Public Assessment Report

Decentralised Procedure

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

UK/H/1305/001/DC

UK licence no: PL 31760/0001

Enturia Limited
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Enturia Limited a Marketing Authorisation (licence) for the medicinal product ChloraPrep® with Tint 2%w/v/70%v/v Cutaneous Solution (PL 31760/0001). This is a general sales medicine (GSL) and is used to disinfect the skin and help prevent infections before invasive medical procedures such as injections, insertion of catheters and minor or major surgery.

ChloraPrep® with Tint 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 new combination of two well known antiseptic agents. The rationale for development of a 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® with Tint 2%w/v/70%v/v Cutaneous Solution outweigh the risks; hence a Marketing Authorisation has been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 1: Information about initial procedure</td>
<td>4</td>
</tr>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflets</td>
<td>9</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>11</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>13</td>
</tr>
<tr>
<td>1 Introduction</td>
<td>13</td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td>15</td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td>18</td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td>20</td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td>23</td>
</tr>
<tr>
<td>Module 6: Steps taken after initial procedure</td>
<td>24</td>
</tr>
</tbody>
</table>
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>ChloraPrep® with Tint 2% w/v / 70% v/v cutaneous solution</th>
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<tr>
<td><strong>Type of Application</strong></td>
<td>Full dossier, Article 8(3)</td>
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<tr>
<td><strong>Active Substance</strong></td>
<td>Chlorhexidine gluconate 2.0% w/v Isopropyl alcohol 70% v/v</td>
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<td><strong>Form</strong></td>
<td>Cutaneous Solution</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>Chlorhexidine gluconate 2.0% w/v Isopropyl alcohol 70% v/v</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Enturia Limited 43 London Road Reigate, Surrey RH2 9PW United Kingdom</td>
</tr>
<tr>
<td><strong>RMS</strong></td>
<td>UK</td>
</tr>
<tr>
<td><strong>CMS</strong></td>
<td>Austria, Belgium, , Germany, Greece, Finland, France, Ireland, Italy, Luxembourg, Malta, The Netherlands, Norway, Portugal, and Sweden</td>
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<td><strong>End of Procedure</strong></td>
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</tr>
</tbody>
</table>
Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
ChloraPrep® with Tint 2% w/v / 70% v/v cutaneous solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Chlorhexidine gluconate 20mg/ml
Isopropyl alcohol 0.70ml/ml
For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM
Cutaneous Solution.
Orange Solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
The medicinal product is to be used for disinfection of the skin prior to invasive medical procedures.

4.2 Posology and method of administration
For cutaneous use.

ChloraPrep with Tint may be used on all age groups and patient populations. However, ChloraPrep with Tint is not recommended for children younger than 2 months old.

One applicator is used containing 3 ml, 10.5 ml or 26 ml of the ChloraPrep with Tint alcoholic solution.

The choice of applicator will depend on the invasive procedure being undertaken and the clinician’s preference.

<table>
<thead>
<tr>
<th>Applicator</th>
<th>Maximum Coverage Area (cm x cm)</th>
<th>For Procedures such as:</th>
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<tbody>
<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>26 ml</td>
<td>50 x 50</td>
<td>- Midline, Peripheral Intravascular Central Catheter (PICC) &amp; CVC insertion and maintenance</td>
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<tr>
<td></td>
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<td>- Cardiac catheterisation and Cardiac Cath Lab procedures</td>
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<tr>
<td></td>
<td></td>
<td>- Interventional Radiology procedure</td>
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</tbody>
</table>

The applicator is removed from the wrapper and held with the sponge facing downward. The applicator is squeezed gently to break the ampoule containing the antiseptic solution, which is released onto the sponge in a controlled flow (for the 26 ml applicator the lever is pressed). The broken ampoule remains safely contained within the applicator. The sponge is gently pressed against the patient’s skin in order to apply the antiseptic solution. A back and forth action of the sponge should be used for 30 seconds. The 26 ml applicator includes two swabs. Clean umbilicus with enclosed swabs when
It is recommended that ChloraPrep with Tint remain on the skin post-procedure to provide continued antimicrobial activity. The tint will slowly fade from the skin. If removal is necessary, remove with soap and water or alcohol.

4.3 Contraindications
The medicinal product is contra-indicated where patients have shown previous hypersensitivity to chlorhexidine, isopropyl alcohol or Sunset Yellow (E110).

4.4 Special warnings and precautions for use
For external use only on intact skin. The solution is an irritant to eyes and mucous membranes. It should therefore be kept away from these areas. If the solution comes in contact with the eyes, they should be washed promptly and thoroughly with water. It should also not be used on open skin wounds, broken or damaged skin, or in children less than 2 months of age. In addition, direct contact with neural tissue or the middle ear must be avoided. Prolonged skin contact with alcoholic solutions should be avoided. The solution is flammable. Do not use with electrocautery procedures or other ignition sources until dry. Remove any soaked materials, drapes or gowns before proceeding. Do not allow the solution to pool.

4.5 Interaction with other medicinal products and other forms of interaction
Alcohol should not be brought into contact with some vaccines and skin test injections (patch tests). If in doubt, consult the vaccine manufacturer’s literature.

4.6 Pregnancy and lactation
There are no known risks for the use of this product in pregnant or lactating women.

4.7 Effects on ability to drive and use machines
No effects are reported.

4.8 Undesirable effects
Very rarely (<1/10,000) allergic or irritation skin reactions have been reported with chlorhexidine, isopropyl alcohol and Sunset Yellow (E110) including: erythema, rash (e.g. erythematous, papular, or maculopapular), pruritus and blisters or application site vesicles. Other local symptoms have included skin burning sensation, pain and inflammation. At the first sign of local skin reaction application of ChloraPrep with Tint should be stopped.

4.9 Overdose
There are no reports of overdose with this product.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC code D08A C52 (Chlorhexidine, combinations).
Mode of Action: Bisbiguanide antiseptics exert their lethal effect upon bacterial cells through non-specific interaction with acidic phospholipids of the cell membranes. Chlorhexidine is both an antiseptic and disinfectant that is bactericidal or bacteriostatic against a wide range of gram-positive and gram-negative bacteria. It is more effective against Gram-positive than Gram-negative bacteria, and some species of Pseudomonas and Proteus have low susceptibility. It is relatively ineffective against mycobacteria. It inhibits some viruses and is active against some fungi. It is inactive against bacterial spores at room temperature. Combinations in alcoholic solution are used to enhance efficacy. It should also be stated that isopropyl alcohol is bacteriostatic at low concentrations but has bactericidal activity at higher concentrations; it does not, however, destroy bacterial spores. The mechanism of action appears to be denaturation of proteins.
Since there is little percutaneous absorption of isopropyl alcohol or chlorhexidine gluconate and the medicinal product is indicated for use on pre-injection sites, pharmacodynamic studies have not been undertaken.

5.2 Pharmacokinetic properties
There is little absorption of isopropyl alcohol or of chlorhexidine gluconate through intact skin. Pharmacokinetic studies have not been conducted with the product.

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber that are not already included elsewhere in the SPC.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Purified water
Sunset Yellow (E110)

6.2 Incompatibilities
Chlorhexidine is incompatible with soap, hypochlorite bleach and other anionic agents. Hypochlorite bleaches may cause brown stains to develop in fabrics, which have previously been in contact with preparations containing chlorhexidine.

6.3 Shelf life
18 months

6.4 Special precautions for storage
Flammable. Do not store above 25°C.
Store in the original packaging; applicator is sterile unless seal is broken.
Avoid exposure of the container and contents to naked flames during use, storage and disposal.

6.5 Nature and contents of container
Chloraprep with Tint is a sterile alcoholic antiseptic solution containing chlorhexidine gluconate and isopropyl alcohol 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 3ml and 10.5ml applicators each have a single glass ampoule within the plastic barrel. The 26ml applicator holds two 13ml glass ampoules. The sterile applicators are individually packaged in an ethyl vinyl acetate film.
The medicinal product is available as 3 ml, 10.5 ml and 26 ml fill volumes.
Pack Size:
3 ml: 25 applicators
10.5 ml: 1 applicator or 25 applicators
26 ml: 1 applicator
Not all pack sizes may be marketed.

6.6 Special precautions for disposal
The solution is flammable. Do not use while smoking, or near any naked flames or strong heat source.
Avoid exposure of the container and contents to naked flames during use, storage and disposal.
This product is for single use only.
Any unused product or waste material should be discarded in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Enturia Limited
43 London Road
Reigate
Surrey
RH2 9PW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 31760/0001
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
23/12/2009

10 DATE OF REVISION OF THE TEXT
23/12/2009
Product Information Leaflet

Chloraprep® with Tint 2%w/v / 70%v/v Cutaneous Solution
chlorhexidine gluconate 2mg/ml isopropyl alcohol 0.7ml/ml
3-ml / 10.5-ml / 26-ml

Read all of this leaflet carefully because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you receive any side effects that you think are serious, please tell your doctor or nurse.

In this leaflet:
1. What is Chloraprep® with Tint and why is it used?
2. Before Chloraprep® with Tint is used
3. How Chloraprep® with Tint will be used
4. Possible side effects
5. How to store Chloraprep® with Tint
6. Further information

1. What is Chloraprep® with Tint and why is it used?
Chloraprep® with Tint is a cutaneous solution of chlorhexidine gluconate 2%w/v and isopropyl alcohol 70%v/v in a plastic applicator with a sponge tip on one end. The applicator contains a fast-acting antiseptic solution, which is used to cleanse the skin and help prevent infections before invasive medical procedures, such as injections, interventions in dentistry and minor or major surgery. Chloraprep® with Tint contains a tint to colour the skin, which makes it easier in the antiseptic properties of the solution.

2. Before Chloraprep® with Tint is used
- If you are allergic to any of the ingredients of Chloraprep® with Tint

3. How Chloraprep® with Tint will be used
Chloraprep® with Tint should only be used on the skin that is inside the body orifice, e.g. the ear canals. In direct contact with neural tissue for example brain and spinal cord above.

Chloraprep® with Tint should only be applied to the skin gently when the solution has been applied in an over-gaseous manner to very fragile or sensitive skin or after repeated use, rash, inflammation, itching, dry and/or flaky skin and pain may occur. At this time sign of any of these reactions, application of Chloraprep® with Tint should be stopped.

Prolonged skin contact should be avoided soiled materials, such as drapes or gowns should be removed before use. The solution should not be allowed to pool.

The solution is flammable, do not use with ignition sources until dry.

Using other medicines
Tell your doctor or nurse if you have recently had a vaccine or skin test injection (patch test is used to test for allergies).

Pregnancy and breast-feeding
If you are pregnant, planning to become pregnant or breast-feeding, Chloraprep® with Tint can still be used. You can talk about this more with your doctor or nurse.

Driving and using machines
Chloraprep® with Tint does not affect your driving or ability to use machines.

4. Possible side effects
Chloraprep® with Tint may cause dryness or irritation of the skin.

5. How Chloraprep® with Tint will be used
The antiseptic solution within the Chloraprep® with Tint system is kept inside the plastic applicator. Your doctor or nurse will hold the applicator and dips the sponge tip into the antiseptic solution. Your doctor or nurse will then wipe the antiseptic solution on the skin to be prepared. Depending on your medical procedure, more than one applicator may be used.

Chloraprep® with Tint is only used on the skin and each applicator is only used once.

If you have any further questions on the use of this product, ask your doctor or nurse.

4. Possible side effects
Chloraprep® with Tint may cause dryness or irritation, although not everybody gets them.

See other side for further instructions.
PAR ChloraPrep® with Tint 2%w/v/70%v/v Cutaneous Solution

- Allow ChloraPrep with Tint to dry completely before starting any medical procedure.
- Do not use with electrocautery procedures until dry. Remove any soiled materials, towels, drapes or gowns before proceeding. Do not allow to pool.
- Chlorhexidine is incompatible with soap and other skin cleansers.
- Alcohol should not be brought into contact with any vacuum and skin test infections or reactions.
- If in doubt, consult the vaccine manufacturer's literature.
- Do not apply the solution in an over vigorous manner to very fragile or sensitive skin. After expected use, local skin reaction may occur including erythema, inflammation, itching, dryness, redness, skin and local application site pain. If at first sign of local skin reaction, stop application of ChloraPrep with Tint.

Special precautions for disposal
- The solution is flammable. Do not use near naked flames or strong heat sources. Avoid exposure of the container and contents to naked flames during use, storage and disposal. Close the applicator after use as per clinical waste procedures.
- Please refer to the Summary of Product Characteristics for ChloraPrep with Tint for further detailed information.

Storage Procedures
- ChloraPrep with Tint is for single use only and is sterile until the packaging is opened. Do not use ChloraPrep with Tint after the expiry date stated on the presentation. The expiry date refers to the last day of that month. Do not store above 25°C. Avoid freezing, store in the original packaging.

Active substances
- The active substances in ChloraPrep with Tint are 2% chlorhexidine gluconate and 70% isopropyl alcohol. The inactive ingredients in ChloraPrep with Tint are purified water and Sunset Yellow E 110.

Marketing Authorisation Holder
- Erika Ltd
- 43 London Road
- Regn No: 094596 SW
- United Kingdom
- ChloraPrep is a registered trademark of Cardinal Health, Leawood, KS 66291, USA

Very rarely fewer than 1 in 10,000 people allergic or sensitized skin reactions to the ingredients in ChloraPrep with Tint (chlorhexidine gluconate and isopropyl alcohol) may have been reported.
- Rash, inflammation, itching, dryness and/or tiny skin and local application site pain. If at first sign of any of these reactions, application of ChloraPrep with Tint should be stopped.
- If the skin reaction persists, or if you notice any side effects not listed in this leaflet, please tell your doctor or nurse immediately.

5. HOW TO STORE CHLORA PreP WITH TINT
- Flammable. Do not store ChloraPrep with Tint above 25°C.
- Store in the original packaging, applicator is sterile until the seal is broken.
- Do not expose the container or its contents to naked flames during use or storage. Do not use past the expiry date.
- Keep out of the reach and sight of children.
- Medicines should not be discarded via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION
- What ChloraPrep contains
- The active substances are chlorhexidine gluconate 20mg/ml and isopropyl alcohol 70%v/v limit. The other ingredients are purified water and Sunset Yellow E 110.
- What ChloraPrep looks like and contents of the pack
- ChloraPrep with Tint is a sterile alcohol-based antiseptic solution containing chlorhexidine gluconate and isopropyl alcohol in an applicator. The applicators consist of a luer-locked spike attached to a plunger. The plunger is housed in a plastic handle through which holds a latex-free rubber and glass ampoule containing the antiseptic solution. The 25ml and 50ml applicators each have a single glass ampoule with the plastic barrel. The 1ml applicators have two 10ml glass ampoules. The sterile applicators are individually packaged in an ethyl vinyl acetate film.

Pack size
- 25 applicators
- 10 pack: 1 applicator or 25 applicators
- 2 pack: 1 applicator

Not all pack sizes may be marketed

Marketing Authorisation Holder and Manufacturer
- The Marketing Authorisation holder of ChloraPrep with Tint is Erika Ltd
- 43 London Road
- Regn No: 094596 SW
- United Kingdom

- This medicinal product is authorised in the Member states of the EEA under the following names:
  - Austria: ChloraPrep® gelfarb.
  - Belgium: Gélée ChloraPrep® colore.
  - Cyprus: ChloraPrep® gelfarb.
  - Denmark: ChloraPrep® luttfarbig
  - Estonia: ChloraPrep® gelborbes.
  - Finnland: ChloraPrep® gelrotblass.
  - France: ChloraPrep® colore.
  - Germany: ChloraPrep® gefärbt.
  - Greece: ChloraPrep® giallo e rosso.
  - Ireland: ChloraPrep with Tint.
  - Italy: ChloraPrep com Colore.
  - Luxembourg: ChloraPrep® gefärbt.
  - Malta: ChloraPrep with Tint.
  - Netherlands: Gelinie ChloraPrep.
  - Norway: ChloraPrep® med farve.
  - Portugal: ChloraPrep® soluto em conto.
  - Sweden: ChloraPrep® färgad.
  - UK: ChloraPrep with Tint.

In this leaflet difficult to read? You can ask for a copy either in large print, Braille, on CD or tape cassette by calling the MA Holder at (014) 737 7535.

This leaflet was last approved in 2009.

ChloraPrep is a registered trademark of Cardinal Health, Leawood, KS 66291, USA

IB: PA X00000
ML: 84076/009001
PL: 35760/0090

Artwork 6-7/5/00002 / A0020
Module 4
Labelling

ChloroPrep with Tint 2%w/v/70% Cutaneous Solution Carton
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® with Tint 2% w/v / 70% v/v cutaneous solution 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® with Tint 2% w/v / 70% v/v cutaneous solution. In the UK, the same product, but without tint, was originally marketed, as Chloraprep, authorised to Insight Health Limited (PL 19803/0001), granted in October 2005, and presented in a wide range of primary containers as applicators – 0.67ml (Sepp); 1.5ml (Frepp), 3ml (Frepp); 10.5ml (Frepp) and 26ml.

This Marketing Authorisation has recently been subject to a Change of Ownership and is licensed to Enturia Limited.

The cutaneous antiseptic drug product ChloraPrep® with Tint contains 2% w/v chlorhexidine gluconate in 70% v/v isopropyl alcohol in unit dose applicators. This is a new combination 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 a fixed combination product containing 2% CHG and 70% IPA 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, pre-clinical and clinical overviews have been submitted.

Pharmacovigilance system

The RMS considers that the Pharmacovigilance system as described by the applicant fulfils 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)**

This product a considered a new combination of a product not currently marketed in the EU. The applicant therefore should submitted a PSUR at least every six months during the first two years of marketing and once a year for the following two years thereafter, unless other requirements have been laid down as a condition of the marketing authorisation. Subsequently, the PSURs should be submitted at three-yearly intervals or immediately upon request.

The RMS has been assured that acceptable standards of GMP are in place for these product types 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® with Tint 2% w/v / 70% v/v cutaneous solution</th>
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<td>Name(s) of the active substance(s) (INN)</td>
<td>Chlorhexidine gluconate 2.0% w/v Isopropyl alcohol 70% v/v</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>ATC code D08A C52 (Chlorhexidine, combinations)</td>
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<td>Cutaneous Solution</td>
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<td>Chlorhexidine gluconate 2.0% w/v Isopropyl alcohol 70% v/v</td>
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<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1305/001/DC</td>
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<td>Reference Member State</td>
<td>United Kingdom</td>
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<td>Member States concerned</td>
<td>Austria, Belgium, Germany, Greece, Finland, France, Ireland, Italy, Luxembourg, Malta, The Netherlands, Norway, Portugal, and Sweden</td>
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<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 31760/0001</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Enturia Limited</td>
</tr>
<tr>
<td></td>
<td>43 London Road</td>
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<tr>
<td></td>
<td>Reigate, Surrey RH2 9PW</td>
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<tr>
<td></td>
<td>United Kingdom</td>
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</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\}amino-
\{4-chlorophenyl\}methanediamine di-
D gluconate

Structure

![Structure of Chlorhexidine Gluconate](image)

Molecular formula: C_{22}H_{30}Cl_{10} \cdot 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 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 European Directorate for the Quality of medicines and Healthcare (EDQM) Certificated 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 and 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 working standards used by the active substance manufacturer and finished product manufacturer during validation studies. 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**

\[
\text{CH}_3\text{CH(OH)}\text{CH}_3
\]

Molecular formula: C\(_3\)H\(_8\)O
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/cm\(^3\), 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 Drug 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 Ph Eur monograph 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
Other ingredients consist of pharmaceutical excipients, namely sunset yellow (E110) and purified water. An in-house (internal) specification has been provided for sunset yellow and is satisfactory. Purified water complies with USP and BP requirements which are identical to the Ph Eur monograph for purified water. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

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.

Manufacturing process
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. The applicant has provided a commitment to provide the results of the full analytical release data for the first three commercial batches, prior to marketing. 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 3ml and 10.5ml applicators each have a single glass ampoule within the plastic barrel. The 26ml applicator holds two 13ml glass ampoules. The sterile applicators are individually packaged in an ethyl vinyl acetate film. The medicinal product is available as 3 ml (pack size of 25 applicators), 10.5 ml (1 applicator or 25 applicators) and 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 Directed 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 18 months 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.

Photostability
It is known that the drug substance is light sensitive; the applicant has provided a commitment to undertake a post-marketing photostability study of the drug product.

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. Colour mock-ups of the labelling and PIL have been provided.

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 PRE-CLINICAL ASPECTS
No new nonclinical studies have been conducted in support of this application and the nonclinical 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 nonclinical overview
outlines the pharmacology, pharmacokinetics and toxicology of both active substances, however it is noted that the applicant does not address the inclusion of the dye and associated implications on pharmacology, pharmacokinetics and toxicology.

Sunset yellow (E110) is commonly used as an excipient or additive in medicinal and food products. In addition, there is a wealth of in vivo and in vitro data in the literature demonstrating that Sunset Yellow dye has low toxic potential.

An ADI of 2.5 mg/kg has been adopted for Sunset Yellow (E110) by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The proposed levels of Sunset yellow are well below the published ADI and additional reassurance is provided when considering the proposed route of administration (cutaneous). In conclusion, there are no toxicological concerns associated with the inclusion of the tint.

**Ecotoxicity/environmental risk assessment**

An Environmental Assessment report has been provided. The higher recommended dose for the proposed tinted product (520 mg/26 ml) is used to calculate the denominator along with the removal of the factor of 100. The corrected PECsurfacewater value is 2.6 μg/L which is over the threshold of 0.01 μg/L from the ERA guideline (EMEA/CHMP/SWP/4447/00) which triggers a Phase II environmental fate and effect analysis.

A Phase II environmental fate and effect analysis was also provided. Based on the projected future sales of ChloraPrep products, refinements to the Phase I Predicted Environmental Concentrations in surface water (PECsurfacewater) have been made. The maximum PECsurface water was calculated to be 0.318 μg/L. Data on the fate and effects of chlorhexidine gluconate in the environment has been sought in the published literature with limited success. However, approval of the active substance chlorhexidine digluconate as a biocide (under the EU Biocidal Products Directive, 98/8/EC) has been sought by third parties, with a dossier submitted recently (2007) to the appropriate EU authorities. The risk to the environment following the use of chlorhexidine digluconate as a disinfectant in hospital settings has been addressed in the submission and Enturia is endeavouring to obtain access to the data and the environmental risk assessments contained therein. As such, Enturia maintains that the use of ChloraPrep products in hospitals is unlikely to pose an unacceptable risk to the environment. Further supporting evidence is provided by the non-designation of chlorhexidine digluconate as hazardous under UN 3077 (transport of dangerous substances).

**Assessment of the Applicant’s response**

The use of the maximum daily dose the PECsurfacewater has been calculated to be 2.6 μg/L using default values for Fpen, WASTEW/inhab and DILUTION. However the applicant has used projected sales figures to refine the Fpen value, resulting in a PECsurfacewater of 0.318 μg/L which is still over the threshold of 0.01 μg/L, thus triggering a Phase II assessment.

Currently, a satisfactory Phase II assessment has not been conducted as literature data reporting the fate and effect of the drug substance is limited. However, it was envisaged that data would become available following approval of the active substance as a biocide. This data was not available during this procedure but the applicant has committed to provide a post-marketing environmental assessment or access to the manufacturer’s assessment package for chlorhexidine gluconate as a follow-up measure.
III.3 CLINICAL ASPECTS

INTRODUCTION

Pharmacokinetics
Chlorhexidine gluconate 2% (w/v) and Isopropyl alcohol 70% (v/v): No studies investigating possible pharmacokinetic drug interaction systematically have been conducted by the applicant. From long-lasting clinical experience, no concerns arise necessitating such studies. Furthermore, the product is not intended to be co-administered with other topical products. The most relevant information for the pharmacokinetic assessment of the drug product is that it is not systemically available after dermal application and only trace amounts are absorbed following oral administration.

Pharmacodynamics
The applicant has submitted data which indicates that the use of untinted 2% CHD and 70%IPA in combination offers superior antiseptic action to each of the components separately. The data is supported by an in vitro study which uses the minimal inhibitory concentration (MIC) and an in vivo study in 12 subjects (Protocol CXA 1007).

Clinical efficacy and Clinical safety
The applicant’s submission package contains a wealth of data focused primarily on the untinted 2%CHD in 70% IPA. In total there are 16 clinical efficacy studies (13 untinted and 3 tinted) measuring primarily the antiseptic potential of this new combination.

The applicant has submitted a licence application only for the tinted 2%CHD in 70% IPA solution. Three different applicator devices are associated with this submission these being the 3ml applicator, 10.5ml applicator and 26ml applicator. Each is targeted for different medical or surgical interventions.

1. 3ml applicator is indicated for midline & central venous catheter (CVC) insertion and maintenance

2. 10.5ml applicator is indicated for minor and major surgical procedures and implantable device placement.

3. 26ml applicator is indicated for prosthetic device placement or removal, midline, peripheral intravascular central catheter, (PICC) & CVC insertion and maintenance cardiac catheterisation and cardiac cath lab procedures interventional radiology procedure.

In order to measure the antiseptic efficacy of the three 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 a combination.
The clinical trial study section can be divided into studies using one of two devices proposed by the applicant for single use: a 3ml applicator, and a 26ml applicator. No clinical efficacy data has been submitted for the 10.5ml applicator.

Five studies will be presented below as central for this submission. Two studies (study code 990326MBT and 990326HRT) has been submitted using the 3ml applicator with untinted 2%CHD in 70%IPA. Three studies using the 26ml applicator have generated data with the tinted 2%CHD in 70%IPA (study codes No 371-106, No 371-108 and No 371-109). No data has been submitted using the 10.5ml applicator as well as the 3ml or 10.5ml tinted solutions.

The combination of Chlorhexidine (CHD) 2% in isopropyl alcohol 70% (IPA) used with the 3ml applicator and 26ml 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 26ml 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 26ml applicator is used in the recommended fashion it will produce consistently the same body coverage and drying associated with no pooling or run-off.

The five trials have not raised any unexpected or serious adverse events due to the combined use of 2% chlorhexidine in 70% isopropyl alcohol.

No data regarding the use of the 10ml applicator have been submitted so no opinion can be made regarding its capacity to reduce bacterial load and surface area coverage.

In addition to the 5 studies measuring the effectiveness and safety of chlorhexidine 2% in 70% isopropyl alcohol with or without tint using the 3ml applicator or 26ml 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 0.3ml volumes of the combination solution used in patch tests or the 3ml, 10.5 and 26ml applicators.

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

Conclusion:
The clinical efficacy and safety data have shown that similar acceptable bacterial reduction levels and safety can be obtained with the un-tinted and tinted formulations of this new combination using the different applicators proposed. Models have used groin and abdomen bacterial load level reduction with the 3ml applicator and 26ml applicator. Comparative data for use of the un-tinted and tinted solution in the 26ml applicator show that there should be not difference between the two solutions regarding antiseptic properties. Therefore, the data should be transposable to the 3ml applicator and 10.5ml applicator.

No efficacy data was given for the 10.5ml applicator however it can be argued that its effects should be similar to the 26ml applicator although the surface area covered will be smaller. The applicant should give a clear explanation as to why they did not submit an efficacy study for the 10.5ml applicator but just a safety study.
BENEFIT RISK ASSESSMENT
The combination of tinted 2% chlorhexidine in 70% isopropyl alcohol when used with the 3ml applicator and 26ml applicator has been shown to have equivalent topical antibacterial properties to other similar topical antiseptic products for the surface areas claimed by the applicant. Data both in healthy volunteers and patients showed no difference in the antibacterial performance of either applicator. The combination of these two products may offer better antiseptic effects seen in the in vitro and pharmacodynamic data.

The use of a tint does not affect the efficacy of the product in the 26ml applicator. These results can be acceptable for the 3ml applicator and 10.5ml applicator. The safety data has shown that this tinted combination is not associated with any additional risk of adverse events as opposed to the un-tinted solution when tested using the 3ml and 10.5ml applicator. No specific safety study was conducted for the 26ml applicator however safety data from STUDY No 371-109 indicates that no there were no unexpected adverse events when this applicator is used. In addition, it may be less of a skin irritant in than products using pvp-iodine. The tint does not affect the adverse event profile of the solution when compared to the un-tinted formulation.

The applicant has provided guidance in Section 4.2 for where each of the applicator should be used.

The impurity profile of the drug product is considered justified.

In conclusion, the risk-benefit profile of the 3ml applicator and 26ml solution is positive. It would appear that the 10.5ml applicator may offer similar efficacy and safety to the 26ml applicator. This combination of 2% chlorhexidine in 70% isopropyl alcohol used in a 3ml applicator, 10.5ml and 26ml applicator has a positive benefit risk balance and as such is approvable.

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 17 studies submitted as well as 69 publications up to July 2007.

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.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of ChloraPrep® with Tint 2%w/v 70%v/v Cutaneous Solution is 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.

PRECLINICAL
No new nonclinical 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. The pharmacological, pharmacokinetic or toxicological implications associated with inclusion of the tint have not been discussed; however, on consideration of literature data, the proposed route of administration and published ADI values it is concluded that no toxicological concerns arise on inclusion of the tint.

EFFICACY
The clinical efficacy and safety data have shown that similar acceptable bacterial reduction levels and safety can be obtained with the un-tinted and tinted formulations of this new combination using the different applicators proposed. Comparative data for use of the un-tinted and tinted solution in the 26ml applicator showed no difference between the two solutions regarding antiseptic properties. Therefore, the data is transposable to the 3ml applicator and 10.5ml applicator.

No efficacy data was given for the 10.5ml applicator however it can be argued that its effects should be similar to the 26ml applicator although the surface area covered will be smaller.

The SmPC and PIL are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Chlorhexidine gluconate 2.0% w/v and Isopropyl alcohol 70% v/v 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

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>25th January 2010</td>
<td>ADD/AMEND</td>
<td>PIL and label mock-ups to be used in the commercial product launch in the UK.</td>
<td>Approved</td>
</tr>
</tbody>
</table>