Chlorhexidine Gluconate 2% w/v Impregnated Pad
(chlorhexidine gluconate)
PL 27821/0004

UK Public Assessment Report

TABLE OF CONTENTS

Lay Summary Page 2
Scientific discussion Page 3
Steps taken for assessment Page 20
Steps taken after authorisation Page 21
Summary of Product Characteristics Page 22
Product Information Leaflet Page 26
Labelling Page 28
Chlorhexidine Gluconate 2% w/v Impregnated Pad

PL 27821/0004

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Baggerman FarmaNet NV a Marketing Authorisation (licence) for the medicinal product Chlorhexidine Gluconate 2% w/v Impregnated Pad (PL 27821/0004) on 7th July 2010. This is a medicine available on the General Sales List (GSL), and can be purchased at pharmacies, supermarkets and other retail outlets without the supervision of a pharmacist.

The active ingredient in these pads is chlorhexidine gluconate 2% (equivalent to 500mg chlorhexidine gluconate per pad), which has antibacterial properties, fighting and killing bacteria. These pads should only be used for disinfecting the skin and can be used before surgery on the advice of your doctor. They can also be used to disinfect your skin generally.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of Chlorhexidine Gluconate 2% w/v Impregnated Pad outweigh the risks; hence a Marketing Authorisation (MA) has been granted.
Chlorhexidine Gluconate 2% w/v Impregnated Pad

PL 27821/0004

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction .......................................................... Page 4
Pharmaceutical assessment ...................................... Page 5
Pre-clinical assessment ............................................. Page 8
Clinical assessment .................................................. Page 9
Overall conclusion and benefit-risk assessment .......... Page 19
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Baggerman FarmaNet NV a Marketing Authorisation for the medicinal product Chlorhexidine Gluconate 2% w/v Impregnated Pad (PL 27821/0004) on 7th July 2010. The product is available on a General Sales Licence (GSL).

This is an abridged application for Chlorhexidine Gluconate 2% w/v Impregnated Pad, submitted under Article 10.3 of 2001/83 EC, as amended. This hybrid application makes reference to the UK product, Hibiscrub (PL 21855/0002), a 4% w/v solution of chlorhexidine gluconate, authorised to Regent Medical Oversees Ltd in December 2004. The cross-referenced product was originally awarded a default conversion licence in November 1993, as Hibiscrub Solution, to Imperial Chemical Industries plc (PL 00029/0129), and subsequently underwent a series of Change of Ownership (CoA) procedures to the current Regent Medical Oversees Ltd licence in December 2004. The reference product has been authorised in the UK for more than 10 years, so the period of data exclusivity has expired.

Chlorhexidine Gluconate 2% w/v Impregnated Pads are indicated for skin antisepsis as part of an advance pre-operative cleansing regimen, as well as general skin antisepsis.

Chlorhexidine gluconate is a disinfectant which is effective against a wide range of vegetative Gram-positive and Gram-negative bacteria. The wide range of microorganisms against which chlorhexidine gluconate is active makes it suitable for broad-spectrum disinfection of skin prior to surgery to reduce risk of infection. It is effective against MRSA (methicillin-resistant *Staphylococcus aureus*), VRE (vancomycin-resistant *enterococcus*), *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and various *Streptococcus* species.

Chlorhexidine gluconate significantly reduces the number of microorganisms on intact skin and demonstrates continued anti-microbial activity for up to 6 hours after application. Chlorhexidine gluconate is inactive against bacterial spores.

The application is supported by a series of clinical studies, which are discussed in the Clinical Assessment section of this report. No new pre-clinical studies were submitted.

The pharmacovigilance system, as described by the Marketing Authorisation Holder (MAH), fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). The active ingredient, chlorhexidine gluconate, is well-established, with a good safety profile.

The MAH has submitted an Environmental Risk Assessment (ERA) in accordance with current guidelines.
PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

Chlorhexidine gluconate (solution)

Nomenclature:

INN: Chlorhexidine gluconate

Structure:

\[
\begin{align*}
\text{Molecular formula: } & \quad \text{C}_{22}\text{H}_{30}\text{Cl}_{2}\text{N}_{10}, \quad \text{2C}_{6}\text{H}_{12}\text{O}_{7} \\
\text{Molecular weight: } & \quad 898 \text{ g/mol} \\
\text{CAS No: } & \quad 18472-51-0 \\
\text{Physical form: } & \quad \text{Almost colourless or pale-yellowish liquid} \\
\text{Solubility: } & \quad \text{Miscible with water, with not more than 3 parts of acetone, and with not more than 5 parts of ethanol (96%)}
\end{align*}
\]

The active substance, chlorhexidine gluconate, is the subject of a European Pharmacopeia (Ph. Eur.) monograph.

All aspects of the manufacture and control of chlorhexidine gluconate are supported by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (CEP). This certificate is accepted as confirmation of the suitability of chlorhexidine gluconate for inclusion in this medicinal product.
MEDICINAL PRODUCT

Description and Composition

The medicinal product is presented as a polyester pad impregnated with chlorhexidine gluconate 2% w/v solution (equivalent to 500mg chlorhexidine gluconate per pad).

Other ingredients of the solution impregnated into the polyester pad consist of pharmaceutical excipients, namely aloe vera gel (containing sodium benzoate and potassium sorbate), dimeticone, fragrance F750485, gluconolactone, glycerol, nonoxinol 9, polysorbate 20, propylene glycol and purified water. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of gluconolactone, which complies with the requirements of the US Pharmacopoeia, and the aloe vera gel and fragrance, which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients. The polyester pads comply with appropriate in-house specifications.

The glycerol has been confirmed as being of vegetable origin. There are no materials of human or animal origin contained in, or used in the manufacturing process for, the proposed product. None of the excipients are sourced from genetically modified organisms. There were no novel excipients used.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted.

Finished product specification

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided and accepted. Certificates of Analysis have been provided for any reference standards used.

Container Closure System

The finished product is licensed for marketing in flexible film, heat-sealed packages. A ‘single-use’ package contains 2 impregnated polyester pads and a resealable package contains 6 impregnated polyester pads. The packages (sachets) are placed, with the Patient Information Leaflet (PIL), into cardboard outer cartons in pack sizes of 24 ‘single-use’ packages or 20 resealable packages.

Specifications and Certificates of Analysis for all packaging components used have been provided and are satisfactory. The packaging materials comply with relevant European Pharmacopoeia monographs and Directives and have been confirmed as being suitable for pharmaceutical use.
Stability
Finished product stability studies have been conducted in accordance with current guidelines, using product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 15 months has been set for the ‘single-use’ (2-pad) package and a shelf-life of 18 months has been set for the resealable (6-pad) package. Storage instructions are ‘Do not store above 25°C. Do not refrigerate or freeze. Store flat’.

Quality Overall Summary
A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

Product Information
The approved Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), and labelling are satisfactory. Mock-ups of the labelling and PIL have been provided. The PIL user test has been evaluated and accepted. It supports the readability of the leaflet.

Conclusion
The product is a polyester pad impregnated with an aqueous solution of chlorhexidine gluconate that contains no alcohol. The use of the product is restricted to unbroken skin and it should not be used immediately prior to invasive techniques, such as surgery or venepuncture. The SmPC states that the ‘regimen should be performed the night before and the morning of a surgical procedure’.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. There are no objections to approval of Chlorhexidine Gluconate 2% w/v Impregnated Pad from a pharmaceutical point of view.
PRE-CLINICAL ASSESSMENT

This abridged application, submitted under Article 10.3 of Directive 2001/83/EC, as amended, is for Chlorhexidine Gluconate 2% w/v Impregnated Pad. This hybrid application makes reference to the UK product, Hibiscrub (PL 21855/0002).

No new pre-clinical data have been supplied with this application and none are required for applications of this type. A pre-clinical overview has been written by a suitably qualified person, whose CV has been supplied.

The MAH has submitted an Environmental Risk Assessment (ERA) in accordance with current guidelines.

There are no objections to approval of this product from a pre-clinical point of view.
CLINICAL ASSESSMENT

INTRODUCTION
Surgical site infection is a serious complication of surgery that may increase length of hospital stay for patients and be associated with an increase in morbidity and mortality (Mangram 1999).

Chlorhexidine gluconate is a widely used anti-microbial agent and is available in a number of different formulations for use in skin disinfection at concentrations in the range of 0.5 to 4%. Solutions are used for both hand disinfection of nursing and medical staff and for cleaning of patient’s skin prior to surgical procedures.

This medicinal product has been specifically designed for use as a pre-surgical skin disinfectant. The solution is alcohol-free and is designed to dry on the skin and not be washed off. The formulation contains a number of excipients that are commonly used in cosmetic products (e.g. emollients and fragrance) to moisturize the skin and provide a more patient acceptable product. The solution is contained in a polyester pad that is rubbed on the patient’s skin. The pad is non-abrasive.

CLINICAL BACKGROUND
Chlorhexidine gluconate is a cationic bisbiguanide anti-microbial agent that acts by disrupting cell membranes and causing denaturation and precipitation of cellular contents (Denton 1991). Chlorhexidine gluconate has a broad spectrum of activity and it is effective against Gram-positive bacteria, somewhat less active against Gram-negative bacteria and fungi, is sporostatic and is only minimally active against tubercle bacilli (Russell 1990). Chlorhexidine gluconate is effective against enveloped viruses (e.g. herpes simplex virus, HIV, cytomegalovirus, influenza, and RSV) but it is substantially less active against non-enveloped viruses (e.g., rotavirus, adenovirus, and enteroviruses) (Denton 1991). Chlorhexidine gluconate is not sporcidal (Russell 1990). Despite its widespread use for several decades, very few reports of resistance to chlorhexidine gluconate exist (Baillie 1987, Hammond 1987, Russell 1997).

INDICATIONS
Chlorhexidine Gluconate 2% w/v Impregnated Pads are indicated for skin antisepsis as part of an advance pre-operative cleansing regimen, as well as general skin antisepsis.

TOXICOLOGY
No new data have been submitted and none are required for this type of application.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Although the efficacy of chlorhexidine gluconate is well-established (Kampf 2004), the product manufacturer has conducted a programme of in vitro studies to determine the ‘Minimum Inhibitory Concentration’ (MIC) and the ‘Time to Kill’ for a large number of microorganisms. Studies were completed with the following organisms – vancomycin-resistant enterococci (VRE), methicillin-resistant Staph aureus (MRSA)
and Clostridium difficile. The solution used in the in-vitro studies was the same formulation as that proposed for the finished product.

The MIC study (MIC 1) involved testing of 1,124 different strains of 22 species. Generally, 25 American Type Culture Collection (ATCC) strains and 25 fresh clinical isolates were tested. The impregnated pad formulation without chlorhexidine gluconate (CHG) was tested as negative control and there was a positive control of the formulation containing 2% CHG and 98% water. The product vehicle and active ingredient testing show that the active ingredient (CHG) provides the anti-microbial activity of the drug product and other components of the formulation do not contribute to (or reduce) the efficacy.

The average MICs were found to be between 1:256 (Candida spp) and 1:65,536 (E. coli, some Staph spp and Strep pyogenes). A separate MIC study (MIC 2) was conducted with Clostridium difficile which gave an MIC of 1:4,096. A Time Kill study (TK 1) tested the drug product, active ingredient and the product vehicle. The drug product was evaluated using a total of 51 strains (25 ATCC strains and 26 clinical isolates). The active ingredient and product vehicle were tested with the 10 ATCC microorganism strains. The percent and log-10 reductions from the initial populations were determined for each microorganism following exposures to the appropriate products for 15 seconds to 30 minutes. With the active drug product, the results demonstrated rapid kill for the majority of organisms (4 to 6 log reduction within 1 minute) with the exception of some organisms such as Staph aureus, Enterococcus faecalis and E. faecium where specific strains required up to 3 minutes to achieve 3-log and above reductions.

A Time Kill study using antibiotic resistant microorganisms (TK 2) tested efficacy against 21 strains (8 ATCC strains and 13 fresh clinical isolates). The log-10 reductions were determined for each microorganism following exposure to a number of test materials for periods ranging from 15 seconds to 15 minutes.

The results demonstrated that the impregnated pad formulation was effective in reducing the microbial population of resistant organisms within a reasonable time period. A summary of results is given below:

<table>
<thead>
<tr>
<th>Species</th>
<th>Log reduction</th>
<th>Time required (mins)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clostridium difficile</td>
<td>&gt;5.0</td>
<td>3</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>&gt;4.0</td>
<td>15</td>
</tr>
<tr>
<td>(vancomycin-resistant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus faecium</td>
<td>&gt;4.0</td>
<td>12</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>&gt;4.0</td>
<td>3</td>
</tr>
<tr>
<td>(mupirocin-resistant)</td>
<td>&gt;3.0</td>
<td>3</td>
</tr>
<tr>
<td>(methicillin or meth/mupirocin resistant)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusion on pharmacodynamics

This product shows similar antiseptic properties to other 2% solutions of chlorhexidine gluconate currently available.
Pharmacokinetics

No formal pharmacokinetic studies have been performed with chlorhexidine gluconate solution in an impregnated pad.

The issue of systemic pharmacokinetics is not relevant as the chlorhexidine gluconate impregnated pad works on the skin surface and it is a well-established point that minimal amounts of chlorhexidine gluconate cross the skin at this concentration. It has been established that minimal quantities of chlorhexidine gluconate are absorbed through the skin (Case 1976, Case 1980) and therefore the issues of pharmacokinetics and pharmacodynamics are not relevant to a product of this sort.

CLINICAL EFFICACY

In order to demonstrate the clinical efficacy of the test product, Chlorhexidine Gluconate 2% w/v Impregnated Pad, a total of 8 studies were conducted in healthy volunteers. Four of these were screening studies to assess application procedures and times. The other four studies assessed the log-10 reduction in bacterial counts when applied to 2 different body sites on healthy volunteers. In three of these studies the comparative efficacy of the test product was tested against Hibiclens (4% chlorhexidine gluconate) which is widely used in Europe as the standard treatment for skin disinfection prior to surgery.

In addition to the efficacy studies conducted in healthy volunteers, data are available from a published report of a patient study in which the test product was used to prevent the bioburden of vancomycin-resistant enterococci (VRE) in an intensive care unit in Chicago, IL, USA (Vernon et al 2006).

The studies in healthy volunteers were conducted at 3 different locations – Site 1, Site 2 and Site 3. The studies comprised the following:

Site 1:
• screening study (Study S-1 A) investigating the test product when used with 30, 45, 60 and 120 second application times in 12 subjects;
• screening study (Study S-1 B) investigating the test product when used with 3 and 4 minute application times in 10 subjects;
• comparative study (Study S-1 C) comparing the test product with Hibiclens in 51 subjects.

Site 2:
• screening study (Study S-2 A) comparing the test product used in 4 different procedures (2 min and 3 min with standard cloth, 2 min with supersaturated cloth and 2 min with standard cloth followed by a further 2 min with standard cloth) in 12 subjects;
• comparative study (Study S-2 B) comparing the test product with Hibiclens 4% in 30 subjects;
• comparative study (Study S-2 C) comparing the test product with 3 other products in a two stage pre-operative skin preparation procedure in 126 subjects.

Site 3:
• pilot comparative study (Study S-3 A) comparing the test product with Hibiclens in 10 subjects using a 3 minute application time;
• comparative study (Study S-3 B) comparing the test product with Hibiclens in 32 subjects using a 3 minute application time.

There are two trials which can be considered pivotal in this submission. These are Studies S-2 B and S-2 C, which are discussed in detail below:

**Study S-2 B:**

**Objective of the study:** This study evaluated the anti-microbial efficacies, in terms of log microbial reductions, of one 2% chlorhexidine gluconate (CHG) anti-microbial test towelette and one reference for use as patient pre-operative skin preparations.

**Methodology:** ‘A single-centre, open, controlled, randomised cross-over study’. This study measured the anti-microbial effectiveness of one test product for use as a patient pre-operative skin preparation. Hibiclens' (4% Chlorhexidine Gluconate) was used as the reference product. 30 human subjects were utilized, employing bilateral product applications. Each of the subjects was assigned randomly to the two products. Thus, each product was used on 30 subjects. The inguinal and abdominal test sites were sampled for baseline microbial populations, prepped, and then sampled for residual populations 10 minutes, 30 minutes, and 6 hours following product application.

**Diagnosis and main criteria for inclusion:** 30 healthy subjects aged between 18-70 years; inguinal and abdominal sites were free from dermatoses, inflammation, injuries and/or any other disorders that could compromise the subject and the study.

**Criteria for Evaluation:** The primary efficacy parameter was microorganism counts.

**Statistical Methods:** Descriptive statistics were calculated and confidence intervals determined for the baseline and post-application recovery populations dated with the application of the two products.

**Results:** 30 subjects were enrolled into the study.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample Size</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>95% Confidence Interval</th>
<th>( \log_{10} ) Reduction From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30</td>
<td>6.15</td>
<td>0.34</td>
<td>6.03 to 6.28</td>
<td>N/A</td>
</tr>
<tr>
<td>10 Minutes Post-Prep</td>
<td>30</td>
<td>2.70</td>
<td>0.82</td>
<td>2.39 to 3.00</td>
<td>3.45</td>
</tr>
<tr>
<td>30 Minutes Post-Prep</td>
<td>30</td>
<td>2.65</td>
<td>0.89</td>
<td>2.32 to 2.98</td>
<td>3.50</td>
</tr>
<tr>
<td>6 Hours Post-Prep</td>
<td>30</td>
<td>2.51</td>
<td>1.04</td>
<td>2.12 to 2.90</td>
<td>3.64</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample</th>
<th>Sample Size</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>95% Confidence Interval</th>
<th>( \log_{10} ) Reduction From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30</td>
<td>6.16</td>
<td>0.43</td>
<td>6.01 to 6.32</td>
<td>N/A</td>
</tr>
<tr>
<td>10 Minutes Post-Prep</td>
<td>30</td>
<td>3.38</td>
<td>0.94</td>
<td>3.03 to 3.73</td>
<td>2.78</td>
</tr>
<tr>
<td>30 Minutes Post-Prep</td>
<td>30</td>
<td>3.53</td>
<td>0.77</td>
<td>3.25 to 3.82</td>
<td>2.63</td>
</tr>
<tr>
<td>6 Hours Post-Prep</td>
<td>30</td>
<td>3.01</td>
<td>1.10</td>
<td>2.60 to 3.42</td>
<td>3.15</td>
</tr>
</tbody>
</table>
Safety: No subjects experienced an adverse event during, or upon completion of, this study.

Conclusions: For the test product (Chlorhexidine Gluconate 2% w/v Impregnated Pad), the bacterial populations recovered from both the inguinal and the abdominal test sites 10 minutes post-application were reduced significantly from the baseline populations. The test product produced a mean log reduction at 10 minutes of 3.45 for the inguinal site and 2.50 for the abdominal site. The microorganism populations from the 30-minute and 6-hour application samples did not return to baseline level. The reductions obtained for the test product met the critical indices of the study. For the reference product (Hibiclens), the bacterial populations recovered from both the inguinal and the abdominal test sites 10 minutes post-application were reduced significantly from the baseline populations. The reference product produced a mean log reduction at 10 minutes of 2.78 for the inguinal site and 2.18 for the abdominal site. The microorganism populations from the 30-minute and 6-hour application samples did not return to baseline level. The reductions obtained for the reference product did not meet the critical indices of the study.

Study S-2 C:
Objective of the study: This study evaluated the anti-microbial effectiveness of full-body pre-operative skin preparations (pre-op prep #1 and pre-op prep #2) performed with either Dial bar soap or Chlorhexidine Gluconate 2% w/v Impregnated Pads (the test product) over the course of two applications: one 12 hours prior to the final pre-operative skin prepping, and one 3 hours prior to the final pre-operative skin-prepping of the subclavicular and inguinal test sites. Three different formulas were used for the final pre-operative skin-prepping - DuraPrep™, Scrub Care Pre-operative Skin Prep Trays, or the Chlorhexidine Gluconate 2% w/v Impregnated Pad. To evaluate efficacy of this three-step procedure (pre-op prep #1 and #2/final pre-operative preparation), samples of skin flora were taken for baseline, 2 hours after each of the two pre-op preps, and 10 minutes and 6 hours following the final pre-operative skin preparation. Comparative antiseptic products were DuraPrep™ (0.7% Available Iodine and 75% [w/w] Isopropyl Alcohol); and Scrub Care Pre-operative Skin Prep Trays (Povidone...
Iodine Cleansing Solution USP [7.5% Povidone Iodine] and Povidone Iodine Topical Solution USP [10% Povidone Iodine]).

Methodology: ‘A single-centre, open, controlled, randomised cross-over study’. Subjects underwent a wash-out period of 14 days, followed by baseline-sampling of microbial flora at the skin of the test sites. Samples of bacterial populations at the test sites were taken 2 hours following each of the full-body pre-operative skin preparation procedures. The final pre-operative skin preparation, assigned randomly, was then applied to the test sites on the skin of the subclavicular and inguinal regions, and bacterial population samples were taken 10 minutes and 6 hours following the application.

Diagnosis and main criteria for inclusion: 126 healthy subjects aged between 18-70 years; all subjects were free from clinically-evident dermatoses or injuries to the skin of the subclavicular and femoral (inguinal) regions.

Criteria for Evaluation: The primary efficacy parameter was microorganism counts. The number of colonies for each plate and the number of colony forming units-per-ml (cfu/ml) of sampling liquid was determined. The calculated cfu/ml value was transformed into common logarithm.

Statistical Methods: All statistical calculations were performed using the 0.05 level of significance for Type I (α) error.

Results: 126 healthy subjects were enrolled in the study.
Safety: Three subjects experienced adverse events, possibly related to the test product used in this study.

Conclusions: Although not consistently significant, the log reductions following the final (surgical site) pre-operative skin prep of test sites with any of the three final skin prep products (Chlorhexidine Gluconate 2% w/v Impregnated Pads, DuraPrep™, or Scrub Care Pre-operative Skin Prep Trays) were greater from subjects who had used Chlorhexidine Gluconate 2% w/v Impregnated Pads for Pre-Op Prep #1 and Pre-Op Prep #2 (full-body preps) than reductions from those who used Dial Bar Soap.

Assessor’s overall conclusions on Clinical Efficacy
The applicant has submitted 8 studies in all, of which two were deemed to be pivotal for this submission. These were Studies S-2 B and S-2 C. Both studies used two different body sites known to contain differing levels of bacterial flora essential in understanding the real effectiveness of this manner of delivering chlorhexidine gluconate. In addition, the test product (Chlorhexidine Gluconate 2% w/v Impregnated Pad) was compared to Hibiclens 4%, Dial Bar Soap and two different solutions of povidone iodine. It was shown to be equivalent to Hibiclens 4% solution and the povidone iodine solutions in its capacity to reduce bacterial load on the skin at two different sites on the body where the bacterial load would be different. The test product was shown to be superior to Dial Bar Soap which would be expected since soap is a mild antiseptic. All other supporting data shows similar efficacy.

CLINICAL SAFETY
Chlorhexidine gluconate is a well-established antiseptic which has been used for many years. Two studies have been presented investigating the irritation potential of the formulation used in Chlorhexidine Gluconate 2% w/v Impregnated Pads:

- A Repeat Insult Patch Test (Study CS 1) gave low to moderate grade irritant responses in approximately one third of the test population and was no more irritating or sensitizing than Exidine (2% CHG) which is a pre-operative skin preparation marketed in the USA. By contrast, Hibiclens gave no significant irritant response.

- A 21-day Cumulative Irritation Test (Study CS 2) with daily application under occlusion for 21 days showed that the test product had a strong potential for a mild to moderate cumulative irritation and was similar to Exidine (2% CHG). By contrast, Hibiclens gave evidence of a slight potential for very mild cumulative irritation.

A total of 239 patients have been exposed to this delivery system in the controlled trials submitted.

Study CS 1:
Objective of the study: This study was to determine, by repetitive epidermal contact, the primary or cumulative irritation and/or allergic contact sensitization potential of the test product material.
Methodology: ‘A single-centre, open-label, controlled, randomised crossover’.

Induction Phase: The patches were applied to the upper back between the scapulae for a total of nine applications (with a days gap between applications). Induction patches were removed 24 hours after being applied. Scoring of the test site was made just prior to re-application. The site was marked to ensure the continuity of repetitive patch application.

Challenge Phase: Approximately two weeks following the final induction patch applications, a Challenge patch was applied to a virgin test site adjacent to the original induction patch site, following the same procedure described for induction. The patch was removed and the site was scored 24 hours after application and scored again 72 hours post-application.

Evaluation Key:  
0 = No visible skin reaction
+ = Barely perceptible or spotty erythema
1 = Mild erythema covering most of the test site
2 = Moderate erythema, possible presence of mild edema
3 = Marked erythema, possible edema
4 = Severe erythema, possible edema, vesiculation, bullae and/or ulceration

With the exception of the first patch removal readings, if at any time during the induction phase of the study, a test site exhibited an evaluation score of "2", re-application of the test material was moved to an adjacent site. If an evaluation score of "2" was observed on this new site, further applications were discontinued. Evaluation scores of "3" or greater required discontinuation of further applications.

Diagnosis and main criteria for inclusion: Male and female subjects, age 18 and over; absence of any visible skin disease which might be confused with a skin reaction from the test material; prohibition of use of topical or systemic steroids and/or antihistamines for at least seven days prior to study initiation.

Criteria for Evaluation: The primary efficacy parameter was the primary or cumulative irritation and/or allergic contact sensitization potential of a test material.

Results: 218 qualified subjects, male and female, ranging in age from 18 to 79 years, were selected for this evaluation and 204 subjects completed the study. Scattered, transient, barely perceptible (+) to moderate (level 2) patch test irritant responses were observed on 11 subjects during the induction phase of the study. None of these low-grade, transient responses was considered evidence of clinically significant irritation potential. There was no evidence of induced allergic contact dermatitis.

Study CS 2:

Objective of the study: To test and compare articles of low irritating potential for human skin irritation elicited by repetitive topical application over a 21-day period.

Methodology: ‘A single-centre, double-blind, controlled, randomised cross-over’. 21 consecutive daily applications of the test articles contacted the skin under occlusion for approximately 23 hours each day. Scoring for cumulative irritation was done approximately every 24 hours. The left scapular area was used as the application site.
Diagnosis and main criteria for inclusion: Male and female healthy subjects, age 18 and over.

Criteria for Evaluation: The primary measurement will be the evaluation of irritation. The scoring scale will be that of ‘Berger and Bowman’.

Results: A total of 30 subjects were empanelled and 23 subjects had evaluable data.

Conclusions
1. No test article ranked as a Class 1 material, i.e. essentially no evidence of cumulative irritation under continuous reapplication and occlusion at concentration tested.

2. Five test articles, including the negative control (normal saline), ranked as Class 2 materials, i.e. evidence of a slight potential for very mild cumulative irritation under conditions of test. The test articles proved to be, in ascending order of cumulative irritation scores:
   a) Test article #00, Antiseptic Body Cleanser bulk solution - placebo
   b) Test article #44, Comfort Bath bulk solution
   c) Test article #99, normal saline
   d) Test article #55, Hibiclens solution
   e) Test article #77, Medline ReadyBath solution removed from cloths

3. Two test articles ranked as Class 3 materials, i.e. evidence of a moderate potential for mild cumulative irritation under conditions of test. The test articles proved to be, in ascending order of cumulative irritation scores:
   a) Test article #11, Medline Anti-bacterial ReadyBath (0.1% BBZR) solution removed from cloths
   b) Test article #66, Calgon Vestal SeptiSoft

4. Two test articles ranked as Class 4 materials, i.e. evidence of a strong potential for mild to moderate cumulative irritation under conditions of test. The test articles proved to be, in ascending order of cumulative irritation scores:
   a) Test article #33, 2% CHG Antiseptic Body Cleanser bulk solution
   b) Test article #22, Exidine solution

5. The positive control (test article #88 - sodium lauryl sulfate 1% solution) ranked as a class 5 material, i.e. evidence of potential for primary irritation under conditions of test.

Deaths and serious adverse events
No deaths or serious adverse events were reported.

Post marketing experience
Post marketing experience data are available on Chlorhexidine Gluconate 2% w/v Impregnated Pads as these have been marketed in the USA since January 2006 and, more recently, in Canada, the UK, Germany, Australia, Brazil and Mexico. To date,
approximately 920,000 packs have been sold and a total of 145 adverse events have been reported, which related to skin irritation, including skin itching, redness, burning, sensation and rash.

There have been no reports of serious and unexpected events, serious and expected events or non-serious and unexpected events. There have been no systemic reactions. The adverse event rate corresponds to approximately 1.6 per 10,000 sachets used and represents a very low rate of adverse event.

Assessor’s overall conclusions on Clinical Safety
The applicant’s safety studies have not identified any unexpected, serious or other adverse events not already identified with chlorhexidine gluconate.

EXPERT REPORT
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

PRODUCT INFORMATION:
Summary of Product Characteristics (SmPC)
The approved SmPC is acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPC and is satisfactory.

Labelling
The labelling is satisfactory.

DISCUSSION AND CONCLUSION
This product has shown similar antiseptic properties to 4% chlorhexidine gluconate solution, povidone iodine and Dial Bar Soap in healthy adult volunteers. No serious safety issues have been raised that could affect the benefit-risk balance.

No paediatric antiseptic studies were submitted using this product. In vitro data shows good bactericidal effects on resistant strains such as MRSA. Overall, the Chlorhexidine Gluconate 2% w/v Impregnated Pad shows acceptable antiseptic properties.

Sufficient clinical information has been submitted to support this application. When used as indicated, the product, Chlorhexidine Gluconate 2% w/v Impregnated Pad, has a favourable benefit-to-risk ratio. The grant of a Marketing Authorisation was therefore recommended on medical grounds.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Chlorhexidine Gluconate 2% w/v Impregnated Pad are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRE-CLINICAL
No new pre-clinical data were submitted and none are required for an application of this type.

EFFICACY
The active ingredient, chlorhexidine gluconate, is well-established. The clinical efficacy is supported by a series of clinical studies (in vitro and in vivo) conducted by the applicant demonstrating the bactericidal and antiseptic properties of Chlorhexidine Gluconate 2% w/v Impregnated Pad. Studies have also been submitted demonstrating the safety of the product. No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory.

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The approved labelling artwork complies with statutory requirements.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new pre-clinical or clinical safety concerns have been identified. Chlorhexidine Gluconate 2% w/v Impregnated Pad has been demonstrated as being a generic (hybrid) version of Hibiscrub (4% w/v solution of chlorhexidine gluconate). Extensive clinical experience with the active substance, chlorhexidine gluconate, is considered to have demonstrated the therapeutic value of the medicinal product. The benefit: risk ratio is, therefore, considered to be positive.
Chlorhexidine Gluconate 2% w/v Impregnated Pad

PL 27821/0004

STEPS TAKEN FOR ASSESSMENT

1. The MHRA received the marketing authorisation application on 17th September 2007.

2. Following standard checks and communication with the applicant the MHRA considered the application valid on 22nd October 2007.

3. Following assessment of the application the MHRA requested further information relating to the quality dossier on 9th February 2009, 8th October 2009 and 3rd February 2010; and further information relating to the clinical dossier on 30th September 2008, 29th June 2009 and 9th September 2009.


5. The application was determined on 7th July 2010.
Chlorhexidine Gluconate 2% w/v Impregnated Pad

PL 27821/0004

STEPS TAKEN AFTER AUTHORISATION

Not applicable
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Chlorhexidine Gluconate 2% w/v Impregnated Pad is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Chlorhexidine Gluconate 2% w/v Impregnated Pad

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Chlorhexidine gluconate 2% w/v solution (equivalent to 500 mg chlorhexidine gluconate per pad).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Impregnated pad.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Skin antisepsis as part of an advance preoperative cleansing regimen and general skin antisepsis.

4.2 Posology and method of administration
Cutaneous use only.

To open, tear seal where indicated (2-pack) or peel open the resealable package (6-pack). Remove pads from package. Avoid contact between pads and outside of package to reduce risk of contamination.

For use as part of an advance preoperative cleansing regimen: Regimen should be performed the night before and the morning of a surgical procedure. Use one pad to prepare each desired area of the body by washing skin, completely wetting treatment area. Use only on intact skin.

2-pack: Use one pad to prepare each desired area of the body by washing skin, completely wetting treatment area.

6-pack: Use one pad to prepare each area of the body by washing skin, completely wetting treatment area as follows:
- Wipe the neck, chest and stomach;
- Wipe both arms, starting each with the shoulder and ending at the fingertips paying particular attention to the axillary area;
- Wipe the right and left hips followed by the groin paying particular attention to the skin folds in the abdominal and groin areas;
- Wipe both legs, starting at the thigh and ending at the toes;
- Wipe the back, starting at the base of the neck and ending at the waistline;
- Wipe the buttocks.

Do not rinse or apply any lotions, moisturizers or cosmetics after prepping.

For General Skin Antisepsis and cleansing:
Use one pad for each area of the body where skin antisepsis is desired. Do not use on open skin wounds or broken skin.

General information:
Discard each pad after a single use. After package has been opened, discard any unused pads.
4.3 Contraindications

Do not use on premature or low birthweight infants, or infants less than 2 months of age or receiving phototherapy. Do not use immediately prior to invasive techniques, such as venepuncture, lumbar puncture or surgery. Do not use on open skin wounds or broken skin.

The pads are contraindicated in patients who have previously shown hypersensitivity to the active substance(s) or to any of the excipients.

4.4 Special warnings and precautions for use

Product and packaging are not sterile.

Keep out of eyes, ears and mouth. May cause serious or permanent injury if permitted to enter and remain. If contact occurs, rinse with water immediately.

Keep out of the reach and sight of children.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and lactation

No known risks.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Skin and subcutaneous tissue disorders:
Common (≥1/100 to <1/10): Skin irritation

Immune system disorders:
Very rare (<1/10,000): Generalised allergic reactions.

When using the chlorhexidine gluconate 2% impregnated pads, the skin should be completely dry and cool. Showering or shaving immediately before using chlorhexidine gluconate 2% impregnated pads may increase skin irritation. Shaving should be suspended at least 2 days prior to surgery on all areas of the body, including the face, legs, underarms, etc. If skin irritation persists, rinse the affected areas and discontinue use.

4.9 Overdose

Overdosage is unlikely because of the low dermal absorption. Ingestion is highly unlikely.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiseptics and disinfectants, ATC code: D08AC02

Chlorhexidine is a disinfectant which is effective against a wide range of vegetative Gram-positive and Gram-negative bacteria. The wide range of microorganisms against which chlorhexidine is active makes it suitable for broad spectrum disinfection of skin prior to surgery to reduce risk of infection. Effective against MRSA, VRE, Acinetobacter baumannii, Pseudomonas aeruginosa and various Streptococcus species.

Chlorhexidine significantly reduces the number of microorganisms on intact skin and demonstrates continued antimicrobial activity for up to 6 hours after application.

Chlorhexidine is inactive against bacterial spores.
5.2 Pharmacokinetic properties
No formal pharmacokinetic studies have been performed with chlorhexidine gluconate solution in an impregnated pad. Chlorhexidine binds strongly to skin and is very poorly absorbed. Percutaneous absorption is minimal.

5.3 Preclinical safety data
Chlorhexidine is a well established active ingredient and relevant information is provided in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Aloe vera gel (contains sodium benzoate and potassium sorbate)
Dimeticone
Fragrance F750485
Gluconolactone
Glycerol
Nonoxinol 9
Polysorbate 20
Propylene glycol
Water, purified
Polyester pad

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
15 months for 2-pad package
18 months for 6-pad package

6.4 Special precautions for storage
Do not store above 25°C. Do not refrigerate or freeze.
Store flat.

6.5 Nature and contents of container
Flexible film, heat-sealed packages contain either 2 or 6 impregnated polyester pads.
Cartons containing 24 packages each comprising of 2 impregnated pads.
Cartons containing 20 packages each comprising of 6 impregnated pads.

6.6 Special precautions for disposal
Dispose of as solid waste. Do not flush pads in toilet.

7 MARKETING AUTHORISATION HOLDER
Baggerman FarmaNet NV
Meidoorn 43
5666 AS Geldrop
The Netherlands
Tel/Fax: +31 (0)40 285 7910
www.farmanet.nl
8 MARKETING AUTHORISATION NUMBER(S)
   PL 27821/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
   07/07/2010

10 DATE OF REVISION OF THE TEXT
    07/07/2010
PATIENT INFORMATION LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER
Chlorhexidine Gluconate, 2% w/v Impregnated Pad

Read all of this leaflet carefully because it contains important information for you.
This medicine is available without prescription. However, you still need to use Chlorhexidine Gluconate 2% Impregnated Pads carefully to get the best results from them.
- Keep this leaflet. You may need to read it again.
- Ask your doctor or pharmacist if you need more information or advice.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Chlorhexidine Gluconate 2% Impregnated Pads are and what they are used for
2. Before you use Chlorhexidine Gluconate 2% Impregnated Pads
3. How to use Chlorhexidine Gluconate 2% Impregnated Pads
4. Possible side effects
5. How to store Chlorhexidine Gluconate 2% Impregnated Pads
6. Further information

1. What Chlorhexidine Gluconate 2% Impregnated Pads are and what they are used for
The active ingredient in these pads is chlorhexidine gluconate, 2% (equivalent to 500mg chlorhexidine gluconate per pad), which has antibacterial properties, fighting and killing bacteria.
These pads should only be used for disinfecting the skin. They can be used before surgery on the advice of your doctor.
They can also be used to disinfect your skin generally.
Each package contains either two or six pads.

2. Before you use Chlorhexidine Gluconate 2% Impregnated Pads
Do not use these pads:
- If you are allergic to the active ingredient chlorhexidine gluconate or to any of the other ingredients (see Section 6 for a list of these);
- on premature or low birth weight babies, babies less than two months of age or babies receiving treatment which uses light (phototherapy);
- in contact with the membranes surrounding the brain and spinal cord;
- immediately prior to invasive techniques, such as venepuncture, lumbar puncture or surgery;
- on open skin wounds or broken skin.

Take special care with Chlorhexidine Gluconate 2% Impregnated Pads.
Keep the pads away from eyes, ears and mouth. The solution inside them might cause serious or permanent injury to these parts of the body. If contact occurs, rinse the affected areas with water immediately.

Using other medicines
There have been no reports of interactions between these impregnated pads and other medicines.

Pregnancy and breast-feeding
These pads may be safely used during pregnancy and breast-feeding.

Driving and using machines
These pads do not affect the ability to drive or to use machines.

3. How to use Chlorhexidine Gluconate 2% Impregnated Pads
These pads are only for use on your skin.

When using these pads:
- make sure your skin is completely dry and cool;
- do not shower immediately before using the pads because this may increase skin irritation;
- do not shave any part of your body, including your face, legs, underarms, etc., for at least two days before surgery, because this may also increase skin irritation;
- do not rinse skin or apply any lotions, moisturizers or cosmetics to the areas that have been cleaned;
- use each pad only once;
- if any skin irritation develops, rinse the affected areas and stop using the pads;
- keep the pads away from eyes, ears and mouth. If contact occurs, rinse the affected areas with water immediately.

For disinfecting the skin before surgery:
Your doctor may instruct you to wipe:
- either the area immediately at and surrounding the proposed surgery site,
- or your entire body from your chin down.
This should be done the night before and/or on the morning of your surgery, according to your doctor's instructions.

There are two types of packages. If you are using:
- packages containing 2 pads:
  - your doctor will instruct you to wipe the areas of your skin chosen for treatment with the impregnated pads;
- use one pad to wipe each area;
- make sure the skin in each area is completely wetted with the solution in the pad;
- do not rinse off. Keeping the solution on your skin is an advantage because the antibacterial effects work for up to 6 hours after application.
- allow the skin to air dry.
- packages containing 6 pads:
  - use one pad to wipe each area of the body, so that each area is completely wetted with the solution in the pad;
  - do not rinse off. Keeping the solution on your skin is an advantage because the antibacterial effects work for up to 6 hours after application
  - wipe the neck, chest and stomach;
  - wipe both arms, starting each with the shoulder and ending at the fingertips, paying particular attention to the underarm area;
  - wipe both hips followed by the groin, paying particular attention to the skin folds in the abdominal and groin areas;
  - wipe both legs, starting at the thigh and ending at the toes;
  - wipe the back, starting at the base of the neck and ending at the waistline;
  - wipe the buttocks;
  - allow the skin to air dry.

For general skin antiseptic purposes:
Use only on intact skin. As instructed above, use one pad for each area of the body, avoiding contact with open wounds or broken skin. In case of contact with an open wound or broken skin, no action is required unless irritation or reaction occurs, in which case you should notify your doctor immediately.

If you use more of these pads than you should:
Using too many pads is unlikely to be harmful because chlorhexidine gluconate is not easily absorbed through the skin.

If you forget to use these pads:
This may result in an increased risk of infection. If you have any concerns about the risk of infection, consult your doctor.

If you stop using these pads:
This may result in an increased risk of infection. If you’re in any doubt, consult your doctor.

4. **Possible side effects**
Like all medicines, Chlorhexidine Gluconate 2% Impregnated Pads can have side effects, although not everybody gets them. Most people use them without any problems.

Allergic reactions (very rare, affecting less than 1 in 10,000) may become very serious. Symptoms may include difficulty breathing, difficulty swallowing, drop in blood pressure, skin rash, and swelling of the lips, tongue and eyes. If an allergic reaction occurs, stop using these pads and consult your doctor immediately or go immediately to the emergency dept. of your nearest hospital, taking this leaflet with you.

Common (affects more than 1 in 100): skin irritation such as itching, burning sensation, redness, and rash can occur. These side effects are usually mild and temporary. However, if skin irritation persists, rinse the affected areas, stop using these pads and tell your doctor or pharmacist.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. **How to store Chlorhexidine Gluconate 2% Impregnated Pads**
Keep Chlorhexidine Gluconate 2% Impregnated Pads out of the reach and sight of children.
Do not store above 25°C. Do not refrigerate or freeze.
Store the product flat.
Do not use after the expiry date printed on the package. The expiry date refers to the last day of that month.
This product should be disposed of as solid domestic waste. Do not flush pads down the toilet.

6. **Further Information**
What Chlorhexidine Gluconate 2% Impregnated Pads contain
The active substance is chlorhexidine gluconate, 2%
The other ingredients are: aloe vera gel (contains sodium benzoate and potassium sorbate), dimethicone, fragrance F750495, gluconolactone, glycerol, nonoxinol 9, polysorbate 20, propylene glycol, purified water and a polyester pad.

What Chlorhexidine Gluconate 2% Impregnated Pads look like and contents of the package
Each 19 cm x 19 cm white polyester pad is impregnated with a colourless solution containing chlorhexidine gluconate 2% (equivalent to 500 mg chlorhexidine gluconate per pad).
These moist pads are contained in a plastic package, supported internally by a blue wrapping made of foam.
There are two types of package: a single-use package containing 2 pads, and a reusable package containing 6 pads.
UKPAR Chlorhexidine Gluconate 2% w/v Impregnated Pad

LABELLING

Sachet

Active Ingredients: Chlorhexidine gluconate 2%, water, impregnated pad

Indications: To be used for presurgical and post-operative cleaning of the surgical site, wound or incision, and surrounding skin. Indicated for use in the prophylaxis or treatment of peritonitis following laparotomy. Impregnated with 13% Chlorhexidine gluconate, 2% Alcohol, Phosphate Buffer pH 7.5, Propylene glycol (For wetting) Water (Impregnated pad)

Warnings: Not for external use only. Keep out of reach of children. Do not use on burns, wounds or infected areas. Do not use on patients who are known to be allergic to chlorhexidine gluconate or any of the other ingredients in this product. Do not use immediately prior to invasive techniques, such as laparotomy, laparoscopy or surgery. Do not use on open wounds, burns or lesions.

Usage: This product is best used to keep the surgical site, wound or incision, and surrounding skin clean and dry.

Precautions: Do not use on babies under 1 month of age or patients with impaired renal or hepatic function.

Instructions: Use as directed. For external use only. Do not exceed the recommended dosage. Store at room temperature.

Sachet comprising

2 disposable, non-stereile, impregnated pads

Lot KXXXX Exp XXX

Medicinal product not subject to medical prescription

REF #9611-X

General Product Pack No. 3399184

European Patent Pending.

Marketing Authorisation Holder: Bioprofarma International B.V.

National Park, Amsterdam. 10

8098, The Netherlands.

TelFax: +31 (0) 255 215 910

www.comfort.nl
Carton for pack size of 20 sachets
Carton for pack size of 24 sachets