**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Hexiprep 2.0% w/v / 70.0% w/v Impregnated Pad
Chlorhexidine digluconate solution
Isopropyl alcohol
PA23120/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

**CONTENTS**

I. INTRODUCTION

II. QUALITY ASPECTS

III. NON-CLINICAL ASPECTS

IV. CLINICAL ASPECTS

V. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

VI. REVISION DATE

VII. UPDATE

## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Hexiprep 2.0% w/v/70% w/v Impregnated Pad, from GAMA Healthcare Ireland Ltd on 16th April 2021 for disinfection of the skin prior to invasive medical procedures that do not require a clean air environment.

The proposed legal basis is 10(3), hybrid.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at *www.hpra.ie*.

| | |
|---|---|
| Name of the product | Hexiprep 2.0% w/v /70.0% w/v Impregnated Pad |
| Name(s) of the active substance(s) (INN) | Chlorhexidine digluconate solution, Isopropyl alcohol |
| Pharmacotherapeutic classification (ATC code) | D08AC52 chlorhexidine combinations |
| Pharmaceutical form and strength(s) | Impregnated Pad 0.2% w/v/70.0% w/v |
| Marketing Authorisation Number(s) in Ireland (PA) | PA23120/001/001 |
| Marketing Authorisation Holder | GAMA Healthcare Ireland Ltd |
| MRP/DCP No. | IE/H/1161/001/DC |
| Reference Member State | IE |
| Concerned Member State | XI (Northern Ireland) |

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Hexiprep 2.0% w/v /70.0% w/v Impregnated Pad.

### II.2 Drug substance

The active substances are chlorhexidine digluconate and Isopropyl Alcohol (IPA).
Chlorhexidine digluconate is an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP). The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements

Isopropyl Alcohol (IPA) is normally characterised as an excipient in medicinal products, for this product it is considered an atypical active substance. The active substance specification is considered adequate to control the quality.

Batch analytical data demonstrating compliance with this specification has been provided.

### II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances

All ingredients comply with Ph. Eur. and are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monographs and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. /EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

*Adventitious Agent Safety*

*N/A*

**II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects**

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Hexiprep 2.0% w/v/ 70% w/v Impregnated Pad.

## III. NON-CLINICAL ASPECTS

**III.1 Introduction**

This active substances are the same as those in Chloroprep with tint on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

**III.2 Ecotoxicity/environmental risk assessment**

The applicant has included an abridged ERA with this submission. Although the submitted data are not directly in line with the current ERA guidance, considering the product in question and specifically that the wipe format is likely to result in decreased environmental exposure relative to liquid formulations on the market, it is accepted that the risk to the environment by authorisation of this product is considered to be low.

**III.3 Discussion on the non-clinical aspects**

Pharmacodynamic, pharmacokinetic and toxicological properties of chlorhexidine and isopropyl alcohol are well known. As chlorhexidine and isopropyl alcohol are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview

on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Non-clinical findings of relevance to the prescriber are adequately mentioned in the appropriate sections of the SmPC

## IV. CLINICAL ASPECTS

### IV.1 Introduction

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

### IV.2 Pharmacology

At physiologic pH, chlorhexidine salts dissociate and release the positively charged chlorhexidine cation. The bactericidal effect is a result of the binding of this cationic molecule to negatively charged bacterial cell walls. At low concentrations of chlorhexidine, this results in a bacteriostatic effect; at high concentrations, membrane disruption results in cell death. Chlorhexidine has been established to be active against Gram-positive and Gram-negative organisms, facultative anaerobes, aerobes, and yeasts. It is particularly effective against Gram-positive bacteria (in concentrations ≥ 1µg/L). Significantly higher concentrations (10 to ≥73µg/mL) are required for Gram-negative bacteria and fungi. Chlorhexidine is ineffective against polioviruses and adenoviruses.
Chlorhexidine, like other cation-active compounds, remains on the skin. It is frequently combined with alcohols (ethanol and isopropyl alcohol) which evaporate rapidly from the skin leaving behind a residue of chlorhexidine on the skin; providing for a persistent antimicrobial effect.

Isopropyl alcohol at a concentration of 70%v/v is however known to have antibacterial properties, in its own right and is well-established as a biocidal disinfectant (particularly in regard to hand washes). Water is required to open up membrane pores of bacteria, which acts as a gateway inside for the isopropyl alcohol. In this context isopropyl alcohol has been reported, in of its own, to be effective against a wide range of bacteria, viruses, protozoa, and fungi, and has a relatively low toxicity to humans. The main effect on microorganisms appears to be the coagulation of essential proteins, rendering them ineffective, and causing cell death or inhibiting reproduction. Isopropyl alcohol may also have a dehydrating effect and may interfere with the functioning of cell membranes. Rapid evaporation, however, means that the effect of the alcohol is very short-lived, and is unlikely to contribute to the prolonged antibacterial action being claimed for Hexiprep Skin.

### IV.4 Clinical Efficacy

The applicant has performed one pivotal trial to provide the required pharmacodynamic and clinical efficacy data to support this indication, GH001

This was a double-blind, randomised, positive (ChloraPrep) and placebo controlled study in healthy volunteers, in which contralateral anatomical sites at the inguinal area, clavicle and anterior cubital fossa of the arm were treated with two of the three allocated treatments (Hexiprep Skin Disinfection, placebo or ChloraPrep) being randomized to left or right side. The microbial population determined prior to treatment with test formulation (baseline population) was then compared with the bioburden for the same treatment at a specified time after treatment application, with the treatment effect size being established by subtracting the placebo response from the investigational product.

The primary endpoint was a log10 reduction of the immediate baseline bacterial count at one to 10 minutes for HEXI PREP Skin compared with placebo at each of the three respective test sites (each site was a co-primary endpoint).
Secondary endpoints included: a log10 reduction of the immediate baseline bacterial count at one to 10 minutes of ChloraPrep compared with placebo (assay sensitivity). The persistence of a log10 reduction of the baseline bacterial counts at 30 minutes, and six hours (groin) and six and 24 hours (clavicle and arm) after application of HEXI PREP Skin to the test site compared to placebo and the immediate and persistent microbial reduction of HEXI PREP Skin compared to ChloraPrep positive control.

For the co-primary end-points of reduction in $\log_{10}$ CFU/cm$^2$ at the three anatomical sites clavicle, cubital and inguinal areas (1 to 10min), results demonstrated statistical significance for both ITT and PP analyses.
Statistical significance was met for all secondary end-points of reduction in $\log_{10}$ CFU/cm$^2$ at the three anatomical sites clavicle, cubital (6 and 24 hrs) and inguinal areas (30 min and 6 hrs) with the exception of the clavicle site at 24 hrs which did not reach statistical significance. As a result, the persistence of effect for Hexiprep has been limited to 6 hours duration in the SmPC (section 5.1), compared to 24 hrs for the comparator product Chloraprep.
The secondary end-points looking at the reduction in $\log_{10}$ CFU/cm$^2$ for Chloraprep compared to the placebo were broadly comparable with the results for Hexiprep compared to placebo. The comparison of Hexiprep versus Chloraprep was not

conducted due to the failure to meet statistical significance for all secondary end-points. However overall it can be generally accepted that: statistical significance for Hexiprep over baseline has been met and these are known actives with known and demonstrated activity.

**IV.5 Clinical Safety**

The safety profile of this hybrid combination is in line with the well known safety profile of the actives. The AEs that occurred in the clinical programme for Hexiprep were mainly mild in intensity. There were no SAEs or discontinuations due to AEs in this trial.

As no SAEs occurred during the clinical development programme, the applicant has performed an extensive literature review of the safety of these active substances to inform upon potential risks for Hexiprep.

In addition, a human patch test (cosmetic trial) was also performed with Clinell Alcoholic 2% Chlorhexidinewipes. The applicant has clarified that this study was performed as a medical device study for the same wipes as used with Hexiprep, however it did not use the same solution as Hexiprep.
Overall from a safety perspective the hybrid product is acceptable

**Risk Management Plan**

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Hexiprep. Routine pharmacovigilance activities and routine risk minimisation measures are considered sufficient.

**Periodic Safety Update Report (PSUR)**
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

**V. OVERALL CONCLUSIONS**

This hybrid is acceptable from a Quality, safety and efficacy perspective.

The HPRA, on the basis of the data submitted, considered that Hexiprep 2.0% w/v /70.0% w/v Impregnated Pad demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

**VI. REVISION DATE**

11.12.2025

**VII. UPDATES**

This section reflects the significant changes following finalisation of the initial procedure.

| SCOPE | PROCEDURE NUMBER | PRODUCT INFORMATION AFFECTED | DATE OF START OF PROCEDURE | DATE OF END OF PROCEDURE |
|---|---|---|---|---|
| | | | | |