COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ophtesic 20 mg/g, eye gel in a single dose container

(lidocaine hydrochloride)

NL/H/4343/001/DC

Date: 12 April 2021

This module reflects the scientific discussion for the approval of Ophtesic 20 mg/g, eye gel in a single dose container. The procedure was finalised on 20 June 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	Central Nervous System
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ophtesic 20 mg/g, eye gel in a single dose container from Laboratoires Doliage Developpement.

The product is indicated for topical anaesthesia during ophthalmic procedures.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of lidocaine hydrochloride. No new (pre)clinical studies were conducted. The MAH submitted non-clinical and clinical overviews based on scientific literature. Lidocaine as an active substance for topical anaesthesia is considered well-established. Though the use of lidocaine 2% gel as a topical anaesthetic in ophthalmic procedures is off-label in Europe, it can be concluded from the literature data that it has been applied as a anaesthetic in several German and French ophthalmic clinics for more than 10 years.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

The concerned member states (CMS) involved in this procedure were Belgium, France, Luxembourg and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Ophtesic is a homogenous, clear transparent gel. 1 g of gel contains lidocaine hydrochloride equivalent to 20 mg of lidocaine hydrochloride anhydrous.

The eye gel is packed in an epoxy coated aluminium tube with a polypropylene cap, overwrapped in a polypropylene/kraft paper blister. The cap/nozzle is inside the blister and should be attached to the tube before administration of the product. One tube contains 3.5 g.

The excipients are: hypromellose (E464) type 2910, sodium hydroxide (E524), hydrochloric acid (E507) (for pH adjustment), water for injections.

II.2 Drug Substance

The active substance is lidocaine hydrochloride, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance a white crystalline powder which is very soluble in water and freely soluble in alcohol. No polymorphism has been reported for lidocaine in the literature.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph. Eur. monograph for lidocaine hydrochloride, the additional test for acetone as included on the CEP and Ph. Eur. requirements for microbial purity. The specification is considered acceptable.
Batch analysis results have been provided for a total of three production-scale batches of lidocaine hydrochloride, which show compliance to the specification.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. For this well-established used application reference is made to the literature reference product Xylocaine 2% gel, containing lidocaine as active substance. The MAH has provided results of an extensive pharmaceutical equivalence study in which preservative-free Xylocaine (syringe) as well as Xylocaine containing parabens (tube) were compared to the test product. Xylocaine is registered by AstraZeneca in several member states.
The critical quality aspects colour, pH, viscosity, osmolality, buffer capacity, opalescence, formulation, density, dry weight and assay of lidocaine have been discussed. The physicochemical equivalence of test and reference product has sufficiently been

demonstrated and the quality requirements of the test product have been set based on the results obtained for reference and test product.

Manufacturing process

The production process consists of the following steps: dissolution of the drug substance, pH adjustment, mixing and homogenisation, adjustment to final weight, cooling, filtration of the bulk, intermediate storage, filling in tubes, blistering of filled tubes, sterilization and secondary packaging. The manufacturing process is considered a non-standard process.
The manufacturing process is regarded acceptable as it is under sufficient control. The manufacturing process has been validated on three commercial scale batches.

Control of excipients

All excipients comply with their current Ph. Eur. monographs. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance , pH, viscosity , osmolality, minimum fill, identification of lidocaine HCl, assay of lidocaine HCl, related substances and sterility. The specification is considered acceptable. Batch analysis data have been presented for three production-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data have been provided for three industrial-scale batches of the drug product packaged in the container closure system proposed for marketing and stored at 25°C ± 2°C/60% ± 5% RH (36 months), 30°C/65% RH (two batches at 12 months) and 40°C ± 2°C/75% ± 5% RH (6 months). The proposed shelf life of 36 months has been granted in view of the results at long-term conditions. Out-of-specification results were obtained for viscosity at accelerated and intermediate conditions; a storage precaution of 'store below 25°C' is therefore applicable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ophtesic 20 mg/g, eye gel in a single dose container has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Lidocaine prevents the generation and conduction of nerve impulses. Its primary site of action is the cell membrane. Lidocaine blocks conduction by decreasing or preventing the large transient increase in the permeability to Na+ of excitable membranes normally produced by slight depolarisation of the membrane. This action of lidocaine is due to its direct interaction with voltage-gated Na+ channels. This action is fully reversible resulting in restored nerve function. *In vivo*, lidocaine has a rapid onset of action and anaesthesia is obtained within a few minutes; it has an intermediate duration of action and provides effective anaesthesia when administered by surface application.

Local anaesthetics exert a depressant effect on cardiac contractility to a degree proportional to their anaesthetic potency. Depression of the conduction by local anaesthetics in both nerve and cardiac tissue is due to blockade of sodium channels. Local anaesthetics may cause stimulation of the central nervous system (CNS), producing restlessness and tremor that may proceed to clonic convulsions. Local anaesthetic agents exert a biphasic effect on respiration. Local anaesthetics may provoke types I and IV hypersensitivity reactions.

III.2 Pharmacokinetics

The rate and degree of absorption of local anaesthetic agents is determined by the site of injection and the physicochemical properties (particularly lipid solubility and inherent vasoactivity) of the agent used. After an intravenous dose lidocaine is rapidly and widely distributed into highly perfused tissues followed by redistribution into skeletal muscle and adipose tissue. Lidocaine is bound to plasma proteins, including α1-acid glycoprotein.

Approximately 70% of dose of injected lidocaine undergoes biotransformation in patients with normal liver function. Extrahepatic metabolism of lidocaine has also been detected *in vitro* and *in vivo*. Lidocaine shows pronounced interspecies variability in its metabolism. The primary route of metabolism in the rat was via hydroxylation. It has been shown that dogs and rabbits can metabolize 2,6-xylidine to 2-amino-3-methylbenzoic acid and that the guinea pig may also be able to produce this metabolite from lidocaine; however it has not been detected in man. 2,6-xylidine has been identified as a carcinogen (see section III.3 'Toxicology').

Biliary excretion of reabsorbed metabolites from the intestinal tract was evident in the rat; however, biliary excretion of lidocaine and its metabolites is not as important in humans. The half-life of lidocaine disappearance was estimated to be less than 30 minutes in rats, as compared to a half-life of 45 to 60 minutes in dogs and 90 minutes in man. Lidocaine crosses the placenta and blood-brain barrier; it is distributed into breast milk.

The MAH has discussed non-clinical pharmacokinetic data after ocular delivery of lidocaine via gel formulations and via other routes including mucosa. Intraocular penetration is high and systemic exposure is expected to be low.

III.3 Toxicology

The systemic toxicity of local anaesthetics mainly involves the CNS and the cardiovascular system. In general, toxic and lethal doses of local anaesthetic drugs result in signs of CNS excitation leading ultimately to convulsive activity followed by CNS depression and respiratory arrest. Cardiovascular alterations consist of myocardial depression leading to profound hypotension and ultimately cardiac arrest. In general, the cardiovascular system is believed to be relatively resistant to the toxic effect of local anaesthetics in comparison to the CNS. Literature data on long term in vivo exposure up to 60 days shows that lidocaine is well tolerated. Lidocaine does not act as a local irritant in the eye.

Sufficient bibliographic data on the carcinogenic potential of lidocaine or its metabolites was provided. Lidocaine is not genotoxic. However, a carcinogenic metabolite, 2,6-xylidine, has been identified. A thorough assessment of the available data confirms that 2,6 xylidine is genotoxic in vivo and that it is carcinogenic in rats. There is a sufficiently large safety margin to suggest that these findings are not relevant for humans when lidocaine is used in normal clinical conditions.

Reproductive toxicity studies in rats given continual lidocaine doses equivalent to or up to five times the IV human dose have not shown teratogenic effects were observed in the offspring. However, when given as single injections in doses up to two times the hourly human dose, lidocaine resulted in neonatal behavioural changes in the offspring. In pregnant mice, single injections of lidocaine in doses 50 to 70% of the daily human infusion dose produced increased frequencies of CNS anomalies in the embryos.

III.4 Ecotoxicity/environmental risk assessment (ERA)

Since Ophtesic is expected to be used in small amounts and use of lidocaine in various products is prevalent, the increased exposure to the environment as a result of use of Ophtesic is negligible. The logKow of lidocaine is below 4.5. and the predicted concentration in surface water is below the action limit. Further environmental risk assessment is not warranted, and the need for ERA study data can be waived.

III.5 Discussion on the non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance lidocaine are well known. The MAH has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lidocaine hydrochloride is a well-known active substance with established efficacy and tolerability.
The dossier is based on well-established use of the active substance. The MAH submitted a clinical overview for the justification of the proposed indications and posology. Sufficient literature references were provided.

Bridging to literature reference products
Lidocaine gel formulations are authorised in Europe, but with other administration routes and therapeutic indications (e.g. for endoscopic/bronchoscopic, urethral intubations, oromucosal route), presented in catheter tube, ampoule, prefilled syringe, oromucosal tube etc., as mono-component products and/or fixed dose combinations.
Xylocaine 2% gel (NL Licence RVG 07830) by AstraZeneca is considered a relevant product for bridging efficacy and safety. The physicochemical equivalence of Ophtesic to this reference product has been sufficiently demonstrated. Xylocaine was used as test product in several studies establishing the efficacy and safety of lidocaine 2% gel in ophthalmic topical anaesthesia. Moreover, Xylocaine is also reported to be used routinely in several German and French ophthalmic treatment centres, based on information from the literature and hospital administration data.
Both the preservative-free Xylocaine and the paraben-containing formulation are considered relevant products. Across the EU, both Xylocaine formulations are used in ophthalmic surgery. Based on non-clinical studies, it has been postulated that preservatives like parabens may enhance penetration of pharmacological products through the cornea. However, multiple studies using preservative free lidocaine 2% gel indicate that efficacy is adequate for preservative-free lidocaine.

IV.2 Pharmacokinetics

The MAH argues that a negligible systemic absorption of lidocaine can be expected from the proposed medicinal product. Although no published studies on the systemic absorption of ophthalmology products containing lidocaine were presented, data reported on the use of lidocaine gel for topical anaesthesia in different mucosa like nasopharyngeal, endotracheal, urethral and vaginal mucosa showed minimal concentrations considerably lower than the reported toxic systemic concentrations of >5 µg/ml in the literature. It is likely that the pharmacokinetics of lidocaine in these different mucosae are comparable to the ocular mucosa. It is also noted that the product is packed in a tube containing 3.5 g gel, with a maximum amount of 70 mg lidocaine. In the event that the whole amount will be absorbed, the plasma concentration will be within the concentrations (1.5 – 5 µg/ml) with IV administration of 50 – 100 mg lidocaine in the treatment of cardiac arrhythmias. Therefore,

it is agreed that even in such an event, the concentrations which will be absorbed are within tolerable and safety limits. In addition, no accumulation is expected as the product is for single use.

IV.3 Pharmacodynamics

Lidocaine has a rapid onset of action and anaesthesia is obtained within a few minutes; it has an intermediate duration of action. In ophthalmology, topical anaesthetics work by reversibly blocking sodium channels and preventing propagation of painful nerve impulses in the cornea, conjunctiva, and sclera. In the cornea, nerve endings are superficial and protected only by the tear film and by a thin layer of stratified epithelium that is permeable to lipid- and aqueous-soluble molecules. Nerves in the conjunctiva are covered by nonkeratinized stratified epithelium, readily penetrated by topical anaesthetics if pH conditions are optimal.

IV.4 Clinical efficacy

The MAH provided an overview of the literature, demonstrating that efficacy of topical lidocaine as an anaesthetic agent in ocular procedures can be considered established. In several studies, the gel was superior to conventional local anaesthetic eye-drops, such as tetracaine. This may be due to prolonged contact time of the gel versus the drop on the conjunctival tissue or cornea. Studies were also performed with EU sourced Xylocaine. In an Italian study by Bardocci (2003)[1], 107 patients undergoing cataract surgery were randomised to preservative-free Xylocaine 2% gel (local sourced) or lidocaine 4% drops. Pain scores and the level of rescue mediation was significantly lower for the gel (3.7% versus 15.1%). In this study, statistically significant difference in intraoperative pain score in favour of the 2% lidocaine gel was demonstrated, indicating assay sensitivity. This was supported by secondary endpoints (sensation of manipulation, patient cooperation, heart rate and blood pressure).
In a study by Theocharis (2007[2], not discussed in the clinical overview by the MAH), using Xylocaine 2% preservative-free gel from the Swedish market in 69 patients, topical anaesthesia with the 2% gel was superior to peribulbar anaesthesia in sutureless vitrectomy in pain reduction (no intra-operative pain: 17-22% for the gel versus 4.4% for peribulbar anaesthesia).

In addition, several randomized studies are available comparing the efficacy of 2% lidocaine gel to another lidocaine formulation:

[1] Bardocci, A., Lofoco, G., Perdicaro, S. et al, Lidocaine 2% gel versus lidocaine 4% unpreserved drops for topical anesthesia in cataract surgery. A randomized controlled trial. Ophthalmology. 2003;110:144–149
[2] Theocharis IP, Alexandridou A, Tomic Z. A two-year prospective study comparing lidocaine 2% jelly versus peribulbar anaesthesia for 25G and 23G sutureless vitrectomy. Graefes Arch Clin Exp Ophthalmol. 2007;245(9):1253–1258.

- 2% lidocaine gel vs. 2% lidocaine subconjunctival injection in intravitreal injection drug delivery (Kozak 2005[3]; Friedman 2006[4])
- 2% lidocaine gel vs. sub-Tenon's anaesthesia with 2% lidocaine for trabeculectomy surgery (Carillo 2004[5])
- 2% lidocaine gel vs. 2% lidocaine injection in chalazion surgery (Li 2003[6])
- 2% lidocaine gel vs. 2% lidocaine injection in pterygium surgery (Öksüz 2005[7])

In the study by Carillo, a statistically significant difference in intraoperative pain in favour of the gel was observed, in other studies the treatments were comparable.

Based on these studies, it is considered demonstrated that 2% lidocaine gel is as effective or in some cases superior to other lidocaine formulations in providing anaesthesia during ophthalmologic procedures.

The MAH applied for a broad indication, i.e. 'topical anaesthesia during ophthalmic procedures'. This indication is considered acceptable based on the various surgery procedures discussed in the clinical overview, demonstrating that lidocaine gel was effective in providing adequate topical anaesthesia.

IV.5 Clinical safety

The safety profile of topical lidocaine administered to the eye is considered well known, the most common adverse events being corneal staining, conjunctival hyperemia and pain. In the literature, about 1200 patients were described that were treated with lidocaine 2% gel in ophthalmic procedures, without apparent safety issues. Based on the available data, if used correctly, there is no increased risk of endophthalmitis associated with the use of topical lidocaine gel.

Preclinical studies did not show relevant safety issues. In rabbits, Xylocaine 2% gel with parabens did not cause histopathological alteration of the ocular tissues (Barequet, 1999[8]).

It has been confirmed by the literature that lidocaine gel does not interfere with visibility of the surgical area. In the SmPC a recommendation has been included to rinse off the gel if it is

[3] Kozak I, Cheng L, Freeman WR. Lidocaine gel anesthesia for intravitreal drug administration. Retina. 2005;25(8):994–998.
[4] Friedman SM, Margo CE. Topical gel vs subconjunctival lidocaine for intravitreous injection: a randomized clinical trial. Am J Ophthalmol. 2006;142(5):887–888
[5] Carrillo MM, Buys YM, Faingold D and Trope G E, Prospective study comparing lidocaine 2% jelly versus subcutaneous-Tenon's anaesthesia for trabeculectomy surgery. Br J Ophthalmol. 2004 Aug; 88(8): 1004–1007.
[6] Li RT, Lai JS, Ng JS, Law RW, Lau EM, Lam DS. Efficacy of lignocaine 2% gel in chalazion surgery. Br J Ophthalmol. 2003;87(2):157–159
[7] Oksuz H, Tamer C. Efficacy of lidocaine 2% gel in pterygium surgery. Acta Ophthalmol Scand. 2005;83(2):206–209
[8] Barequet IS, Soriano ES, Green R, et al. Provision of anesthesia with single application of lidocaine 2% gel. J Cataract Refract Surg 1999;25:626–31.

bothersome during the procedure. This does not influence efficacy since the gel is applied before the procedures and anaesthesia is settled before surgery.

IV.6 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 Ophtesic.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	--
Important potential risks	Hypersensitivity reactions
Missing information	--

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Benefits

Beneficial effects

Lidocaine as an active substance for topical anaesthesia is considered well-established. The efficacy of 2% lidocaine gel is ophthalmologic procedures is considered shown and is considered comparative, or even superior, to conventional treatment with local anaesthetic eyedrops in providing anaesthesia based upon the provided literature.

The use of lidocaine 2% gel in ophthalmic anaesthesia is off-label, since no marketing authorisation has yet been granted for the ophthalmic indication within the Community. However, well-established use of the reference product Xylocaine 2% has been sufficiently shown in multiple member states for over 10 years.

Uncertainty in the knowledge about the beneficial effects

There are no sufficient data about the efficacy of 2% lidocaine gel in ocular anaesthesia in children. Children undergoing ocular surgeries are commonly put under general anaesthesia. The current SmPC, which states that the safety and efficacy of this medicine have not been established in children is considered appropriate.

Risks

Unfavourable effects

The safety profile of lidocaine in ophthalmologic procedures is well known, with most common adverse events being local irritation/uncomfort, corneal staining and conjunctival hyperemia. When used correctly, i.e. administered after povidone-iodine, there is no increased risk of endophthalmitis associated with the use of topical lidocaine gel.

Benefit-risk balance

Based on the submitted dossier, it can be concluded that the well-established medicinal use of lidocaine 2% gel has been demonstrated within the EU for at least 10 years, with recognised efficacy and an acceptable level of safety.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the PL 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

Ophtesic 20 mg/g, eye gel in a single dose container has a proven chemical-pharmaceutical quality. Lidocaine is an effective drug, and its use is considered widely established. The benefit/risk balance is considered positive.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for this medicinal product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 June 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse