LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Mediwash
(chlorhexidine digluconate)

SE/H/2306/01/DC

This module reflects the scientific discussion for the approval of Mediwash. The procedure was finalised on 2023-10-04. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Mediwash, 40 mg/ml, Cutaneous solution.

The active substance is chlorhexidine digluconate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Mediwash, 40 mg/ml, Cutaneous solution, is submitted according to Article 10a of Directive 2001/83/EC. The applicant, ESPL Regulatory Consulting Limited applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, DK, ES, IS, LU, NO and PT as concerned member states (CMS).

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

No specific pharmacology, pharmacokinetics or toxicology studies of CHX have been performed. The data supporting the nonclinical documentation are bibliographic.

Pharmacology
The antibacterial effect of CHX is achieved via binding of the positively charged, hydrophobic CHX molecule to negative charges on the cell membrane of bacteria. When used topically, the N-chlorinated derivative of CHX binds covalently to proteins in the skin and mucosa resulting in a limited systemic absorption, also after an oral ingestion.

The available bibliographic data on pharmacology are primarily focused on primary pharmacology of CHX and are considered adequate.

Pharmacokinetics
After topical administration, systemic absorption of CHX is low due to covalent binding to proteins in the skin and mucosa. The bibliographic data provided by the Applicant suggest limited metabolism of CHX and no evidence for the formation of p-chloroaniline (pca), a known metabolite of CHX.

Toxicology
The overall data provided by the Applicant suggest that toxicity of CHX is low and that CHX is not genotoxic or carcinogenic. There is no evidence to suggest that CHX is a developmental or reproductive toxicant. It can be noted that CHX has been known to cause hypersensitivity.

In conclusion, the bibliographic data cover all important nonclinical aspects of CHX, including genotoxicity, carcinogenicity and developmental and reproductive toxicity and are considered adequate for approval of the product. The limits for impurities and degradation products have been justified.

Environmental Risk Assessment (ERA)
Based on an absence of increased overall environmental exposure, no environmental risk assessment has been conducted which is acceptable and in accordance with the EMA Guideline EMEA/CHMP/SWP/4447/00 on the environmental risk assessment of medicinal products for human use.

Conclusions on studies:
The use of CHX is not expected to alter its concentration or distribution in the environment. Therefore, CHX is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
Chlorhexidine is poorly absorbed from both the gastrointestinal tract following oral administration and the skin after topical application.

Cases of percutaneous absorption of chlorhexidine in newborns are found in the literature. Trace levels have been detected in some cases following daily full-body bathing of newborns. However, there have been no reports of systemic adverse consequences arising from chlorhexidine absorption in paediatric patients and there are no data to suggest that trace absorbed levels have clinical importance.

No data have been found in the literature on the distribution, metabolism, or excretion of topically applied chlorhexidine.

The systemic absorption is practically non-existing, with only occasional reports of trace amounts of chlorhexidine detected in blood samples from newborns following topical administration.

Pharmacodynamics
Chlorhexidine has bacteriostatic, bactericidal, fungicidal, fungistatic, some antiviral properties (against enveloped viruses) and is reported to have some effect against certain protozoa and amoeba. Minimum inhibitory concentrations (MICs) are lower for Gram-positive bacteria than for Gram-negative bacteria because chlorhexidine has an increased affinity for the cell wall of Gram-positive organisms. Prolonged exposure increases the bactericidal effect for most bacteria. The molecule is positively charged and reacts with the negatively charged microbial cell surface, thereby destroying the integrity of the cell membrane. Subsequently, chlorhexidine gluconate penetrates the cell and causes leakage of intracellular components leading to cell death.

Chlorhexidine is used as an antiseptic agent with topical antimicrobial activity. The clinical experience with chlorhexidine is extensive, in medical praxis as an antiseptic agent, in dentistry, as a biocide, as an ingredient of medical device formulations and within cosmetic formulations.

Chlorhexidine can be formulated with various salts; the most common salt is formulations with the gluconate salt. The medical uses of the chlorhexidine salts include use on skin at a concentration of 4.0% w/v (as for Mediwash); for antisepsis of damaged skin at a typical concentration of 1.0% w/v; in obstetric procedures typically at 1.0% w/v; and in peritoneal cavity and bladder procedures, including irrigation, at a concentration of 0.02% w/v.

Clinical efficacy
Mediwash is an aqueous antiseptic formulation that is identical to Hibiscrub®; a well-established colourless and fragrance-free drug product that has been sold and supplied by Mölnlycke HealthCare AB and its associated companies in Scandinavia since the early 1980s. It is also closely related to a red/fragranced formulation of Hibiscrub® that is available in other EU Member States and worldwide.

Chlorhexidine and its related salts were first discovered in 1940s and have been in use as biocides (surface disinfectant), as cosmetic ingredient (as a preservative), within medical devices (for example impregnated dental cleansers) and as a medicine and in dental indications for more than 60 years. The extent of use of chlorhexidine formulations as topical antiseptic in clinical practice is considerable. There is a significant body of supporting data available in the public domain, including several more recent Cochrane Reviews that have investigated chlorhexidine with other antiseptic treatments.

Clinical safety
The safety profile of topical chlorhexidine when used as a disinfectant is well known. As a substance that is not absorbed, the adverse effects associated with its use are limited to hypersensitivity (both immediate and delayed), contact dermatitis and other manifestations of skin irritation.

Overall, the efficacy and safety documentation are considered adequate for approval of the product. The SmPC is considered acceptable from a clinical point of view. The therapeutic indication of the product has been mutually agreed to read: *Mediwash is indicated in adults and children aged 2 months and older as an antiseptic for pre-operative and post-operative disinfection of the hands and skin.*

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 Mediwash.

Safety specification

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.

Summary of the RMP
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly. The submitted Risk Management Plan, version 1.1 signed February 2023 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was multilingual, with English and French as tested languages.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Mediwash is an aqueous antiseptic formulation that is identical to Hibiscrub®; a well-established colorless and fragrance-free drug product that has been sold and supplied by Mölnlycke HealthCare AB and its associated companies in Scandinavia since the early 1980s. It is also closely related to a red/fragranced formulation of Hibiscrub® that is available in other EU Member States and worldwide.

Chlorhexidine has been in clinical use as an antiseptic agent for approximately 60 years with varying recommendation for use depending on different clinical practice in different countries where the substance is marketed. There are numerous reports on chlorhexidine gluconate as an antiseptic agent. Chlorhexidine is recognized and recommend in clinical practice guidelines (WHO 2019, NICE 2019).

It is acknowledged that chlorhexidine is an old substance with well-recognized and established clinical use within the EU. The extent of both the efficacy and the safety information provided by the Applicant fulfils the claims for a WEU application.

The benefit/risk of the product is positive, and the application is recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Mediwash, 40 mg/ml, Cutaneous solution was positively finalised on 2023-10-04.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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