IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Medispray oromucosal spray, solution Chlorhexidine digluconate 2 mg/ml Lidocaine hydrochloride 0.5 mg/ml
LIDOCAINE HYDROCHLORIDE
Chlorhexidine digluconate solution
PA0126/300/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Medispray Oromucosal Spray, Solution containing chlorhexidine digluconate 2 mg/ml, lidocaine hydrochloride 0.5 mg/ml from Clonmel healthcare on 25th March 2022 for:
the symptomatic relief of painful, irritated sore throats.
It is a sugar free preparation and can be used by patients with diabetes.
Additional therapy is required in the event of bacterial infection accompanied by fever.
Medispray is indicated for use in adults, adolescents and children over 12y.

This is a well-established use national application, as per Article 10a of Directive 2001/83/EC.

This product will not be subject to prescription.

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	Medispray Oromucosal Spray, Solution
Name(s) of the active substance(s) (INN)	Chlorhexidine digluconate, Lidocaine Hydrochloride
Pharmacotherapeutic classification (ATC code)	R02AA05- throat preparations
Pharmaceutical form and strength(s)	2/0.5 milligrams/millitre- Oromucosal spray, solution
Marketing Authorisation Number(s) in Ireland (PA)	PA0126/300/001
Marketing Authorisation Holder	Clonmel Healthcare Ltd
Case number	CRN008LHV

II. QUALITY ASPECTS

II.1. Introduction

This application is for Medispray Oromucosal Spray, Solution, Chlorhexidine digluconate 2 mg/ml, Lidocaine Hydrochloride 0.5 mg/ml.

II.2 Drug substance

The active substances are Chlorhexidine Digluconate and Lidocaine Hydrochloride. These are both established active substances which are described in the European Pharmacopoeia and are manufactured in accordance with the principles of Good Manufacturing Practice (GMP).

The active substance specifications are considered adequate to control the quality and meet current pharmacopoeial requirements. Batch analytical data demonstrating compliance with these specifications has been provided.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product

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 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 monograph for the dosage form (Oromucosal sprays), 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.

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 Medispray Oromucosal Spray, Solution, Chlorhexidine digluconate 2 mg/ml, Lidocaine Hydrochloride 0.5 mg/ml.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC as amended, a well-established use application. Chlorhexidine and lidocaine have well-established use within the European Union for more than ten years, demonstrating a recognised efficacy and safety profile. A non-clinical overview has been provided, it is based on relevant published literature and written by an appropriately qualified person. Overview based on literature review is, thus, appropriate. A brief summary of the literature submitted is provided below:

III.2 Pharmacology

Chlorhexidine
Chlorhexidine is a commonly used disinfectant and topical antiseptic agent. In vitro tests confirmed the value of chlorhexidine in the treatment of upper respiratory tract infections such as sore throat. It has bactericidal activity on bacteria considered to be pathogenic in the upper respiratory tract.
Chlorhexidine shows also some antiviral activity in relation to the influenza A virus (H1N1).

Lidocaine
Lidocaine hydrochloride is a local anaesthetic of the amide type. Lidocaine i.v. is used as an antiarrhythmic. Lidocaine, like other local anaesthetics, blocks conduction of nerve endings impulses in a reversible way by interfering with processes fundamental to generation of nerve action potential, namely, large transient increase in permeability of membrane to sodium ions that is produced by slight depolarisation of membrane

III.3 Pharmacokinetics

Chlorhexidine
Chlorhexidine is virtually not absorbed when administered topically. Minute amounts are detected in the urine of laboratory animals. LD50 varies from 21 mg/kg (rat i.v.) to 5000 mg/kg (rat oral). Subchronic toxicity showed minimal dermal irritation (erythema, oedema, desquamation and/or fissuring) at the lowest dose tested.

Lidocaine
From observations in rabbits administered lidocaine HCl i.v. and portally, a first pass hepatic elimination of approximately 30% could be calculated. The fraction of rectal venous drainage bypassing the portal circulation and thus hepatic metabolism is about 40%. In the rabbit, the hepatic first pass effect for lidocaine can be avoided by administering the compound via the rectum. Intrinsic clearance of lidocaine was consistently reduced in the dog after repeated administration.

III.4 Toxicology

Chlorhexidine
No observable malformations or developmental toxicity were found at any dose level tested.
Mutagenic effects were not observed in two mammalian in vivo mutagenesis studies evaluating chlorhexidine gluconate. No carcinogenicity has been reported with chlorhexidine during long-term toxicity studies in rats.

Lidocaine
LD_{50} varies from 19.5 mg/kg (mouse i.v.) to 317 mg/kg (rat oral). Lidocaine showed neurotoxicity to sensory neurons, resulting from a direct action on sensory neurons, and that a lidocaine-induced increase in intracellular Ca^{2+} is a mechanism of lidocaine-induced neuronal toxicity. Lidocaine is less cardiotoxic than bupivacaine. The neurotoxic effects observed after a continuous intrathecal infusion were dose related. No significant effects were observed in offspring of SD rats administered lidocaine. Lidocaine did not show any mutagenicity. Lidocaine effectively inhibited the invasive ability of human cancer cells at concentrations used in surgical operations.

III.5 Ecotoxicity/environmental risk assessment

The active substances, chlorhexidine and lidocaine hydrochloride are not PBT substances.
Chlorhexidine and lidocaine are not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

Chlorhexidine digluconate and lidocaine hydrochloride have been in well-established use within the European Union for more than 10 years, demonstrating a recognised efficacy and safety profile. An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. No new nonclinical studies were submitted. The non-clinical evidence in support of this application is based on relevant published scientific literature which is appropriate. An environmental risk assessment was submitted and no environmental concerns are apparent.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application for marketing authorization is presented in bibliographical format under Article 10 a of Directive 2001/83/CE, the applicant does not have to provide the results of further toxicological or pharmacological tests, as it has been clearly demonstrated from the existing literature that the medicinal product in question has an established and extensively medical use for more than a 10-year period.

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

IV.2 Pharmacokinetics

Small amounts may enter the digestive system if some of the Medispray solution or saliva is swallowed.
Chlorhexidine
Absorption
In oral or topical use, absorption of chlorhexidine is insignificant. In topical use on intact skin, chlorhexidine is adsorbed on the outside layers of the skin, providing long-term antimicrobial effect. After rinsing the oral cavity, approximately 30% of chlorhexidine is retained, which is then slowly released into the saliva. In view of the insignicicant bioavailability of chlorhexidine after oral or topical administration, the following elements are just for information.
Distribution
Chlorhexidine tightly binds to saliva proteins. It was shown that chlorhexidine is stable in the oral cavity for at least 9 h and high concentrations of the drug (2 µg/ml total) are still present in saliva even after 8 h from mouth rinsing.
Biotransformation
Chlorhexidine is not accumulated in the body and is only minimally metabolised.
Elimination
In a case of ingestion of a massive dose (300 mg) of chlorhexidine gluconate, approximately 90 % was excreted in faeces via biliary routes and less than 1 % was eliminated into urine.

Lidocaine
Absorption
Lidocaine absorption varies, depending on the site and the method of use. It is quickly resorbed from the digestive organs, mucous membranes and through damaged skin. In healty adults, no detectable plasma lidocaine levels were noted after use of a 2 % mouth rinse. Children and immune impaired adults do resorb lidocaine from the oral mucosa into the plasma. The levels were approximately 0,2 micrograms/ml but the toxic plasma concentration is 5 micrograms/ml. The anaesthetic effect is limited to the surface and does not extend to the submucosal structures.

Distribution
Lidocaine is distributed well in the tissues (kidneys, lungs, liver, heart, skeletal muscle and adipose tissue).
Lidocaine passes through the blood-brain barrier and placenta and into mother's milk.

Biotransformation
It is metabolised during the first pass through the liver and the bioavailability is about 35 % after oral administration. 90 % isdeethylated in the liver to monoethylglycinexylide and glycinexylide. Both primary metabolites are pharmacologically active. Further cleavage of the amide bonds forms the metabolites xylidine and 4-hydroxyxylidine.

Elimination
Lidocaine is eliminated in the form of metabolites through the kidneys. Approximately 10% is eliminated unchanged. The biological half life of lidocaine is one and a half to two hours in adults. The biological half life of the primary metabolites is two to ten hours.

IV.3 Pharmacodynamics

No new data on primary and secondary pharmacodynamics are included in the present application.

Lidocaine hydrochlorideis a local peripheral anesthetic of the amide group, which has a superficial analgesic effect. Lidocaine as a local anaesthetic has the same mechanism of action as other medicines from this group in that it prevents generation and

conduction of nerve impulses in sensoric, motoric and autonomous nerves. It primarily affects the cell membrane where it blocks the ion channels and thereby reduces the permeability of sodium ions. Due to the progressive propagation of the anaesthetic effect in the nerve, the electric stimulation threshold is increased, impulse conduction is slowed down and the propagation of the action potential is contracted. Finally, the conductivity is interrupted completely. In principle, local anaesthetics block autonomous nerve fibres, small non-myelinated (sensation of pain) and small myelinated (sensation of pain and temperature), more quickly than large myelinated fibres (sensation of touch and pressure). On a molecular level, lidocaine specifically blocks sodium ion channels in the inactive state, thereby preventing the formation of an action potential. This mechanism prevents the conduction of stimuli when lidocaine is used locally in the vicinity of nerves.

Chlorhexidine is a bisbiguanide cationic antiseptic. It is effective against Gram-positive (e.g. *Micrococcus* sp., *Staphylococcus* sp., *Streptococcus* sp., *Bacillus* sp.) and to a lesser extent against Gram-negative bacteria, especially in the vegetative form (it is not effective against spores at normal temperature). It also has an antimycotic effect on dermatophytes and fungi. It quickly inactivates the infectiousness of certain lipophilic viruses (influenza virus, herpes virus, HIV). In smaller concentrations, it has a bacteriostatic effect, while in larger concentrations, it functions as a bactericide. The chlorhexidine molecule has a strong positive charge, and therefore adsorbs to the negatively charged areas on the cell surface. The adsorption is specific and takes place in special parts of the bacterial cell wall containing phosphates. This damages the cell membrane, increasing permeability. It is also adsorbed onto the surfaces of the teeth, plaque or the oral mucosa, thereby persisting in the oral cavity. The effectiveness of antiseptics and disinfectants depends on the concentration, temperature and exposure time.

IV.4 Clinical Efficacy

This is a well-established application, as per Article 10a of Directive 2001/83/EC which is based on a systematic review of the literature. The applicant did not have to provide the results of further toxicological or pharmacological tests, as it has been clearly demonstrated from the existing literature that the medicinal product in question has an established and extensively medical use for more than a 10-year period.

The applicant provided a detailed clinical overview outlining that the active substances and the formula have a very well established medical use with recognized efficacy in adults, adolescents and children over 12y. The data related to the clinical properties are chlorhexidine digluconate and lidocaine hydrochloride are collected from and based upon a careful and extensive literature search.This product is comparable to several analogous products combining a local anaesthetic and an antiseptic currently marketed in the European Community for more than 10 years.

Medispray oromucosal spray is indicated for : *the symptomatic relief of painful, irritated sore throats.*
It is a sugar free preparation and can be used by patients with diabetes.
Additional therapy is required in the event of bacterial infection accompanied by fever.
Medispray is indicated for use in adults, adolescents and children over 12y.

The claimed therapeutic indications for Medispray Oromucosal Spray, Solution containing chlorhexidine digluconate 2 mg/ml, lidocaine hydrochloride 0.5 mg/ml are consistent with the spectrum of activity reported in standard references and published literature and also with the currently established clinical use of the drug.

The proposed dosing regimen is based on the posology of the products long-time present on European markets and are considered effective and safe.

IV.5 Clinical Safety

The applicant provided a detailed clinical overview demonstrating that the active substances have a very well established safety profile. No new safety concerns were found in the safety data submitted in support of the present application.

Please see the product information for the full prescribing safety information.

Risk Management Plan

Risk Management Plan version 0.3, with date of final sign off of 17/01/2018 is considered acceptable. The approved summary of safety concerns is outlined below:

Summary of safety concerns	
Important identified risks	• Hypersensitivity (allergic reactions including anaphylaxis) • Food aspiration due to glottis insensitivity at high doses (> 1 bottle/day)
Important potential risks	• None
Missing information	• Use in pregnancy

Routine pharmacovigilance and routine risk minimisation measures are proposed and this is considered acceptable.

Periodic Safety Update Report (PSUR):

The PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

The applicant has submitted sufficient published scientific literature results to support 10 years of use of Medispray Oromucosal Spray, Solution containing chlorhexidine digluconate 2 mg/ml, lidocaine hydrochloride 0.5 mg/ml for this well -established use application.

V. OVERALL CONCLUSIONS

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 Medispray Oromucosal Spray, Solution demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES