IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

ChloraPrep 2% w/v / 70% v/v impregnated cutaneous swab
Chlorhexidine digluconate
Isopropyl alcohol
PA2287/001/003

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

Name of the product	ChloraPrep 2% w/v / 70% v/v impregnated cutaneous swab
Name(s) of the active substance(s) (INN)	Chlorhexidine digluconate Isopropyl alcohol
Pharmacotherapeutic classification (ATC Code)	D08AC52
Pharmaceutical form and strength(s)	impregnated cutaneous swab
Marketing Authorisation Number(s) in Ireland (PA)	PA2287/001/003
Marketing Authorisation Holder	Becton Dickinson France 11 Rue Aristide Bergès 38800 Le Pont de Claix France
MRP/DCP No.	IE/H/0662/003/DC
Reference Member State	IE
Concerned Member State(s)	DE FI FR IT NO PT SE UK

II. QUALITY ASPECTS

II.1. Introduction

This application is for ChloraPrep 2% w/v / 70% v/v impregnated cutaneous swab.

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 a novel 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. or 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 ChloraPrep 2% w/v / 70% v/v impregnated cutaneous swab.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The cutaneous antiseptic ChloraPrep™ solution contains 2% w/v chlorhexidine gluconate and 70% v/v isopropyl alcohol.
While a range of ChloraPrep™ products containing the same antiseptic solution are already marketed worldwide in a variety of single-use applicator sizes, the new product comprising a sterile solution of 2% w/v chlorhexidine gluconate / 70% v/v isopropyl alcohol sealed in an aluminium foil pouch together with one or three swabsticks has been developed as an alternative to the other applicator presentations.

III.2 Pharmacology

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 is not neutralised in the presence of organic matter.
Isopropyl alcohol is a rapidly bactericidal and a fast acting broad spectrum antiseptic, but is not considered persistent. Its mechanism of action appears to be denaturation of proteins.
Chlorhexidine and isopropyl alcohol have been used together in various antiseptic formulations for more than 35 years. Time-kill kinetic studies demonstrated the rapid and prolonged kill rates of the combination chlorhexidine gluconate / isopropyl alcohol across a battery of organisms selected based on resident and transient microbial skin flora.
The applicant has provided studies that demonstrate a combination of 2% Chlorhexidine gluconate in 70% Isopropyl alcohol, is effective for both rapid and persistent reduction of bacterial load for a broad spectrum of organisms.

Overall the studies support the inclusion of both antiseptics into the ChloraPrep™ formulation in order to achieve a fast-acting, broad-spectrum, and persistent preparation that significantly reduces the number of microorganisms on intact skin.

III.3 Pharmacokinetics

Studies have shown that absorption of chlorhexidine or isopropyl alcohol through the skin is negligible or absent; chlorhexidine is also poorly absorbed from the gut. Minimal systemic absorption of chlorhexidine occurred in rats following percutaneous administration; over 98% of the dose was recovered from the area of application. Following oral administration, in rats, mice, dogs, marmoset, and Rhesus monkeys, 90% or more of the administered dose was recovered in the feces. Following percutaneous administration of isopropyl alcohol in rats, there was minimal systemic absorption, in which approximately 85% of the dose was recovered from the area of application. Isopropyl alcohol is readily absorbed from the gut; however, the intended administration of ChloraPrep™ is topical application to the skin in preparation for invasive procedures.

III.4 Toxicology

A single-dose toxicity study conducted by the Applicant supports this evidence and demonstrated no treatment-related effects noted on any parameter examined. Therefore, following a single administration of the proposed chlorhexidine product and the proposed chlorhexidine product with exaggerated impurity on non-abraded skin and abraded skin, the dose evaluated (2% chlorhexidine gluconate), was considered the no-observed-effect-dose-level.
There is no evidence of carcinogenicity or genotoxicity for chlorhexidine or isopropyl alcohol. Carcinogenicity studies have been performed in both rats and mice given oral chlorhexidine (fortified with PCA); there was no evidence of carcinogenicity after 2 years.
Studies where chlorhexidine or isopropyl alcohol were administered by oral gavage demonstrate reproductive toxicities. However this product is proposed for disinfection of the skin and absorption of chlorhexidine or isopropyl alcohol through the skin is negligible or absent. Therefore the risk for reproductive toxicity in humans is negligible.
Topical application of chlorhexidine has produced sensitization in some animal models. Isopropyl alcohol is not generally considered to be a dermal irritant; however, clinical reports of skin burns in neonates have been reported. Results of the 7-day rabbit irritation study demonstrate that the test materials containing nonsterile or sterile chlorhexidine gluconate in isopropyl alcohol are non-irritants when administered over a 4-hour (acute) period but are moderate irritants when administered cumulatively over a 7-day period.
Following direct application, chlorhexidine has produced ototoxicity in both cats and guinea pigs. Chlorhexidine and isopropyl alcohol caused ocular irritation on direct application, although there did appear to be a dose-related effect. Furthermore, isopropyl alcohol has been reported to cause irritation to mucous membranes and to cause CNS depression; these are, however, reversible effects. The reported toxic effects are primarily as a result of oral or inhalation exposure to isopropyl alcohol or chlorhexidine; therefore, as long as the product is used in accordance with the recommended posology and instructions for use, the safety risk to individuals is minimal. Furthermore, the warnings in the label clearly highlighted that ChloraPrep™ use should be restricted to application to intact skin.
p-Chloroaniline (PCA) is present as an impurity; however, limits are included in the specification for testing both the chlorhexidine gluconate drug substance and finished drug product. The current limit for PCA is 100 ppm at release and 100 ppm at end of shelf-life, which is adequate to control patients' exposure levels to within an order of magnitude of the WHO calculated tolerable intake of PCA of 2 µg/kg body weight per day.

III.5 Ecotoxicity/environmental risk assessment

Chlorhexidine and isopropyl alcohol are already used in existing marketed products and no significant increase in environmental exposure is anticipated.

III.6 Discussion on the non-clinical aspects

This line extension application concerns a new applicator for the ChloroPrep™ range. The submitted overview of the available non-clinical pharmacodynamic, pharmacokinetic and toxicological data is acceptable. Nonclinical data, where available for each component, reveal no special hazard for humans.

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 Pharmacokinetics

The applicant has not conducted any new pharmacokinetic studies to support this application. ChloraPrep impregnated cutaneous swab is a new applicator for delivery of the already authorised ChloraPrep solution which contains chlorhexidine gluconate 2% and isopropyl alcohol 70% and as such the pharmacokinetics are unlikely to differ.

Absorption
There is little absorption of isopropyl alcohol or of chlorhexidine gluconate through intact skin.

IV.3 Pharmacodynamics

No new pharmacodynamics studies have been conducted by the applicant in support of this application. See the SmPC for more details.

Bisbiguanide antiseptics exert their lethal effect upon bacterial cells through non-specific interaction with acidic phospholipids of the cell membranes.

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

IV.4 Clinical Efficacy

One recently conducted Phase III, partially blinded active and placebo-controlled efficacy and safety pivotal study of the single ChloraPrep swabstick was presented in support of this line extension application for ChloraPrep impregnated cutaneous swab (Study MPS-171PVSS02). An additional previous study report (Study 371-121) was submitted during the procedure in support of the triple swabsticks.

Results
Study MPS-171PVSS02: The reduction in Colony Forming Units (CFUs) was measured following treatment with one Swabstick compared to an active comparator (ChloraPrep product), a reference standard (propanol) and a placebo (normal saline). The outcomes were measured at 30 seconds, 10 minutes and 6 hours following study drug application. One ChloraPrep Swabstick was found to be superior to placebo and non-inferior to the active comparator at all time-points under the conditions of study.

Study 371-121: The aim of the study was to compare the antimicrobial effectiveness potential of ChloraPrep Triple Swabsticks using two application procedures, three swabsticks at once (T1) and the three swabsticks sequentially (T3). The active comparator contained 4% chlorhexidine gluconate. 335 subjects (662 groin sites, 662 abdomen sites total) were treated with the investigational medicinal products. The $\log_{10}$ reductions in CFU/cm^2 of skin on the abdomen and groin sites achieved by the test product ("ChloraPrep® Triple Swabsticks" using two application procedures, three swabsticks at once and the three swabsticks used sequentially) and the active comparator product met and exceeded the regulatory $\log_{10}$ reduction criteria for the specific sites at the 10 minute sampling interval. The CFU/cm^2 recovered at the 6-hour sampling interval but did not exceed the test-day baseline.

IV.5 Clinical Safety

No adverse events were reported in the two main studies submitted to support this line extension application. The safety profile of ChloraPrep solution involving other types of applicators has previously been considered 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 Chloraprep.

The submitted Risk Management Plan, version 1.0 signed 26.04.2020 is considered acceptable. Summary of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

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.

Common renewal date
The common renewal date shall be 5 years following authorisation.

IV.6 Discussion on the clinical aspects

In this line extension application, the applicant proposes a new skin disinfectant applicator type for the already authorised ChloraPrep solution range. No Scientific Advice was sought from the EMA or the RMS. No specific EMA guidance exists for the clinical development of liquid skin disinfectants.

One Phase III efficacy and safety study (MPS-171PVSS02) has been presented as justification for the new Swabstick product. The pivotal study involved the use of one ChloraPrep Swabstick on defined surface areas of the abdomen and the groin. 1121 healthy adults with no underlying dermatology conditions completed the study. The study of one ChloraPrep Swabstick met its primary, secondary and exploratory endpoints under the specific conditions of study (mITT and PP analyses). During the study, no subjects experienced any adverse events or skin irritation.

A second earlier study (Study 371-121) was presented during the procedure in support of use of the triple swabsticks sequentially. The aim of this 2007 study was to compare the antimicrobial effectiveness potential of ChloraPrep Triple Swabsticks using two application procedures, three swabsticks at once (T1) and the three swabsticks sequentially (T3). 335 subjects were treated with the investigational medicinal products. No obvious pattern of treatment failures were observed with respect to swabbing technique used (all together vs sequential), body site (groin vs abdomen) or gender (potential greater hair bearing in males).

No data in special populations have been presented but this is considered acceptable as systemic absorption is negligible and it is already well-known that ChloraPrep solution can cause local skin reactions, especially in vulnerable populations such as neonates.

V. OVERALL CONCLUSIONS

In summary, in Study MPS-171PVSS02, one ChloraPrep Swabstick was found to be superior to placebo and non-inferior to the active comparator at all time-points under the conditions of study. The efficacy data presented for the single ChloraPrep Swabstick is considered adequate.

In Study 371-121, the log_{10} reductions in CFU/cm^2 of skin on the abdomen and groin sites achieved by the test product (using two application procedures, three swabsticks at once and the three swabsticks used sequentially) and the active comparator product met and exceeded the regulatory log_{10} reduction criteria for the specific sites at the 10 minute sampling interval. The CFU/cm^2 recovered at the 6-hour sampling interval but did not exceed the test-day baseline.

The applicant states that the sequential application method was selected for the Product Information because this most accurately reflects clinical practice, this can be agreed. The proposed use for the triple swabsticks is for midline and central venous catheter insertion and maintenance and peritoneal dialysis site cleansing.

No adverse events were reported in the two main studies submitted to support this line extension application. The safety profile of ChloraPrep solution involving other types of applicators has previously been considered acceptable.

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

The HPRA, on the basis of the data submitted, considered that ChloraPrep 2% w/v / 70% v/v impregnated cutaneous swab demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

09.12.2026