitro performance test data
- Literature review of honey and honey based products
- Clinical performance data, PMS and complaints trend analysis
it was concluded that there are no foreseeable clinical performance or safety risk of the Revamil with regards to its intended use in combination with the information provided to the user/patient.

The risks identified in the risk management report have been addressed by the clinical data. To cover all hazards and to limit any residual risks with regards to product handling, use and performance information about clinical indications or complications is provided in the Instructions for Use in the subsections
- INTENDED USE
- INDICATIONS
- CONTRAINDICATIONS,
- SAFETY PRECAUTIONS
- STORAGE CONDITIONS
and subsequent label information on the packages.

Since the evaluation of this information has been part of the clinical validation the information accompanied with the Revamil is suitable and appropriate for its safe and
proper use, taking into account the training and knowledge of potential users (usability). No other risks are foreseen.

12. OVERALL CLINICAL EVALUATION SUMMARY AND CONCLUSION

Based on the results of clinical literature studies of equivalent products and the main equivalent product component, honey, and based on in vitro performance studies Bfactory concludes that Revamil product group is safe and performs as claimed when used and applied as intended and that the claims as laid down in the Instructions for Use are in consistence with the outcome of these studies.

These studies provided clinical evidence for the establishment of the following safety, performance and product handling claims:

The clinical performance of Revamil product group is based on influencing the micro-environment of the wound by the characteristics of the main product component, honey:

- In its initial stage honey forms on a protective layer against bacterial ingress over the wound:
  o by means of its physical (osmotic, pH) characteristics
  o by means of a high sugar concentration
- In its second stage honey creates a wound moist environment
  o by means of a high sugar concentration and osmolarity which attracts wound moisture. Wound moisture on its turn facilitates (autolytic) debridement and granulation

The combination of a protective layer and a moist environment provides a micro-environment for a wound which, on its turn, indirectly enables the healing process.

Post Market case study data and Surveillance data showed:
- Revamil is used in the clinical field for periods up to 30 weeks, with an average of 8 weeks uninterrupted
- Revamil wound gel facilitates cleaning of the wound site, and as an indirect consequence, the formation of granulation tissue and wound closure
- Revamil does not induce additional or increased wound microbial contamination
- The overall effect of treatment with Revamil wound gel is reduction of ulcer pain.
- During treatment, even at the longer time periods of 30 weeks, no side effects or risks were identified.

Post Marker Surveillance data showed:
- Revamil products are used successfully on various type of acute and chronic wounds (diabetic foot, ulcus cruris, decubitis, light and potential infection risk)
- The products can be well used according to instructions for use and indications.
- Some pain complaints were reported, more with the 18 gr and Single Dose, less or none with the dressing

Post Market interviews have lead to clear product innovations: Revamil wound dressing in various sizes.

It was acknowledged that Revamil was used beyond its intended use period: longer than 30 days (even up to 30 weeks) rather than less than 30 days. After communication with the clinicians it became clear that in the wound treatment field wound treatment devices (including honey containing devices) and therapies are continued for longer periods of time.
than 30 days in cases chronic wounds respond positive on the treatment and start to heal, and particular when they had failed to heal in the past with other treatments.

Since by the update of the risk analysis and biological safety evaluation no clinical safety or performance risks were identified, Bfactory concluded that the extended (but unintended) use period does not impair a safety risk so no additional control measures need to be taken.

Based on the results it was concluded that the Revamil product group performs as intended and that no new risks were identified. Therefore no specific additional PMCF study was felt needed, however, PMS is regarded as a continuous process for Bfactory to monitor clinical safety and performance of its products, with special focus on long term use, and to obtain new (design) market input as well.

All risks associated with the use and application of Revamil product group are acceptable when weighed against the benefits to the patient

Taken the intended use, application and indication of Revamil product group into consideration, Bfactory concludes that for all listed claims the clinical safety and performance data demonstrate conformity with the Essential requirements of Annex 1, MDD 93/42/EC.
13. REFERENCES


34 http://bio.waikato.ac.nz/honey/honey_intro.shtml#Acidity


http://bio.waikato.ac.nz/honey/honey_intro.shtml#Osmotic


Challenge test various concentration Revamil, Bactimm, 2005


