COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lumobry 0.25 mg/ml, eye drops, solution (brimonidine tartrate)

NL/H/5324/001/DC

Date: 28 June 2024

This module reflects the scientific discussion for the approval of Lumobry 0.25 mg/ml, eye drops, solution. The procedure was finalised on 2 August 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ANCOVA	Analysis of covariance
ASMF	Active Substance Master File
BAK	Benzalkonium Chloride
CAC	Conjunctival Allergen Challenge
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
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
IOP	Intraocular Pressure
ISS	Integrated Safety Summary
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
QID	Quater in die (four times daily)
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Lumobry 0.25 mg/ml, eye drops, solution, from Bausch + Lomb Ireland Limited.

The product in form of eye drops is indicated in topical treatment of isolated conjunctival hyperemia due to minor eye irritation in adults.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 8(3) (Full or full-mixed application (complete dossier)) of Directive 2001/83/EC. It concerns a mixed application including quality, pre-clinical and clinical data, where the studies conducted by the MAH are supplemented with bibliographical data.

This medicinal product has been developed for the treatment of conjunctival hyperaemia. The product contains brimonidine tartrate, which is not considered to be a new active substance. However, the new product is re-formulated to 0.025% (0.25 mg/mL) of the usual products on the market with a concentration of 0.10-0.20%. In addition, there are some differences in the indications of this product compared to the already marketed brimonidine tartrate products. The aim of the re-formulation was to design a lower dose brimonidine topical formulation, which will still provide a potent vasoconstrictive effect without the related side effects.

The concerned member states (CMS) involved in this procedure were Greece, France, Poland, Portugal, Slovakia, Slovenia and Spain. NL/H/5324/001/E/001 was used to register the product in Austria, Belgium, Bulgaria, Cyprus, Czechia, Germany, Denmark, Finland, Croatia, Hungary, Ireland, Italy, Norway, Romania and Sweden.

For this application, scientific advice has been given by the MEB.

II. QUALITY ASPECTS

II.1 Introduction

Lumobry 0.25 mg/ml, eye drops is a clear, colourless to slightly yellow ophthalmic solution with a pH value of 6.3 - 6.7 and a osmolality value of 275 - 320 mOsmol/kg). Each mL of ophthalmic solution contains 0.25 mg (0.025% w/w) of brimonidine tartrate. This is equivalent to 0.0085 mg brimonidine tartrate per drop.

The excipients are: glycerin (glycerol) E422, sodium borate decahydrate (borax) E285, boric acid E284, potassium chloride E508, calcium chloride dihydrate, sodium chloride, benzalkonium chloride (BAK) 25% solution, sodium hydroxide (to adjust pH) E524, hydrochloric acid (to adjust pH) E507 and water for injection.

The product is presented in 10 mL low-density polyethylene (LDPE) bottles, with linear low-density polyethylene (LLDPE) dropper applicators (tips) and two-piece child-resistant polypropylene/high-density polyethylene (PP/HDPE) screw caps. Each bottle contains 7.5 mL of the ophthalmic solution and it is packaged in a paperboard carton.

II.2 Drug Substance

The active substance is brimonidine tartrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is an amorphous white to yellow white powder and is freely soluble in water. The substance is not polymorphic and the pharmaceutical formulation and solubility nature of the substance makes particle size not a critical parameter either. Brimonidine itself is not chiral, but the anion (tartaric acid) is chiral. For this product, a polymorphic form is consistently produced and controlled by optical rotation as recommended by the monograph.

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur and the CEP with additional requirements for methanol, microbial purity and titration of tartaric acid. Batch analytical data demonstrating compliance with this specification have been provided for four production scale batches.

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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The formulation is based on marketed product of 0.2% strength. The pharmaceutical development of the product has been adequately performed and is mostly based on prior knowledge. Some steps of the manufacturing process have been

optimised for the new strength; this haven been adequately justified. The pH of the product has been chosen based on the pH of ocular tissue for more comfort to the eye. Furthermore, to meet the new USA regulations, the packaging of the product was changed to a packaging provided with a child-resistant closure. Batch data were provided for several batches with the new packaging showing no impact on the quality of the product or delivered drop size/volume.

As the product is a solution, an extractables study for each component (both primary and secondary) of container closure system and a leachables study for drug product were performed. One contaminant for leachables, was identified for the secondary packaging. Therefore, a control method was developed and a routine specification limit was set. Other tested parameters for the studies were in accordance with the applicable guidelines.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for four (two small and two large) batches of commercial batch sizes in accordance with the relevant European guidelines. Additionally, media fill runs were submitted. Packaging components are individually sterilised in accordance with the EMA´s sterilisation guideline.

Control of excipients

The excipients comply with Ph. Eur or USP requirements. These specifications are acceptable.

Microbiological attributes

As the product is sterile, the integrity of the container closure system was investigated to prevent microbial contamination. Biological reactivity tests (of the plastic and label components) were performed in accordance with the USP. The test articles were considered noncytotoxic and met the USP <87> requirements.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification for release includes tests for description, visible particulates, identification and assay for brimonidine and benzalkonium chloride (BAK), pH, osmolality, particulate matter, related substances, sterility, fill volume and tightness of container. The tests meet the USP, Ph. Eur. or in house requirements. Limits in the specification for release have been justified and are considered appropriate for adequate quality control of the product. Adequate nitrosamines risk evaluation and ICH Q3D elemental impurities (including confirmation batch data) reports have been provided. No risk for the presence of nitrosamines in the drug product was identified, additional controls are not necessary.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from four (two small and two large) batches of commercial batch sizes from the proposed production site(s) have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for a total of 14 batches (from clinical, registration and commercial batches, all of commercial scale) stored at 25°C/ 40% RH (up to 36 months) for long term, 30°C/ 35% RH and 30°C /65% RH (up to 27 months) for intermediate and 40°C/20% RH (up to 6 months) for accelerated conditions. The tests for stability are specification for stability includes tests for description, visible particulates, assay for brimonidine and benzalkonium chloride (BAK), pH, osmolality, particulate matter, related substances, leachables, sterility and antimicrobial effectiveness, weight loss/gain. The tests meet the USP, Ph. Eur. or in house requirements. Limits in the specification for release and stability have been justified and are considered appropriate for stability studies. The stability was tested in accordance with applicable European guidelines. Results showed some OOS values at higher temperatures (accelerated and intermediate conditions). Therefore, the limits of the relevant release tests were tightened. Furthermore, special precautions for storage temperature were included in the SmPC.

In-use stability data have been provided demonstrating that the product remains stable for 121 days following first opening of the container and when stored at or below 25°C.

On basis of the data submitted, a shelf life was granted of 24 months. The labelled shelf life and storage conditions are 'shelf life 2 years (unopened). Discard 121 days after the first opening'. 'Do not store above 25°C'.

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 Lumobry 0.25 mg/ml 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

Mechanism of action

Brimonidine tartrate is an imidazoline compound that has been shown to be a selective α2-adrenergic receptor (α2-AR) agonist. The ARs are the primary receptors in the sympathetic nervous system. The α-ARs regulate changes in the vasculature and are further subdivided into α1-AR and α2-AR (Burke & Schwartz, 1996). Within the vascular system, α2-AR-mediated

vasoconstriction occurs primarily on the venous-side (Corboz et al., 2008; Guimarães & Moura, 2001). Brimonidine acts on α2-ARs to mediate intraocular pressure (IOP), which has been studied extensively (Crosson et al., 1992; Potter et al., 1990). It has been known for brimonidine that it also mediates vasoconstrictive activity at the ocular surface (Görnemann et al., 2007; Gyires et al., 2009), although other current topical decongestants are either α1-AR agonists or mixed α1-AR/α2-AR agonists (MacDonald et al., 1997; Piletz et al., 1996; Piwnica at al., 2014).

Primary pharmacology

Supported by pharmacological evidence, studies have demonstrated the presence of α2-ARs in several ocular tissues (Bylund & Chacko, 1999; Crosson et al., 1992; Chu & Candia, 1988; Diebold et al., 2005; Grueb et al., 2008; Huang et al., 1995; Matsuo & Cynader, 1992; Wikberg-Matsson & Simonsen, 2001; Woldemussie et al., 2007). The identification of α2-ARs in human conjunctival biopsy samples support the vasoconstrictive (blanching) effects observed in the conjunctiva upon treatment with brimonidine (Dahlmann-Noor et al., 2009; Derick et al., 1997; Desco et al., 2005; Norden, 2002; Pasquali et al., 2013). The mechanism of this vasoconstrictive activity of brimonidine in the conjunctival vasculature has not been fully elucidated but is most likely similar to activity in other superficial vascular beds. Here, low concentrations of brimonidine were shown to induce a dose-dependent vasoconstriction in the mouse tail artery and human dermal veins. Brimonidine is a potent vasoconstrictor for topical dermal medicinal products that are on the EU market (Tong & Moore, 2014). With either α1-AR agonists or mixed α1-AR/α2-AR agonists, tachyphylaxis and/or rebound congestion are common and restrict long term use (Abelson & Smith, 2012; Stafford-Smith et al., 2007; Vaidyanathan et al., 2010). There is no literature on α2-AR expression after chronic exposure, but the effective IOP-lowering effects after continuous exposure as seen in the clinic with 0.1 to 0.2% brimonidine suggests that a change in receptor number is likely to be minimal with 0.025% brimonidine (Derick et al., 1997). The MAH mainly describes clinical literature that demonstrated the pharmacological efficacy of brimonidine (0.025%) administration to patients. By reducing the blood vessel surface and ocular bleeding, the substance was able to control bleeding during ocular surgeries. Considering that brimonidine is a well-known active substance, the overview based on literature adequately described the primary pharmacodynamics of brimonidine.

Secondary pharmacology

Non-clinical studies on secondary pharmacodynamic effects have demonstrated dose-dependent effects of brimonidine on IOP-lowering in rabbits, cats and monkeys, with doses of 0.01% - 1%. In the same study, brimonidine induced dose-dependent changes in pupillary diameter (Burk & Potter, 1986; Derick et al., 1997). In humans, brimonidine has been used extensively to lower IOP with a concentration of 0.2%. In a clinical study, the lowest dose used of 0.08% gave an initial IOP reduction of 16.1%, but continued drug administration declined and stabilised the IOP reduction (Derick et al., 1997). For the anticipated dose and use of the current formulation, the MAH expects minimal or no effect on IOP or pupillary diameter, which is agreed. Considering that brimonidine is a well-known active substance, the overview based on literature adequately described the secondary pharmacodynamics of brimonidine.

Safety pharmacology

Regarding safety pharmacology, cardiovascular effects of brimonidine (0.1%, two drops) in cats included a decreased heart rate (HR) and mean arterial pressure, in addition to sedation, which are effects usually associated with α_2-AR agonists (Ogata, et al., 2017). The clinical relevance of these results for the current product is considered limited, as the dose of brimonidine will be four times lower than the dose used in this study. Further, clinical studies are described, showing no effect on the cardiovascular system after brimonidine (0.08, 0.2 or 0.5%) treatment (Derick et al., 1997; Walters, 1996) or 0.2% brimonidine treatment in subjects who were concurrently receiving systemic β-blocker therapy (Schuman, 2000). It is agreed that significant systemic cardiovascular effects are unlikely at the proposed concentration of 0.025% brimonidine when dosed topically. Regarding Central Nervous System (CNS) effects, sedation which is a known clinical effect, was observed in rabbits after topical ocular administration of 0.5% brimonidine, but not with 0.2% brimonidine. In monkeys, sedation was observed with high oral doses of 2.5 mg/kg/day but not with 0.1 mg/kg/day (approximately 100-fold higher than the proposed dose) or after topical ocular dosing of up to 0.8% brimonidine (Angelov et al., 1996). From these studies, it is likely that the proposed dose of 0.025% brimonidine will not cause sedation. One non-clinical study is discussed on respiratory effects of brimonidine (intravenous 10 to 1000 nmol kg^{-1}) in guinea pig airways. Here it was shown that brimonidine attenuated the neurotransmission in excitatory non-adrenergic, non-cholinergic nerves in a dose-related manner, which may cause respiratory depression (Jacobsson et al., 1991). This finding has only been observed in animals. The human relevance of this finding is limited. Considering that brimonidine is a well-known active substance, the safety pharmacology of brimonidine has been adequately addressed by the provided literature. There is no apparent risk of adverse changes to the CNS, respiratory or cardiovascular system after ocular administration of brimonidine.

Pharmacodynamic drug interactions

The MAH did not provide data or literature on pharmacodynamic drug interactions. However, extensive information is known from clinical studies and long-lasting clinical experience of brimonidine.

III.2 Pharmacokinetics

Absorption

Four non-clinical studies on absorption of ocularly applied brimonidine in rabbits have been described by the MAH. Overall, it is apparent that brimonidine is rapidly distributed and absorbed in all intraocular tissues that were assessed (conjunctiva, cornea, aqueous humour, iris/ciliary body, and retina/choroid) (Acheampong et al., 2002a; Benkali et al., 2014; Shinno et al., 2017, 2019). Further, one clinical study was described where ocular administration of 0.2% brimonidine led to low systemic levels (~34 pg/mL). The C_{max} for this formulation is 54 pg/mL (Benkali et al., 2014). The concentration in the present product is eighth times lower than tested in this study. Therefore, the systemic exposure after the concerned product use is considered to be much lower.

Distribution

The MAH refers to non-clinical studies in several species on the distribution of brimonidine in ocular tissues after topical administration. In rabbits, brimonidine was distributed to all ocular

tissues that were assessed, that included conjunctiva, sclera, cornea, aqueous humour, iris, ciliary body, and lens (Chien et al., 1990). Brimonidine targeted the intraocular tissues largely via the cornea (cornea, aqueous humour, iris) (Acheampong et al., 2002b). Systemic plasma levels of brimonidine after treatment with current products were relatively low compared to ocular tissue levels (Acheampong et al., 1995). Ocularly administered brimonidine is able to penetrate the blood-brain barrier and reach the CNS (Abdulrazik et al., 2003) and is most likely the reason for the sedative effects that have been reported. In monkeys and rabbits, topically administered brimonidine (0.2% and 0.5%) reached posterior ocular tissues, probably through both corneal and the conjunctival/scleral pathways [64, 65]. In monkeys, binding of brimonidine was higher in pigmented tissues than in nonpigmented tissues, leading to accumulation after repeated dosing (Acheampong et al., 1995, 2002b). As brimonidine is a well-known substance, this is considered to be an expected clinical effect.

Metabolism

A pharmacokinetic study, characterising brimonidine metabolism, has been conducted *in vitro* in rat, rabbit, dog, monkey and human liver fractions, in rabbit and human liver slices, and *in vivo* in rats. The results demonstrated a similar metabolite pattern among rats, rabbits, monkeys and humans that included the involvement for liver aldehyde oxidase in the brimonidine metabolism. Hepatic oxidation of brimonidine to 2-oxobrimonidine, 3-oxobrimonidine and 2,3-dioxobrimonidine was a major pathway in all the species studied, except the dogs, who had lower activity of liver aldehyde oxidase. In monkeys and rabbits, metabolites are formed in ocular tissues. Similar metabolites were also formed in humans (Acheampong et al., 2002b, 1996). As the proposed concentration of brimonidine 0.025% is lower than current registered products, the safety of brimonidine metabolites is covered by existing non-clinical and clinical data. In a third study, *in vitro* and *in vivo* formed metabolites of brimonidine were characterised using on-line hydrogen/deuterium exchange Liquid Chromatography/Mass Spectrometry (LC-MS/MS). Besides the previously mentioned metabolites, novel metabolites (formed in rat urine following oral dosing) were found with this analytical method. All the metabolites formed in human microsomes were also observed in rat microsomes *in vitro* tests (Ni et al., 2007).

Elimination

There is limited non-clinical data available concerning brimonidine elimination after ocular application. In one non-clinical study with ocularly applied brimonidine, it was shown that the elimination half-life of brimonidine after systemic absorption of small amounts were 3.5 hours in albino rabbits and 2.3 hours in pigmented rabbits (Acheampong et al., 1995). These data are consistent with the data obtained in humans which show a half-life of ~ 3 hours (Lexicomp, database). The elimination of brimonidine after ocular application has been sufficiently addressed.

Pharmacokinetic Interactions

The MAH indicates that there is no data concerning ocular brimonidine tartrate formulations pharmacokinetic interactions in a preclinical (*in vivo and in vitro*) setting. Since brimonidine is a well-known substance and has a low absorption into systemic circulation (see Table 2, clinical study 13-100-0007) after ocular application, the pharmacokinetic drug interactions are considered sufficiently addressed.

III.3 Toxicology

Single dose toxicity

There is no preclinical *in vivo* data on single dose toxicity of ocularly administered brimonidine or other modes of single administration. One *in vitro* study has been described that evaluated cellular cytotoxicity of brimonidine in bovine corneal endothelial cells. It was found that 100 minutes exposure to high concentrations of brimonidine may induce cytotoxicity in corneal endothelial cells (Wu et al., 2007). Considering the limited relevance of single dose toxicity studies and that brimonidine is a well-known substance, the submitted data are considered sufficient to assess the single dose toxicity of brimonidine.

Repeated dose toxicity

The MAH refers to a study in rabbits and monkeys. In rabbits, transient sedation was observed at doses of 0.5% and 0.8% brimonidine [55]. With these doses, the peak plasma concentrations were at least 46 times higher than the plasma concentrations of brimonidine in a clinical study with 0.025% brimonidine (see Table 2, clinical study 13-100-0007). No treatment-related organ toxic or cardiovascular effects were observed in neither rabbit nor monkeys (Angelov et al., 1996). The C_{max} of the doses used in monkeys were 9, 20 and 24 times higher than the plasma levels from the clinical study with 0.025% brimonidine. In the same study, brimonidine dosed orally for one year in monkeys revealed a NOEL of 0.1 mg/kg/day, of which the C_{max} is a 5-fold higher than the human plasma drug concentration with 0.025% brimonidine (Angelov et al., 1996). Overall, these results indicate that the proposed brimonidine dose of 0.025% has a low potential to have effects on organ toxicity. The provided data were sufficient to address the repeated-dose toxicity of brimonidine from a non-clinical point of view.

Genotoxicity

Genotoxicity data on brimonidine were not provided. Solely relying on human data for genotoxicity would be insufficient. However, based on the weight of evidence, mostly relying on the absence of carcinogenicity findings as described below, but also taking into account the outcome of the reproduction toxicity studies and long clinical experience, it is plausible that brimonidine has no genotoxic potential.

Carcinogenicity

Carcinogenicity of brimonidine was studied in mice (21 months) and rats (2 years). In both species, no tumorigenic effects or neoplastic changes were observed, but tables with non-neoplastic changes were provided. In mice, reversible microscopic changes of hypertrophy of the tunica muscularis and hyperplasia of the epithelial mucosa were evident at the high dose of 2.5 mg/kg/day (Angelov et al., 1996). At this dose, the plasma drug concentration was 4.53 ng/mL, which is 180 times higher than the human peak plasma concentration. Similar reversible effects were seen in rats at doses from 0.25 mg and 1.0 mg, for which the maximal plasma drug concentrations were 1.51 and 6.90 ng/mL, respectively [55] (Angelov et al., 1996), which are approximately 60 times and 272 times higher than the maximal human plasma concentration. These changes are considered rodent specific as in one-year ocular- and oral monkey studies no clinical pathology parameters, macroscopic or microscopic changes were observed. It can therefore be agreed that no concerns for humans are anticipated.

Reproductive and developmental toxicity

Maternal and foetal toxicity/teratogenicity of orally dosed brimonidine during the gestation period were evaluated in pregnant rats. Doses of 0.1 and 0.4 mg/kg/day were no effect doses (approximately 20 times and 77 times the human exposure). Doses of 1.0 mg/kg/day produced maternal toxicity, while 2.5 mg/kg/day resulted in both maternal and foetal toxicity. None of the doses resulted in teratogenic effects. It is agreed that brimonidine has a large safety margin when administered systemically in high doses to pregnant rats. Furthermore, for the reproductive toxicity, the MAH refers to the prior safety findings (Pharmacology review and literature) for brimonidine tartrate, 0.2% ophthalmic solution, registered by Alphagan via the United States Food and Drug Administration (US FDA) under the New Drug Application (NDA) 020613). This described the reproductive toxicity evaluated in rats. Fertility was not affected in rats following oral brimonidine administration at doses ranging between 0.01 to 1.0 mg/kg/day. In this study, male rats were administered brimonidine beginning 70 days prior to and during mating and females were treated for 14 days prior to mating through gestation and lactation. Observed systemic effects were characterised by sedation and decreased body weight gain in high-dose males and females. No drug-related effects were observed with regard to reproductive indices, including mating, fertility, natural deliveries, and litter observations. The effect of oral brimonidine on peri- and postnatal development was evaluated in rats and rabbits. The parental (F0) generation was administered brimonidine at doses up to 2.5 mg/kg/day in rats and up to 5.0 mg/kg/day in rabbits. Following drug administration to the F0 generation, offspring through two subsequent generations (F1 and F2) were delivered and reared. Sedation and decreased body weight were observed in the high-dose groups in the treated F0 generation of each species. There were no drug-related impairments in behaviour, fertility, reproductive indices, or growth and development in the subsequent F1 and F2 generations of either species.

Local tolerance

Three animal studies have been described that evaluated the local tolerance of brimonidine and benzalkonium chloride (BAK) (Noecker et al., 2004; Von Zup et al., 2017) both of which are components of the Lumobry eye drops. Although the studies describe different effects on the local toleration of BAK, it is a well-known excipient and known to be an irritant. For the current product that contains 0.01% BAK, the local tolerance of Lumobry has been adequately evaluated.

Impurities excipients toxicology

The MAH provided a table summary of Lumobry eye drops medicinal product excipients' toxicological properties. None of the excipients are anticipated to pose a risk in humans. Impurities and leachables are present in the final formulation. A literature and database search were performed for applicable leachables. Quantitative Structure-Activity Relationships (Q(SAR)) analyses, for genotoxicity predictions in bacterial and mammalian species, were conducted on the potential active substance-related impurities. The potential impurities were classified in line with the ICH M7 guidelines. Most of the potential impurities are considered non-mutagenic, while two of them have the potential to be mutagenic. The MAH calculated that the amount of potential mutagenic impurities in the product at the maximum dose was well below than the acceptable dose limit in the ICH M7 guidelines (120 µg/day for a treatment duration not exceeding 1 month. Hence, it is agreed that the potential mutagenic impurities do not pose a safety concern if the active substance is controlled in line

with ICH Q3B, and no further toxicological evaluations are needed for the concerned medicinal product. Overall, no further genotoxicity and toxicological assessments are needed.

III.4 Ecotoxicity/environmental risk assessment (ERA)

The MAH has submitted an estimation of environmental exposure to the drug substance, based on the determination of $PEC_{surface\ water}$ (Predicted Environmental Concentration). The assessment is according to the Phase I requirements of EMEA/CHMP/SWP/4447/00 corr 2 "Guideline on the environmental risk assessment of medicinal products for human use". The main results of the assessment are shown in the table below.

Table 1. Main results Ecotoxicity/environmental risk assessment of testosterone.

Substance (INN/Invented Name): Brinzolamide			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-0.82 (pH 10)	Potential PBT - No
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)	7×10^{-3}	µg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			No
Substance (INN/Invented Name): Brimonidine			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	0.42 (pH 9)	Potential PBT No
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surfacewater, default or refined (e.g. prevalence, literature)	1.4×10^{-3}	µg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			No

Conclusions on studies:

Based on the formula, the estimated $PEC_{surface\ water}$ for brimonidine tartrate is 0.0005 µg/L. Therefore, as this value is below the action limit of 0.01 µg/L, it is agreed that the product is considered unlikely to represent a risk for the environment following its indicated use in patients. For the log K_{ow}, reference was made to the Bhagav et al., 2010. Using the shake flask method, the log K_{ow} was demonstrated to be lower than 4.5. Overall, it is agreed that brimonidine does not require a Phase II assessment as a high environmental risk is not apparent.

III.5 Discussion on the non-clinical aspects

Since brimonidine is a well-known substance, the submitted non-clinical overview to support the pharmacology, pharmacokinetics and toxicology of Lumobry 0.25 mg/ml is adequate and is of sufficient high quality in view of the present European regulatory requirements.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lumobry 0.25 mg/ml, eye drops, solution, is intended for the topical treatment of isolated conjunctival hyperemia due to minor eye irritation in adults. To support the proposed indication, the MAH conducted two clinal studies, one study on pharmacodynamics (PD) (10-100-008) and one study on pharmacokinetics (PK) (13-100-0007). The MAH also submitted additional PK and PD data available from the literature to supplement the pharmacology information of brimonidine tartrate. An overview of the clinical studies in is presented in the table below.

Table 2. Overview of clinical studies performed with brimonidine tartrate 0.01% to 0.025%, ophthalmic solution.

Study ID	Design	Population	Treatment	Duration	Key Efficacy Endpoints
Efficacy included as primary outcome measure					
10-100-0008	SC, RD, DB, PB, MD, PG	68 adult CAC	Brimonidine 0.01% = 17 0.025% = 17 Oxymetazoline 0.025% = 17 Vehicle = 17 Randomization 1:1:1:1	doses administered over 42 days	*Ocular redness* * evaluated by the investigator prior to study medication instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes post study medication instillation
11-100-0015	SC, DB, RD, VC, PA	Adult (45) Geriatric (12)	Brimonidine 0.025% QID = 38 Vehicle QID = 19 Randomization 2:1	28 days	*Ocular redness* * evaluated by the investigator prior to study medication instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes post study medication instillation
13-100-0005	SC, DB, RD, VC, PA	Adult (50) Geriatric (10)	Brimonidine 0.025% QID = 40 Vehicle = 20 Randomization 2:1	~5 weeks	*Ocular redness* * evaluated by the investigator prior to study medication instillation and at 5(+1),

					15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes post study medication instillation
Safety as primary outcome measure					
12-150-0001	SC, RD, DB, CO	Adult (15)	Brimonidine 0.025% QID = 15 Vehicle QID = 15	~1-5 weeks screening + 4 weeks QID dosing	Intraocular pressure **
13-100-0006	MC, DB, RD, VC, PA	Pediatric (50) Adult (408) Geriatric (49)	Brimonidine 0.025% QID = 337 Vehicle = 170 Randomization 2:1	~4 weeks	Safety
13-100-0007	PR, SC, OL	Adult (14)	Brimonidine 0.025% QID =14	7 days	Safety

Abbreviations: **CAC**= Conjunctival Allergen Challenge, **CO**= crossover, **DB**= double blind, **MC**= multi centre, **MD**=multiple dose, **OL**= open label, **PA**= parallel grouped, **PB**=Placebo controlled, **PR**=prospective, **QID**= four times daily, **RD**= randomised, **SC**= single centre, **VC**= vehicle controlled.
* Ocular redness was scored using a 5 point scale: 0=none, 1= mild, 2=moderate, 3 =severe, 4=extremely severe. The eyes were not scored individually but the average of both eyes was used.
** Study had the assessment of IOP as primary outcome; hence it provides primary safety information for the proposed indication.

All studies conducted by the MAH were approved by an institutional review board (Alpha IRB, San Clemente, California, USA) and conducted in compliance with the ethics principles of the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines (ICH GCP).

IV.2 Pharmacokinetics

Study 13-100-0007 (NCT02039765)

Desing

This study was a prospective, single-centre, open-label study designed to characterise the plasma PK and safety profile of brimonidine tartrate ophthalmic solution 0.025% following topical administration of a single dose and following Four Times Daily (QID) dosing bilaterally for 5 days. The study population comprised 14 healthy, adult subjects aged 18 to 55 years old. Pharmacokinetic blood draws post-instillation of a single dose at 15 ± 3 minutes, 30 ± 5 minutes, 1 hour ± 10 minutes, 1.5 hours ± 10 minutes, 2 hours ± 10 minutes, 3 hours ± 15 minutes, 4 hours ± 20 minutes, 6 hours ± 20 minutes, 8 hours ± 20 minutes, 12 hours ± 60 minutes, and 18 hours ± 60 minutes and 24 hours ± 60 minutes. The PK parameters C_{max}, T_{max}, $AUC0\text{-}_{24h}$, $AUC0\text{-}_{\infty}$, Kel, RAUC, RC_{max}, $T_{1/2}$ were determined.

Results

Only 1 out of the 14 subjects had a plasma brimonidine tartrate concentration greater than the LLOQ of 0.0250 ng/mL. For this subject, the T_{max} was 1 hour and the C_{max} value was 0.0253

ng/mL (25.3 pg/mL). In comparison, the mean C_{max} after administration of brimonidine tartrate 0.2% twice a day for 10 days was 0.06 ng/mL. It can be therefore concluded that the systemic exposure of brimonidine after QID of 0.025% brimonidine tartrate ophthalmic solution was considered negligible.

IV.3 Pharmacodynamics

Study 10-100-008 (NTNCT01275105)

Desing

In this study the effects of brimonidine on ocular redness was examined by conjunctival allergen challenge (CAC) in 68 adult subjects. Furthermore, the MAH compared 0.01% brimonidine and 0.025% brimonidine to placebo and Oxymetazoline which is used as a positive control due to its vasoconstrictive properties. Subjects were randomly assigned to a treatment group of 17 subjects to receive a single drop in each eye of one of the following study treatments:

- Brimonidine tartrate 0.01% ophthalmic solution
- Brimonidine tartrate 0.025% ophthalmic solution
- Oxymetazoline hydrochloride 0.025% ophthalmic solution
- Vehicle of brimonidine tartrate ophthalmic solution (placebo)

The CAC was performed 15 minutes (Day 42 ± 3) (visit 6), 4 hours (Day 28 ± 3) (Visit 5B), 6 hours (Day 14 ± 3) (Visit 4B), and 8 hours (Day 0) post-instillation (visit 3B). Ocular redness was scored using a 5-point scale: 0=none, 1= mild, 2=moderate, 3 =severe, 4=extremely severe. The eyes were not scored individually but the average of both eyes was used. The primary efficacy measure was the conjunctival redness at visit 6 evaluated by the investigator at 7-, 15- and 20-minutes post-challenge at each of the 4 CAC visits. The secondary efficacy measure included ocular itching evaluated by the subject at 3-, 5-, and 7-minutes post-challenge (0–4-unit scale, allowing half unit increments). Efficacy analyses were performed on the ITT population with the last observation carried forward (LOCF) method of imputation for missing data. All analyses were repeated for the PP population with observed data only as supportive analyses.

Results

72 subjects were selected based on inclusion and exclusion criteria and randomised at Visit 1. A total of 68 subjects completed the study. 4 subjects were discontinued from the study due to non-treatment-related adverse events. The primary outcome measure is shown in Table 3. A mean treatment difference of -0.78 to -0.97 from placebo was observed. Overall, there was no difference between the placebo and the positive control. The MAH provided a plausible explanation for a lack of efficacy of the active comparator in the CAC model, i.e., use of an inappropriate/too low dose for efficacy. This matter is not further pursued. The secondary efficacy measure shows no statistically significant differences in ocular itching between the different groups at any time point (supportive analyses, data not shown).

Table 3. Conjunctival Redness at Visit 6- ITT population with LOCF.

Time Point \ Group		Brimonidine 0.01% (*N* = 17)	Brimonidine 0.025% (*N* = 17)	Oxymetazoline 0.025% (*N* = 17)	Placebo (*N* = 17)
7 min post-CAC					
N		14	14	16	16
mean (SD)		0.66 (0.800)	0.68 (0.717)	1.30 (0.726)	1.44 (0.520)
Treatment difference		-0.78	-0.76	-0.14	- - -
vs. Placebo	*P*-value[1]	***0.0067***	***0.0116***	0.6182	- - -
	P-value[2]	***0.0052***	***0.0033***	0.5341	- - -
vs. Oxymetazoline	*P*-value[1]	***0.0265***	***0.0382***	- - -	0.6182
	P-value[2]	***0.0317***	***0.0266***	- - -	0.5341
15 min post-CAC					
N		14	14	16	16
mean (SD)		0.79 (0.814)	0.73 (0.710)	1.50 (0.769)	1.96 (0.552)
Treatment difference		-0.90	-0.96	-0.19	- - -
vs. Placebo	*P*-value[1]	***0.0056***	***0.0025***	0.3942	- - -
	P-value[2]	***0.0020***	***0.0004***	0.4350	- - -
vs. Oxymetazoline	*P*-value[1]	***0.0225***	***0.0168***	- - -	0.3942
	P-value[2]	***0.0206***	***0.0083***	- - -	0.4350
20 min post-CAC					
N		14	14	16	16
mean (SD)		0.82 (0.857)	0.61 (0.712)	1.28 (0.785)	1.58 (0.705)
Treatment difference		-0.76	-0.97	-0.30	- - -
vs. Placebo	*P*-value[1]	***0.0165***	***0.0038***	0.2621	- - -
	P-value[2]	***0.0148***	***0.0009***	0.2694	- - -
vs. Oxymetazoline	*P*-value[1]	0.1274	***0.0326***	- - -	0.2621
	P-value[2]	0.1392	***0.0200***	- - -	0.2694

[1] *P*-value calculated using a Wilcoxon rank sum test to compare each treatment to Placebo or to Oxymetazoline hydrochloride.
[2] *P*-value calculated using a two-sample t-test to compare each treatment to Placebo or to Oxymetazoline hydrochloride.
Source Table 14.2.1.1

IV.4 Clinical efficacy

The full clinical data package in support of the treatment of mild conjunctive hyperaemia includes six studies, of which three included an efficacy outcome measure as either primary or secondary outcome. One study (10-100-008) was already discussed in section pharmacodynamics. The other two efficacy studies (11-100-0015 and 13-100-0005) were similar in design. The subjects included had pre-existing ocular redness (i.e., a baseline redness score of >1 unit in both eyes on a 0-4 scale). The studies are described below.

Study 11-100-0015 (NCT01675609)

Desing

This was a Phase 2, single-centre, double-masked, randomised, vehicle-controlled, parallel-group, safety and efficacy study which comprised four visits over approximately five weeks. Subjects were healthy adult (≥ 40 years of age) and geriatric subjects (≥ 65 years of age) with normal ocular health. Subjects were randomised at a ratio of 2:1 (active: vehicle) at Visit 1, to receive either brimonidine tartrate 0.025% ophthalmic solution or the vehicle of brimonidine tartrate solution bilaterally by ocular instillation four times daily (QID). Subjects were not stratified by age group when assigned to investigational product. At Visit 1 (Day 0), subjects instilled study medication under the supervision of a trained study technician and then assessed drop comfort immediately following instillation and 30 seconds and 1 minute post instillation. The investigator assessed ocular redness at 5 to 240 minutes post study

medication instillation. Subjects were instructed to dose bilaterally, QID until Visit 3 (Day 28 +2 days) with no less than a 3.5-hour separation between doses for approximately 4 weeks beginning the next morning. Subjects were instructed to assess ocular redness for each eye prior to dosing and record the time of dosing in the diary. For the first dose of each day, the subject was to assess whether the drop made their eyes whiter. If so, subjects were to record how long the whitening effect lasted. Subjects were instructed to not dose within 3.5 hours of the time of their appointment for Visit 2 (Day 14 ±2 days). At Visit 2 (Day 14 ±2 days), study medication was instilled by a trained study technician and ocular redness was assessed by the investigator at 5 minutes post-instillation. Subjects continued to dose QID through the evening before Visit 3 (Day 28 + 2). At Visit 3 (Day 28 + 2), study medication was instilled by a trained study technician and ocular redness was assessed by the investigator at 5 minutes post instillation. From Visit 3 (Day 28 + 2) to Visit 4 (Day 35 + 1 day), subjects recorded their ocular redness QID. At Visit 4, the investigator assessed ocular redness.

Outcomes/endpoints

- Primary Efficacy Measurements:
    - Ocular redness score evaluated by the investigator prior to investigational drug instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation (0–4-unit scale, allowing half unit increments) at Visit 1.
    - Ocular redness evaluated by the subject once before each dose and then approximately 2 minutes after each dose and recorded in subjects' diaries throughout the treatment period (between Visit 1 and Visit 3). Each subject was given a redness scale of a 0-4 with photographic examples of degrees of staining.
- Secondary Efficacy Measurements: Ocular redness evaluated (0–4-unit scale) by the investigator prior to study medication instillation and at 5 minutes post study medication instillation at Visits 2 and Visit 3.
- Exploratory Efficacy Measurements: Duration of the whitening effect on the eyes evaluated by the subject throughout the treatment period. Subjects were asked to record in their diaries whether the drops made their eyes whiter and, if so, how long did the whitening effect last.

Results

57 subjects were selected based on inclusion and exclusion criteria and randomised at Visit 1. A total of 43 subjects completed the study. 14 subjects were discontinued from the study mostly due to administrative reasons/protocol violation and a relative low number due to adverse events. The results show a statistically significant reduction in ocular redness based on both investigators and patient reported scores with brimonidine. The summary of this study is shown in Table 4.

Table 4. Overview clinical study 11-100-0015, efficacy of brimonidine tartrate 0.025%.

Title: 11-100-0015				
Study identifier	11-100-0015			
Design	A Single-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution 0.025% Used Four Times Daily in a Population of Adult and Geriatric Subjects With Conjunctival hyperemia			
	Duration of main phase:		approximately 4 weeks, 28 (+2) days	
Hypothesis	Superiority of Brimonidine 0.025% eyedrop solution to vehicle			
Treatments groups	Brimonidine 0.025%		4 times a day for a duration of approximately 4 weeks	
	vehicle		4 times a day for a duration of approximately 4 weeks	
Endpoints and definitions	Primary endpoint	Average Ocular redness In-Office	The investigator assessed each subject's ocular redness prior to study medication instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes post study medication instillation at Visit 1	
	Secondary endpoint	Ocular redness subject diary	Subjects evaluated their redness once before each dose and then approximately 2 minutes after each dose for first 2 week treatment period	
Database lock	13-Oct-2012			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT with LOCF			
Descriptive statistics and estimate variability	Treatment group		Brimonidine 0.025%	vehicle
	Number of subject		38	19
	Average Change from baseline in ocular redness (In-Office)		-1.56	-0.20
	SE		0.054	0.0077
	LS mean daily ocular redness first 2 weeks (Subjects diary)		0.5	1.38
	SE		0.650	0.189

Effect estimate per comparison	Primary endpoint	Comparison groups	Brimonidine 0.025% vs vehicle
		LS mean difference	-1.37
		95% CI	-1.56,-1.18
		P-value	<0.0001
	Secondary endpoint	Comparison groups	Brimonidine 0.025% vs vehicle
		LS mean difference	-0.86
		95% CI	-1.37, -0.49
		P-value	0.0005
Notes	ANCOVA= analysis of covariance, LOCF= last observation carried forward, LS= least square, SE= Standard error, CI= confidence interval		
Analysis description	Ocular redness was assessed by the investigator on a 0-4 scale. 0.5 increments were allowed. A lower score is indicative of less redness. Primary endpoint & Secondary endpoint: The ANCOVA for all post installation time points is presented for the primary endpoint and not the individual time points. The P value was calculated using a repeated measures ANCOVA model and comparing the active treatment to the vehicle.		

Abbreviations: **ANCOVA**= analysis of covariance, **LOCF**= last observation carried forward, **LS**= least square, **SE**= Standard error, **CI**= confidence interval, **QID** = four times daily, **ITT**=Intended To Treat.

*Ocular redness was scored using a 5 point scale: 0=none, 1= mild, 2=moderate, 3 =severe, 4=extremely severe. The eyes were not scored individually but the average of both eyes was used.

<u>Study 13-100-0005 (NCT01959230)</u>

Desing

The study was a single-centre double-masked, randomised, vehicle-controlled, parallel-group study to evaluate the efficacy and safety of brimonidine tartrate 0.025% ophthalmic solution in healthy adult (≥ 18 years of age) subjects and geriatric (≥ 65 years of age) subjects with ocular redness. The study occurred over 36 (±1) days. There were four study visits scheduled: Visit 1 (enrolment/screening/randomisation, Day 1), Visit 2 (Day 15±2 days), Visit 3 (Day 29±2 days) and Visit 4 (Day 36±1 day). At the screening visit, baseline redness and safety assessments were performed. The safety assessments included best corrected visual acuity (BCVA) at distance, slit-lamp bio microscopy, intraocular pressure (IOP) measurements, dilated ophthalmoscopy, ocular redness assessment, and a physical exam with alertness assessment and vital signs. Subjects who met the inclusion and exclusion criteria were randomised 2:1 (active: vehicle) to receive one drop of either brimonidine tartrate 0.025% ophthalmic solution or the vehicle of brimonidine tartrate solution bilaterally by ocular instillation four times daily (QID), approximately four hours apart, for up to four consecutive weeks. Adverse event (AE) queries and drop comfort scales were recorded and subjects were instructed to begin at-home dosing the following day. At Visits 2 (Day 15±2), 3 (Day 29±2), and the follow-up visit (Visit 4, Day 36±1), ocular redness was assessed by the investigator, subject diaries were collected, AEs were queried, and safety assessments were performed according to the protocol.

Outcomes/endpoints

- Primary Efficacy Measurements: Ocular redness score evaluated by the investigator prior to investigational drug instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes after investigational drug instillation (0–4-unit scale, allowing half unit increments) at Visit 1.
- Secondary Efficacy Measurements:
    - Change from pre-instillation ocular redness score (using the Ora CalibraTM Ocular Hyperemia Scale and after investigational drug instillation (0–4-unit scale, allowing half unit increments) were evaluated by the investigator at:
        - 1 (+0.5) minute at Visits 1
        - 1 and 5 minutes at Visits 2 and 3
        - 360 (+15) minutes at Visits 1
        - 480 (+15) minutes at Visits 1
    - Ocular redness score evaluated by the subject as captured in subjects' dosing diary throughout the treatment period (0–4-unit scale, not allowing half unit increments).
    - Total clearance of ocular redness assessed by the Investigator at each post-instillation time point and at each visit.

Results

60 subjects were selected based on inclusion and exclusion criteria and randomised at Visit 1. A total of 55 subjects completed the study. 5 subjects were discontinued from the study due to administrative reasons/protocol violation. The results show a statistically significant reduction in ocular redness based on both investigators and patient reported scores with brimonidine. The summary of this study is shown in Table 5.

Table 5. Overview clinical study 13-100-0005, efficacy of brimonidine tartrate 0.025%.

Title: 13-100-0005		
Study identifier	13-100-0005	
Design	A Single-Center, Double-Masked, Randomized, Vehicle-Controlled, Parallel-Group Study Evaluating the Efficacy and Safety of Brimonidine Tartrate Ophthalmic Solution 0.025% Used Four Times Daily in a Population of Adult and Geriatric Subjects With Ocular Redness	
	Duration of main phase:	approximately 4 weeks, 28 (+2) days
Hypothesis	Superiority of Brimonidine 0.025% eyedrop solution to vehicle	
Treatments groups	Brimonidine 0.025%	4 times a day for a duration of approximately 4 weeks
	vehicle	4 times a day for a duration of approximately 4 weeks

Endpoints and definitions	Primary endpoint	Average Ocular redness In-Office	The investigator assessed each subject's ocular redness prior to study medication instillation and at 5(+1), 15(+1), 30(+1), 60(+10), 90(+10), 120(+15), 180(+15), and 240(+15) minutes post study medication instillation at Visit 1
	Secondary endpoint	Ocular redness subject diary	Subjects evaluated their redness once before each dose and then approximately 2 minutes after each dose for first 2 week treatment period
Database lock	20-Dec-2013		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT with LOCF		
Descriptive statistics and estimate variability	Treatment group	Brimonidine 0.025%	vehicle
	Number of subject	40	20
	LS mean Change from baseline in ocular redness (In-Office) visit 1 MMRM	-1.16	-0.29
	SE	0.076	0.108
	LS mean daily ocular redness first 2 weeks (Subjects diary)	0.85	1.85
	SE	0.135	0.188

Effect estimate per comparison	Primary endpoint MMRM	Comparison groups	Brimonidine 0.025% vs vehicle
		LS mean difference	-0.87
		95% CI	-1.13,-0.06
		P-value	<0.0001
	Secondary endpoint	Comparison groups	Brimonidine 0.025% vs vehicle
		LS mean difference	-1.00
		95% CI	-1.46, -0.54
		P-value	<0.0001
Notes	ANCOVA= analysis of covariance, LOCF= last observation carried forward, LS= least square, MMRM = mixed model repeated, SE= Standard error, CI= confidence interval		

Analysis description	Ocular redness was assessed by the investigator on a 0-4 scale. 0.5 increments were allowed. A lower score is indicative of less redness. Primary endpoint: p-value calculated using a generalized linear mixed model with treatment, time point, the treatment by time point interaction, and baseline score (pre-instillation value at the corresponding visit) in the model and comparing the active treatment to the vehicle. Secondary endpoint: p-value calculated using a repeated measures generalized linear mixed model with treatment and day in the model comparing the active treatment to the vehicle

Abbreviations: **ANCOVA**= analysis of covariance, **LOCF**= last observation carried forward, **LS**= least square, **SE**= Standard error, **MMRM** = mixed model repeated, **ITT**=Intended To Treat, **CI**=confidence interval, **QID** = four times daily.
*Ocular redness was scored using a 5 point scale: 0=none, 1= mild, 2=moderate, 3 =severe, 4=extremely severe. The eyes were not scored individually but the average of both eyes was used.

Overall results efficacy

Efficacy was assessed based on three studies that included efficacy outcome measure as either primary or secondary outcome, study 10-100-008 (already discussed in PD), 11-100-0015 and 13-100-0005. In study 11-100-0015, the ANCOVA at visit 1 for all post instillation time points showed an LS mean reduction of -1.37 (95%CI: -1.56-1.18) from placebo (p<0.0001). In study 13-100-0005, the mean difference with placebo is -0.78 (95%CI: -1.13-0.06; p<0.0001). The subjects rated reduction in ocular redness score was -0.86 (LS mean, 95%CI: -1.37-0.049, p=0.0005) in study 11-100-0015 and -1.0 (LS mean, 95%CI: -1.46, -0.54; p<0.0001) in study 13-100-0005. Both studies showed a reduction in ocular redness. However, both studies were single-centre studies with limited number of subjects. This raises the question of whether the effects can be generalised. Therefore, the results were combined and analysed. The pooled analysis of the investigators assessment showed that the LS mean change in ocular redness was -1.36 (SE 0.05) and -0.24 (SE 0.07) for the brimonidine and placebo group, respectively. This difference was statistically significant (p<0.0001). Overall, the MAH shows statistically significant improvement on ocular redness scores on both investigators and patient reported assessments. The average ocular redness evaluated by the investigator was separated from placebo from 5 to 240 minutes post installation.

Ocular hyperaemia is usually accompanied by other symptoms such as pain, watery eyes/tearing, itching and in general there is an underlying aetiology (cause). In that case, the underlying cause should be treated. Therefore, a warning is included the SmPC (in section 4.4, Special warnings and precautions for use) stating: *"Lumobry 0.25 mg/ml, eye drops, solution is for intermittent or occasional use only. If possible, to be defined, the underlying cause of eye hyperaemia (e.g., allergic reaction, dry eye disease) should be primarily treated".* Furthermore, the indication specifies that brimonidine should only be used in subjects with isolated hyperaemia.

IV.5 Clinical safety

The MAH has submitted four clinical studies to assess the safety of brimonidine tartrate ophthalmic solution (study 11-100-0015, 13-100-0005, 13-100-0007 and 13-100-0006). Across the four studies, a total of 475 subjects were exposed to at least one dose of 0.01%-0.025% brimonidine tartrate ophthalmic solution. 426 subjects were included in the integrated safety

summary (ISS), 15 in the IOP study and 34 in the multiple dose study. The median exposure was 29 days. The results of these studies and the main conclusions regarding the medical safety of brimonidine tartrate ophthalmic solution are described below.

Adverse events

A total of 16/475 (3.4%) subjects withdrew due to adverse events. Most of the events were unrelated to the product. Three serious adverse events were reported. However, it is likely that these are unrelated to the use of 0.025% brimonidine. Limited non-ocular events are expected due to low systemic exposure. This was confirmed by the study outcome, generally the proportions of adverse events are comparable between the 0.025% brimonidine and vehicle in type of adverse events reported in the ISS group. Infections and infestations were the most common reported non-ocular adverse events in the ISS and study 10-100-0008. The adverse events reported in study 12-150-0001 seem unrelated to brimonidine. Ocular adverse events are of interest as this is related to the installation site. Comparable proportions of ocular events were observed for both brimonidine and the vehicle.

Risks for ocular rebound

The MAH has investigated the risks for ocular rebound by assessing the effects of discontinuation of study drug treatment between two visits, i.e., for 7 days. Ocular redness was assessed by the subjects using a conjunctival hyperaemia diary. The data showed that there was no ocular rebound when subjects discontinued treatment for 7 days as the mean ocular redness 7 days post treatment was similar to the baseline mean ocular redness.

Effects on IOP

The MAH indicates that *"Approximately 29% and 25% of brimonidine-treated and vehicle-treated eyes, respectively, saw a decrease in IOP of -1 to -4 mm Hg"*. The effects on IOP were evaluated in a 5-day study, a 2-week cross over study and a 4-week study. The outcome of the studies was comparable with an IOP decrease of approximately 2-3 mm Hg, which is within the normal fluctuations over a course of 24 hours. As the product is restricted to short term use only, the fluctuations are acceptable. They also resolve when the product is no longer used, therefore no additional warnings or monitoring is required. Moreover, benzalkonium chloride (BAK), which increases the permeation of brimonidine over the cornea, is a component present in the product in a concentration of 0.01%. BAK may have caused the eye irritation and installation site pain and may contribute to the IOP effect. These resolve when the product is no longer used.

Clinical examinations

Besides assessing ocular redness, the MAH also performed other ocular tests such us best-corrected visual acuity (BCVA), slit lamp bio- microscopy and ophthalmoscopy. The laboratory findings did not show any concerning or abnormalities. Changes, if present, were generally also observed for the vehicle group. Two cases of bradycardia were reported. However, it is unclear if this could also be related to underlying conditions.

Tested population

The analysis on TAES by race, ethnicity, gender and age showed generally comparable proportions, indicating that no special warnings should be included for race, ethnicity, gender and age.

Effect of concomitant
In the clinical studies concomitant use with other topical ophthalmic agents was not permitted, therefore the eventual effect of concomitant use is unknown. The SmPC contains a warning regarding this.

Duration treatment
Long term use of the product is not recommended as the underlying cause for conjunctival hyperaemia should be reviewed by a specialist. If the cause is an infection, the infection should be treated. Therefore, a warning is included in the SmPC (in section 4.4, Special warnings and precautions for use) recommending short term use only in the posology. Also, other relevant warnings and precautions for use are included in the SmPC.

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 Lumobry 0.25 mg/ml.

Table 6. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

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

For this application, the MAH submitted one pivotal study on pharmacodynamics and one pivotal study on pharmacokinetics. The MAH also submitted additional data available from the literature on the pharmacology of brimonidine tartrate. Risk management is adequately addressed. Based on the data, the necessary warnings and recommendations have been included in the SmPC of the medicinal product. Overall, this medicinal product can be used for the specified indications. The clinical aspects of this product are approvable.

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 language used for the purpose of user testing the PL was Polish. The test consisted of: a pilot test with 3 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

Lumobry 0.25 mg/ml, eye drops, solution has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements. The overall benefit-risk is considered approvable. The efficacy of the medicinal product was confirmed, reduction in ocular redness was numerically better for the 0.025% compared to the 0.01% brimonidine.

The application was discussed in the Board meeting of 1 April 2021 (see openbaar verslag Collegevergadering, Agendapunt 7.c 975e), the following was discussed:

First round, Quality aspects
Major objections have been formulated about the sterilisation process for the container closure system and the specifications for the pH value of the solution.

First round, Clinical aspects
A total of six clinical studies were conducted, including one pharmacokinetics study and three studies examining efficacy. Based on the data submitted to date, there are several major objections regarding the proposed indications, product information for the patient, possible dependence that may occur with long-term use of this medicinal product and the clinical relevance and applicability of the study results. Additional data are required to adequately support the quality and clinical aspects of the product.

As requested by the CBG, the additional data were submitted by the MAH. Furthermore, the required warnings and recommendations were included in the product information for the patient. Based on this, the major objections were considered resolved.

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 considered that the risk-benefit balance for Lumobry 0.25 mg/ml, eye drops, solution is positive and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 August 2022.

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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
NL/H/5324/ 001/IA/001	Replacement or addition of a manufacturer responsible for importation and/or batch release: - Not including batch control/testing.	Yes	23-03-2023	Approved	N.A.
NL/H/5324/ 001/IB/002	Change in the (invented) name of the medicinal product: - For Nationally Authorised Products.	Yes	25-05-2023	Approved	N.A.
NL/H/5324/ 001/IB/003	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance: - Minor changes to an approved test procedure.	Yes	05-07-2023	Approved	N.A.
NL/H/5324/ 001/E/001	Repeat-use application	Yes	12-3-2024	Approved	N.A.
NL/H/5324/ IA/004/G	Change in the specification parameters and/or limits of the immediate packaging of the finished product: - Addition of a new specification parameter to the specification with its corresponding test method. - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter). Change in supplier of packaging components or devices (when mentioned in the dossier).	No No	21-5-2024	Approved	N.A.