Public Assessment Report

Decentralised Procedure

ChloraPrep 2% w/v / 70% v/v Cutaneous Solution

UK/H/1305/002/DC

UK licence no: PL 31760/0004

CareFusion UK 244 Limited
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted CareFusion UK 244 Limited a Marketing Authorisation (licence) for the medicinal product ChloraPrep 2% w/v / 70% v/v Cutaneous Solution (PL 31760/0004). This is a general sales licence (GSL) medicines used to disinfect the skin and help prevent infections before invasive medical procedures, such as injections, blood sampling, insertion of catheters and minor or major surgery.

ChloraPrep 2% w/v / 70% v/v Cutaneous Solution contains the active ingredients chlorhexidine gluconate 2%w/v and isopropyl alcohol 70% v/v. This is a combination products of two well-known antiseptic agents. The rationale for development of the fixed combination product containing 2% chlorhexidine gluconate and 70% isopropyl alcohol was to develop an antiseptic with rapid onset and long lasting activity against potential pathogens.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using ChloraPrep 2%w/v / 70%v/v Cutaneous Solution outweigh the risks; hence a Marketing Authorisation has been granted.
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</table>
**Module 1**

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>ChloraPrep 2% w/v / 70% v/v cutaneous solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Full dossier, Article 8(3)</td>
</tr>
</tbody>
</table>
| **Active Substance** | Chlorhexidine gluconate 2.0% w/v  
Isopropyl alcohol 70% v/v |
| **Form** | Cutaneous Solution |
| **Strength** | Chlorhexidine gluconate 2.0% w/v  
Isopropyl alcohol 70% v/v |
| **MA Holder** | CareFusion UK 244 Limited  
43 London Road  
Reigate, Surrey RH2 9PW  
United Kingdom |
| **RMS** | UK |
| **CMS** | Austria, Belgium, Germany, Finland, France, Ireland, Italy,  
Luxembourg, Malta, The Netherlands, Norway, Portugal, and  
Sweden |
| **Procedure Number** | UK/H/1305/002/DC |
| **End of Procedure** | Day 205 – 12th October 2012 (UK/H/1305/002/DC) |
Module 2
Summary of Product Characteristics

The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.
Module 3
Product Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.
Module 4
Labelling
PAR ChloraPrep 2%/w/70%/v Cutaneous Solution

UK/H/1305/002/DC
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for ChloraPrep 2% w/v / 70% v/v Cutaneous Solution (PL 31760/0004) to be used for disinfection of the skin prior to invasive medical procedures is approvable.

This application is submitted under Article 8.3 of Directive 2001/83/EC (as amended) for ChloraPrep 2% w/v / 70% v/v Cutaneous Solution (PL 31760/0004).

The cutaneous antiseptic drug product ChloraPrep contains 2% w/v chlorhexidine gluconate in 70% v/v isopropyl alcohol in unit dose applicators. This is a combinations of two well-known antiseptic agents. The drug product was developed to provide a clinical option to iodophors, alcohol, and other agents for skin antisepsis prior to and following invasive medical procedures.

The rationale for development of the fixed combination product containing 2% w/v chlorhexidine gluconate in 70% v/v isopropyl alcohol was to develop an antiseptic with rapid onset and long-lasting activity against potential pathogens relevant for the proposed indications and a benign safety profile.

The combination not only fulfils these criteria, but also demonstrates the synergy of antiseptic activity of the single substances against pathologically relevant organisms, which results in a level of efficacy above the one achievable by a single active substance.

It also allows for low concentrations of chlorhexidine gluconate in the fixed combination and provides a highly effective product with a good safety profile.

The submitted documentation in relation to the proposed product is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory quality, non-clinical and clinical overviews have been submitted.

Pharmacovigilance system
The RMS considers that the Pharmacovigilance System as described by the applicant fulfills the requirements and provides adequate evidence that the applicant 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.

Risk Management Plan
A risk management plan is not necessary for this product.

Periodic Safety Update Report (PSUR)
The proposal is for 3-yearly PSUR cycle with a data lock point in line with the PSUR European harmonised birthdate.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
Since a literature review has been presented for the Non-Clinical Overview, it is not known whether the studies cited were conducted in accordance with the GLP regulations. However, it is assumed that the studies conducted by the innovator would have been in compliance with the standards prevailing at the time.

The PIL is in compliance with current guidelines and user testing results have been submitted. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>ChloraPrep 2% w/v / 70% v/v cutaneous solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Chlorhexidine gluconate 2.0% w/v</td>
</tr>
<tr>
<td></td>
<td>Isopropyl alcohol 70% v/v</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Chlorhexidine, combinations (D08A C52)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Cutaneous Solution</td>
</tr>
<tr>
<td></td>
<td>Chlorhexidine gluconate 2.0% w/v</td>
</tr>
<tr>
<td></td>
<td>Isopropyl alcohol 70% v/v</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1305/002/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Austria, Belgium, Germany, Finland, France, Ireland, Italy, Luxembourg, Malta, The Netherlands, Norway, Portugal, and Sweden</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 31760/0004</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>CareFusion UK 244 Limited</td>
</tr>
<tr>
<td></td>
<td>43 London Road</td>
</tr>
<tr>
<td></td>
<td>Reigate, Surrey RH2 9PW</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE (1)

Chlorhexidine gluconate

General Information

Nomenclature
Name: 1-{amino-[6-[amino-4-chlorophenyl]aminomethylidene]aminomethylidene}aminohexylimino)methyl]imino-N-(4-chlorophenyl)-methanediamine di-D gluconate

Structure

![Structure Diagram]

Molecular formula: C$_{22}$H$_{30}$Cl$_2$N$_{10}$ • 2C$_6$H$_{12}$O$_7$
Molecular weight: 897.8

General Properties
Chlorhexidine gluconate solution is an aqueous, almost colourless to pale-yellowish solution. It is miscible with water and soluble in ethanol and acetone. The drug substance is an adequately characterised molecule that is the subject of USP, BP and Ph.Eur. monographs.

The drug substance is a white or almost white powder soluble in chloroform and acetic acid.

Manufacture
All aspects of the manufacture and control of chlorhexidine gluconate are supported by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability from the active substance manufacturer. This certificate is accepted as confirmation of chlorhexidine gluconate for inclusion in the medicinal product.

The active substance, chlorhexidine gluconate, is controlled by the Ph Eur monograph.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active substance.
An appropriate specification is provided for the active substance chlorhexidine gluconate, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analyses are provided that comply with the proposed specification. Suitable certificates of analysis have been provided for all reference standards used.

Satisfactory certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug and supporting an appropriate re-test period.

**DRUG SUBSTANCE (2)**

**Isopropyl Alcohol**

**General Information**

**Nomenclature**
Name: Propan-2-ol

**Structure**

![Structure of Isopropyl Alcohol](image)

Molecular formula: C₃H₈O  
Molecular weight: 60.10g/mol

**General Properties**
Isopropyl alcohol (IPA) is a well-known, well-characterized chemical. These data are obtained from generally accepted secondary sources (such as the US National Institute for Occupational Safety and Health, the US Occupational Safety and Heath Administration, and the US Department of Energy).

**Appearance**  
Colorless liquid

**Boiling Point (760 mm Hg)**  
82.4 °C

**Density and phase**  
0.785 g/cm³, liquid

**Melting Point**  
-88.5 °C

**Solubility**  
Fully miscible in water, ethyl ether, and ethyl alcohol

**Specific Gravity (20 °C)**  
0.78

Flammable, keep away from heat and open flame
Manufacture
The applicant does not use either the Certificate of Suitability procedure or the Active Substance Master File procedure for submission of data, instead summary information is provided in the dossier, which is satisfactory for this type of active drug substance.

The active substance, isopropyl alcohol, is controlled by the USP and Ph Eur monographs and an appropriate specification has been provided.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Batch data are provided which comply with the proposed specification.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug and supporting an appropriate re-test period.

Isopropyl alcohol is normally characterised as an excipient in medicinal products, however for this product, it is classed as a drug substance as it plays an important role in the efficacy of the product for its intended use. Although the data are limited, it is considered acceptable, given the nature of this material.

DRUG PRODUCT
Other ingredients
The only other ingredient is purified water. Purified water complies with USP and Ph Eur requirements and is supported by satisfactory certificates of analysis.

No material of animal or human origin is used in manufacture of the product.

Pharmaceutical Development
The product development provided is considered to be acceptable.

Impurity Profile
The impurity profile has been characterised and the release and shelf life limits are in-line with the batch and stability data which is satisfactory.

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

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has been shown satisfactory results. Process validation data on three batches of each size of applicator have been provided and are satisfactory.

In-process controls are appropriate considering the nature of the product and the method of manufacture.

Finished product specification
The finished product specification is 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. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.
Container Closure System
The finished product is contained in an applicator. The applicators consist of a latex-free sponge attached to a plastic handle/barrel, which holds a latex-free dyed pledget and glass ampoule containing the antiseptic solution. The pack sizes are:
- 0.67 ml (Sepp): 200 applicators
- 1.5 ml (Frepp): 20 applicators
- 1.5 ml and 3 ml: 25 applicators
- 10.5 ml: 1 applicator or 25 applicators
- 26 ml: 1 applicator

Not all pack sizes may be marketed. The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging for assessment before those pack sizes are commercially marketed.

Satisfactory declarations have been provided by the suppliers of all the materials stating that the materials comply with the EC Directive 2002/72, as well as with the relevant Ph Eur monograph for containers. Specifications and satisfactory certificates of analysis are provided.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. The precautions “Flammable. Do not store above 25°C” and “Store in the original packaging; applicator is sterile unless seal is broken” and “Avoid exposure of the container and contents to naked flames during use, storage and disposal” are considered acceptable.

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

Product Information
The approved SmPC, leaflet and labelling are satisfactory.

Conclusion
All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted for this application.

III.2 NON-CLINICAL ASPECTS
No new non-clinical studies have been conducted in support of this application and the non-clinical overview is based on published literature. This is acceptable given that use of both chlorhexidine and isopropyl alcohol as antiseptics is well-established, having been used for many years as disinfectants for skin and other surfaces. The non-clinical overview outlines the pharmacology, pharmacokinetics and toxicology of both active substances.

An Environmental Risk Assessment has been provided and concludes that it is unlikely that there will be any risk to the environment from the new formulation. Also, since the proposed product is intended to replace the currently marketed version, there will be no increase in environmental exposure to chlorhexidine gluconate and isopropyl alcohol following marketing authorisation.
The grant of a marketing authorisation is recommended from a non-clinical viewpoint.

### III.3 CLINICAL ASPECTS

#### Pharmacokinetics

No new pharmacokinetic data are submitted or required for this application.

Absorption of chlorhexidine through the skin barrier is very low, except when used in preterm infants (gestational age < 26 weeks).

#### Pharmacodynamics

No new pharmacodynamic data are submitted or needed for this application.

Chlorhexidine gluconate is a cationic biguanide. Its antimicrobial action is due to the disruption of the cell membrane and the precipitation of cell contents. It has a bactericidal or bacteriostatic action against a wide range of gram-positive and gram-negative bacteria. It is relatively ineffective against mycobacteria. It inhibits some viruses and is active against some fungi. It is inactive against bacterial spores. It has a superior residual property in comparison to currently available skin antiseptics. Chlorhexidine gluconate has a strong binding property to skin and has a residual property on the skin that has been documented at 48 hours. Chlorhexidine gluconate is not neutralised in the presence of organic matter.

Isopropyl alcohol is rapidly bactericidal and is a fast acting broad spectrum antiseptic, but is not considered persistent. Its mechanism of action appears to be denaturation of proteins.

#### Clinical efficacy

Twenty-seven clinical efficacy studies were conducted by the sponsor to evaluate the antimicrobial properties of 2% w/v chlorhexidine gluconate (CHG)/70% v/v isopropyl alcohol (IPA) topical solution (brand name ChloraPrep), in non-tinted and tinted variations, for the indications of preoperative and/or pre-injection skin preparation. During the 17-year development history, the sponsor assessed the use of other CHG formulations, developed innovative applicators of varying volumes and differing configurations, tested alternative anatomic sampling sites, and explored non-standard cylinder sampling intervals/times while continuing the development of the 2% w/v CHG/70% v/v IPA drug product.

In order to measure the antiseptic efficacy of the different applicators used, four concepts need to be considered:
- The reduction in bacterial load over time.
- The effective surface area covered where there is an even reduction in bacterial load.
- Reductions in bacterial load in at least two areas which have different baseline bacterial load. Often the approach is to measure antiseptic effects in the groin and abdominal areas.
- Comparative efficacy to the monocomponents or other antiseptics.

The studies used in the submission approach these four different concepts in a variety of ways to measure the risks/benefits of using the two compounds in combination.

#### Comparable Efficacy of Tinted and Untinted ChloraPrep

In addition to the untinted formulation, ChloraPrep is also marketed in orange-tinted and teal-tinted formulations. The tinted and untinted ChloraPrep products use the same active drug product solution contained in identical glass ampoules and applicators. The only difference between the two products is the dye-impregnated pledget used for the tinted product. The dye is added to the drug product upon activation of the applicator during use. Clinical trials and
stability studies have been conducted for the tinted and untinted products. The chemical studies and process validation for the drug product is the same for both the tinted and untinted products because the active drug product is the same. Therefore, clinical efficacy data are presented for both the tinted and untinted products.

Efficacy results from these studies were consistent for both tinted and untinted products (ChloraPrep with Tint and ChloraPrep) for all applicator sizes.

**Justification and Choice of Applicator Size (Posology)**
Compared to the previously approved tinted product, this product contains two new application volumes, i.e. 0.67 ml and 1.5 ml as in the proposed SmPC:

<table>
<thead>
<tr>
<th>Applicator</th>
<th>Coverage Area (cm x cm)</th>
<th>For Procedures such as:</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.67 ml (Sepp)</td>
<td>5 x 8</td>
<td>- Routine venipuncture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Blood culture collection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Peripheral (arterial line) cannulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Simple biopsy</td>
</tr>
<tr>
<td>1.5 ml</td>
<td>10 x 13</td>
<td>- Routine venipuncture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Blood culture collection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Peripheral (arterial line) cannulation</td>
</tr>
<tr>
<td>1.5 ml (Frepp)</td>
<td>10 x 13</td>
<td>- Simple biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Dialysis Fistula/Graft site cleansing</td>
</tr>
<tr>
<td>3 ml</td>
<td>15 x 15</td>
<td>- Midline &amp; Central Venous Catheter (CVC) insertion and maintenance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Peritoneal dialysis site cleansing</td>
</tr>
<tr>
<td>10.5 ml</td>
<td>25 x 30</td>
<td>- Minor and major surgical procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Implantable device placement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Prosthetic device placement or removal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Midline, Peripheral Intravascular Central Catheter (PICC) &amp; CVC insertion and maintenance</td>
</tr>
<tr>
<td>26 ml</td>
<td>50 x 50</td>
<td>- Cardiac catheterisation and Cardiac Cath Lab procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Interventional Radiology procedure</td>
</tr>
</tbody>
</table>

Good antisepsis is more likely to occur with convenient products. One of the therapeutic justifications for the drug product is the convenience offered by the selection of single-use applicators offered in different sizes for various medical procedures. Currently, there are no clinical guidelines for selecting antiseptic applicators for specific medical procedures. As such, applicator choice is based on the medical judgment of clinicians.
The various ChloraPrep applicators contain the same active ingredient (2% w/w CHG and 70% v/v IPA) in the same concentration but in different volumes. Therefore, the efficacy demonstrated for the 3 ml and 26 ml applicators, for example, applies equally to the 10.5 ml applicator. Also, as discussed previously, the efficacy of ChloraPrep with Tint is comparable to the untinted product.

**Main studies**
Five studies presented in the application are central for this submission. Two studies (study code 990326MBT and 990326HRT) have been submitted using the 3 ml applicator with untinted 2% CHG in 70% IPA. Three studies using the 26 ml applicator have generated data with the tinted 2% CHG in 70% IPA (study codes No 371-106, No 371-108 and No 371-109).

The combination of chlorhexidine (CHG) 2% in isopropyl alcohol 70% (IPA) used with the 3 ml applicator and 26 ml applicator produces effective reduction of bacterial load as per the requirements of the FDA guidelines. Five studies presented data derived from testing and sampling in areas where comparative bacterial loads are different (abdomen: low and groin: high). In addition, the 26 ml applicator was shown to be superior to another comparative applicator which used povidone iodine as an antiseptic agent (Study 371-109).

The use or not of tint in this combination solution does not affect its antiseptic properties (Study 371-109). Study 371-108 has shown that when the 26 ml applicator is used in the recommended fashion it will produce consistently the same body coverage and drying associated with no pooling or run-off.

**Time Kill Studies According to European Standards**
The bactericidal and fungicidal activity of ChloraPrep cutaneous solution (2% w/v chlorhexidine gluconate / 70% v/v isopropyl alcohol) was evaluated in four in vitro time kill studies (Studies 091035-201, 091036-201, 091037-201, and 091038-201). ChloraPrep cutaneous solution was evaluated at full strength, three-quarter strength, and half-strength for log_{10} reduction from the initial population of each challenge species at 15-minute exposure times. Two test articles, ChloraPrep and ChloraPrep with Tint, were evaluated. The tinted and untinted ChloraPrep products use the same active drug product solution in the same concentration; therefore, clinical results for the tinted product are relevant to the effectiveness of the untinted product. Results for both tinted and untinted products at each strength are included in the study reports, but only the results for the untinted product are presented here. Test organisms, methodology, and specification limits were established by European Standards EN 1040, EN 1275, EN 13624, and EN 13727, as detailed in the following table.
ChloraPrep rapidly produced a 4 log reduction for the following organisms: *Enterococcus hirae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans*. ChloraPrep® did not meet the 4 log reduction standard for the fungus *Aspergillus brasiliensis*, formerly known as *Aspergillus niger*, after 15 minutes. A summary of results is presented in the following table.

<table>
<thead>
<tr>
<th>EN Norm</th>
<th>Test Material</th>
<th>Exposure Conditions</th>
<th>Test Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>EN 1040 (Study 091035-201)</td>
<td>ChloraPrep</td>
<td>100%, 75%, 50%</td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td>ChloraPrep</td>
<td>100%, 75%, 50%</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>EN 1275 (Study 091037-201)</td>
<td>ChloraPrep</td>
<td>100%, 75%, 50%</td>
<td><em>Candida albicans</em></td>
</tr>
<tr>
<td></td>
<td>ChloraPrep</td>
<td>100%, 75%, 50%</td>
<td><em>Aspergillus brasiliensis</em></td>
</tr>
<tr>
<td>EN 13727 (Study 091036-201)</td>
<td>ChloraPrep</td>
<td>100%, 75%, 50% in clean 0.3 g/L bovine serum albumin</td>
<td><em>Enterococcus hirae</em></td>
</tr>
<tr>
<td></td>
<td>ChloraPrep</td>
<td>100%, 75%, 50% in clean 0.3 g/L bovine serum albumin</td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td>ChloraPrep</td>
<td>100%, 75%, 50% in clean 0.3 g/L bovine serum albumin</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>EN 13624 (Study 091038-201)</td>
<td>ChloraPrep</td>
<td>100%, 75%, 50% in clean 0.3 g/L bovine serum albumin</td>
<td><em>Candida albicans</em></td>
</tr>
<tr>
<td></td>
<td>ChloraPrep</td>
<td>100%, 75%, 50% in clean 0.3 g/L bovine serum albumin</td>
<td><em>Aspergillus brasiliensis</em></td>
</tr>
</tbody>
</table>

ChloraPrep rapidly produced a 4 log reduction for the following organisms: *Enterococcus hirae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Candida albicans*. ChloraPrep® did not meet the 4 log reduction standard for the fungus *Aspergillus brasiliensis*, formerly known as *Aspergillus niger*, after 15 minutes. A summary of results is presented in the following table.

<table>
<thead>
<tr>
<th>Species tested</th>
<th>EN criterion</th>
<th>Duration of exposure (mins)</th>
<th>Mean Log&lt;sub&gt;10&lt;/sub&gt; reduction by concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Full strength (1X)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>EN 1040</td>
<td>5 min</td>
<td>&gt;5.50</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>EN 1040</td>
<td>5 min</td>
<td>&gt;5.69</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>EN 1275</td>
<td>15 min</td>
<td>&gt;4.25</td>
</tr>
<tr>
<td><em>Aspergillus brasiliensis</em></td>
<td>EN 1275</td>
<td>15 min</td>
<td>3.75</td>
</tr>
<tr>
<td><em>Enterococcus hirae</em></td>
<td>EN 13727</td>
<td>5 min</td>
<td>&gt;5.70</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>EN 13727</td>
<td>5 min</td>
<td>&gt;5.50</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>EN 13727</td>
<td>5 min</td>
<td>&gt;5.70</td>
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<tr>
<td><em>Candida albicans</em></td>
<td>EN 13624</td>
<td>15 min</td>
<td>&gt;4.17</td>
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<tr>
<td><em>Aspergillus brasiliensis</em></td>
<td>EN 13624</td>
<td>15 min</td>
<td>3.75</td>
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* Additional shaded areas indicate lack of fungicidal activity.

Additional testing of ChloraPrep against *Aspergillus brasiliensis* and *Candida albicans* for exposure time of up to 60 minutes was undertaken to further describe the product’s fungicidal characteristics (Protocol #100314-210). At full concentration, ChloraPrep met European Standard EN 13624 (≥ 4.0 Log<sub>10</sub> reduction within 60 minutes or less) for *Aspergillus brasiliensis*. Given the mode of action of chlorhexidine, the level of activity against fungi of the genus Aspergillus is as expected.

**Clinical safety**

**Patient exposure**

Total exposure to ChloraPrep and chlorhexidine gluconate-containing investigational test articles was 3,923 subjects, 2,175 in the 26 efficacy studies and 1,748 in the 21 safety studies. In the efficacy trials previously summarized, the observed adverse drug reaction after topical application of the drug product included local minimal or moderate erythema with minimal oedema and popular response. Systemic adverse drug reactions were not observed.
The five trials previously mentioned have not raised any unexpected or serious adverse events due to the combined use of 2% chlorhexidine in 70% isopropyl alcohol.

In addition to the five studies measuring the effectiveness and safety of chlorhexidine 2% in 70% isopropyl alcohol with or without tint using the 3 ml applicator or 26 ml applicator, the applicant has submitted 6 studies where the primary outcome measure involved safety parameters using this combination. These studies used a series of different models involving 0.3 ml volumes of the combination solution used in patch tests or the 3 ml, 10.5 ml and 26 ml applicators.

The safety studies have not highlighted any additional or unexpected serious adverse events when compared to the mono components of this combination.

From a post-marketing perspective, the most commonly reported adverse events associated with the use of the 2% w/v CHG/70% v/v IPA drug product are skin reactions, primarily confined to the area of application. Of the medically confirmed, non-serious reactions, the most commonly reported symptoms were application site pruritus, erythema, rash, papules and vesicles. This pattern of events is entirely consistent with the known profile of adverse reactions that occur with topical antiseptic products. The current MedDRA coding reference includes a single term “irritation skin reactions.” This term addresses the observed events. No outstanding safety issues have been identified, and no regulatory actions related to safety have been elicited.

Considering the extensive worldwide exposure to the 2% w/v CHG / 70% v/v IPA drug products, the incidence of adverse reactions (0.0014%) is extremely low. No significant safety issues have been identified in the period of this review and therefore it is concluded that the risk-benefit ratio for the 2% w/v CHG / 70% v/v IPA drug product remains acceptable.

**Pharmacovigilance system (DDPS)**
The applicant has submitted a detailed description of the pharmacovigilance system which generally fulfils requirements.

**Periodic Safety Update Report (PSUR)**
The proposal is for 3-yearly PSUR cycle with a data lock point in line with the PSUR European harmonised birthdate.

**Expert Report**
The clinical overview has been written by a suitably qualified person and refers to clinical efficacy studies and bibliographical data submitted on 2% chlorhexidine gluconate and 70% isopropyl alcohol used in combination. The overview comprised a thorough review of the efficacy and safety of 2% chlorhexidine gluconate and 70% isopropyl alcohol with and without tint using the studies submitted as well as publications from relevant journals.

**PRODUCT INFORMATION**
**Summary of Product Characteristics (SmPC)**
The approved SmPC is satisfactory for this product.

**Patient Information Leaflet (PIL)**
The final PIL is in line with approved SmPC and is satisfactory.
Labelling
The labelling is satisfactory.

CONCLUSIONS
The efficacy and safety of the product is satisfactory for the grant of this product licence.

IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of ChloraPrep 2%w/v 70%v/v Cutaneous Solution 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.

NON-CLINICAL
No new non-clinical studies have been submitted by the applicant, which is acceptable given that the use of both chlorhexidine and isopropyl alcohol as antiseptics is well-established.

CLINICAL
Clinical trial data show that the efficacy of ChloraPrep is not affected by presence or absence of dye. Data indicate that ChloraPrep significantly reduces microorganisms on the skin, leading to lower incidence of post surgical and post procedure infections. Superiority of ChloraPrep compared to povidone iodine for catheter-related bloodstream infection rates has been demonstrated. ChloraPrep’s bactericidal activity covers a wide range of organisms. Broad spectrum and fast antibacterial activity provided by isopropyl alcohol combined with lasting antimicrobial effect of chlorhexidine provide an advantageous combination compared to using each of the two components individually. Safety data are based on a fairly large database. Patient exposure is considered adequate to characterise the safety profile of this product. Adverse Drug Reactions were of relatively low incidence, limited to local reactions and generally of mild to moderate nature. The safety of this product in the proposed indication has been demonstrated.

ChloraPrep cutaneous solution can be considered to have a favourable benefit/risk.

The SmPC and PIL are satisfactory.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with chlorhexidine gluconate and isopropyl alcohol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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