Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lumobry 0.25 mg/mL eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

Excipient with known effect: Benzalkonium Chloride (0.01%)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Ophthalmic solution, eye drops

Clear, colorless to slightly yellow ophthalmic solution (pH 6.3-6.7, osmolality 275-320 mOsmol/kg)

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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Posology

One drop in the affected eye(s) every 6 – 8 hours, no more than four times daily.

A reduction in ocular redness should occur within 5-15 minutes. If the condition worsens or persists for more than 72 hours, the use of the product should be discontinued and the patient should be re-evaluated (see section 4.4).

Method of administration

Ocular use.

Lumobry should be applied in the affected eye(s) with pressing nasolacrimal duct and closing the eyelids for 2 minutes. These procedures enable to reduce the systemic absorption of the drug what result in a decrease in systemic side effects occurrence and an increase in local (ocular) activity.
If Lumobry is used with other topical ophthalmic medicinal product, the 15-minute interval should be maintained.
Hands should be thoroughly washed before and after using the product.
The tip of the dispensing container should not contact with the eye or surrounding structures in order to prevent contamination

Renal / Hepatic Impairment
Lumobry 0.25mg/ml, eye drops, solution has not been studied in patients with renal or hepatic impairment (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Lumobry should not be used in the following conditions:

- prolonged hyperaemia of the eye
- prolonged irritation of the eye
- ocular infections – mucopurulent discharge from the ocular tissues
- eye pain
- vision changes/disturbances

4.4 Special warnings and precautions for use

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.
A reduction in ocular redness should occur within 5-15 minutes. However, if the condition worsens or persists for more than 72 hours, the use of the product should be discontinued and the patient should be reevaluated.
Eye irritation or redness caused by a serious ocular disease, such as infection, foreign body or damage to the cornea, acute glaucoma or iritis requires immediate medical attention.

Cardiovascular disorders
In case of systemic absorption of brimonidine (when used incorrectly or for prolonged time) cardiovascular disturbances may be observed and thus special caution should be applied in patients with:
- severe or unstable and uncontrolled cardiovascular disease
- cerebral or coronary insufficiency
- Raynaud's phenomenon
- orthostatic hypotension
- thromboangiitis obliterans

CNS depression
In case of systemic absorption of brimonidine (when used incorrectly or for prolonged time) which easily pass the blood-brain barrier, the attenuation of central nervous system functions may be observed (dizziness, somnolence, sedation etc.). Such activity may result in the increase of disease symptoms and thus special caution should be applied in such patients treated with the product.

Simultaneous use of other ophthalmic topical drugs
If Lumobry is used with other topical ophthalmic medicinal product simultaneously, the 15-minute interval should be maintained.

Hepatic / Renal Impairment
Brimonidine has not been studied in patients with hepatic or renal impairment, therefore special caution should be used in treating such patients.

Paediatric population
Lumobry 0.25 mg/ml, eye drops, solution should not be used in paediatric patients.

Excipients-specific
The medicinal product contains benzalkonium chloride and may cause eye irritation.
Benzalkonium chloride is known to discolour soft contact lenses. The contact of the drug with contact lenses should be avoided. Contact lenses should be removed prior the application and 15-minute interval maintained before lenses reinsertion.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Other ocular medication:
Currently there is no information regarding the use of Lumobry 0.25 mg/ml, eye drops, medicinal product and the absorption of concomitant ocular products. However, a short, 15-minute interval between the application of Lumobry 0.25 mg/ml, eye drops, medicinal product and other ocular products should be maintained.

Systemic medication:
There is no information available regarding the use of Lumobry 0.25 mg/ml, eye drops medicinal product with other systemically administered drugs. Systemic absorption of brimonidine after topical ophthalmic application of the Lumobry 0.25 mg/ml, eye drops is limited and such amount of the drug is unlikely to pose a systemic threat to the use of other systemically administered drugs (see section 5.2). For higher brimonidine concentrations than Lumobry (i.e. 0.2%), the interactions with the following drug has to be taken into account.

Monoamine oxydase (MAO) inhibitors
Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine and potentially result in an increased systemic side effect such as hypotension. Caution is advised in patients taking MAO inhibitors, which can affect the metabolism and uptake of circulating amines.

Tricyclic or tetracyclic antidepressants
Caution is advised in patients taking antidepressants which can affect the noradrenergic transmission.

CNS depressants
Although specific drug interactions studies have not been conducted with brimonidine tartrate ophthalmic solution, the possibility of an additive or potentiating effect with central nervous system depressants (alcohol, barbiturates, opiates, sedatives, or anesthetics) should be taken into consideration.

Betablockers, antihypertensives, cardiac glycosides
Alpha-agonists, as a class, may reduce pulse and blood pressure. Caution in using concomitant drugs such as beta-blockers (ophthalmic and systemic), antihypertensives and/or cardiac glycosides is advised.

Adrenoceptor agonists/antagonists
Caution is required during initial concomitant use (or with a change in dosage) of a systemic drug (regardless of pharmaceutical form) that can cause interactions with α-adrenergic agonists or that can affect their effectiveness such as adrenoceptor agonists or antagonists (e.g. isoprenaline, prazosin).

Clonidine, chlorpromazine, methylphenidate, reserpine
Although no actual data on the level of circulating catecholamines after administration of brimonidine tartrate ophthalmic solution are available, caution is advised when using the eye drops in patients who are taking medications such as chlorpromazine, methylphenidate and reserpine, which can affect the metabolism and uptake of circulating amines.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of brimonidine in pregnant women. Brimonidine, at plasma levels higher than are achieved during therapy in humans, has been shown to cause pre-implantation loss and postnatal growth reduction in rabbits (see section 5.3). As a precautionary measure, the use of the Lumobry 0.25 mg/ml, eye drops medicinal product should be avoided during pregnancy.

Lactation
It is not known to what extent brimonidine tartrate may pass to the milk of breastfeeding women after ocular use. Studies on animals have shown that brimonidine and its metabolites are excreted with milk (for details see 5.3). A risk to the newborns/infants cannot be excluded. Therefore, the use of the Lumobry 0.25 mg/ml, eye drops medicinal product should be avoided during lactation.

Fertility
There is no human data indicating that topically applied brimonidine tartrate affects the fertility.

4.7 Effects on ability to drive and use machines

Lumobry 0.25 mg/ml, eye drops, medicinal product has minor influence on the ability to drive and use machines. As all products administered to eye, it may cause transient blurred vision, which may impair the ability to drive or to use machinery, especially at night or in reduced lighting. The patient should wait until these symptoms have cleared before driving or using machinery.

4.8 Undesirable effects

The frequency of occurrence of side effects was arranged as specified below:

Very Common: (≥ 1/10)
Common: (≥ 1/100, < 1/10)
Uncommon: (≥ 1/1,000, < 1/100)
Rare: (≥ 1/10,000, < 1/1 000)
Very rare: (< 1/10,000)
Frequency unknown (cannot be estimated from the available data).

The safety profile of Lumobry 0.25 mg/ml, eye drops was shown to be similar to the safety profile of the vehicle.

System organ class	Frequency of occurrence	Side effects
Eye disorders	Common	Ocular hyperemia
	Uncommon	Dry eye, photophobia, eye discharge, eye irritation, eye pain, foreign body sensation in eyes
General disorders and administration site conditions	Common	Instillation site pain
	Uncommon	Instillation site burn, instillation site irritation, instillation site pruritus
Nervous system disorders	Uncommon	Headache
Cardiac disorders	Uncommon	Palpitations
Musculoskeletal and connective tissue disorders	Uncommon	Muscle twitching
Blood and lymphatic system disorders	Uncommon	Lymphocytosis, monocytosis
Respiratory, thoracic and mediastinal disorders	Uncommon	Nasal discomfort
Vascular disorders	Uncommon	Hypotension

Due to the lower concentration of Lumobry 0.25 mg/ml, eye drops medicinal product, the potential risk of occurrence of known pharmacological class effects is expected to be lower than with brimonidine 0.2% eye drops, especially the systemic effects because of the negligible systemic exposure of Lumobry 0.25 mg/ml, eye drops medicinal product (see section 5.2).

In clinical studies with children treated with brimonidine eye drops at higher concentration (0.2%) as part of the medical treatment of congenital glaucoma, symptoms of brimonidine overdose such as loss of consciousness, lethargy, somnolence, hypotension, hypotonia, bradycardia, hypothermia, cyanosis, pallor, respiratory depression and apnoea have been reported (see section 4.9). Taking into consideration that 0.025% concentration of brimonidine in Lumobry is 8-times lower than that used in the treatment of glaucoma (0.2%), it may be assumed that the risk of serious side effects related to the CNS and peripheral tissues should also be significantly lower for Lumobry product.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Ophthalmologic overdose
There is no data available regarding any overdoses in adults following ophthalmological use regardeless on dosage.

Systemic overdose in the case of accidental ingestion
There is very limited information regarding accidental ingestion of brimonidine in adults. The only adverse event reported to date was hypotension reported after ingestion of 0.2% solution of brimonoidine. It was reported that the hypotensive episode was followed by rebound hypertension.

Treatment of an oral overdose includes supportive and symptomatic therapy – patient's respiratory function should be maintained.

Oral overdoses of other alpha-2-agonists have been reported to cause symptoms such as hypotension, asthenia, vomiting, lethargy, sedation, bradycardia, arrhythmias, miosis, apnoea, hypotonia, hypothermia, respiratory depression and seizure.

Paediatric population
Reports of serious adverse effects following inadvertent ingestion of 0.2% solution of brimonidine (8-times higher than in the Lumobry product) by paediatric subjects have been published or reported. The subjects experienced symptoms of CNS depression, typically temporary coma or low level of consciousness, lethargy, somnolence, hypotonia, bradycardia, hypothermia, pallor, respiratory depression and apnoea, and required admission to intensive care with intubation if indicated. All subjects were reported to have made a full recovery, usually within 6 -24 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals, ATC code: S01GA07

Mechanism of action
Brimonidine is an alpha-2 adrenergic receptor agonist that acts on sympathetic nerves to cause vasoconstriction. It is 1000-fold more selective for the alpha-2 adrenoceptors than the alpha-1 adrenoceptors. Alpha-2-adrenoceptors are present both pre- and post-synaptically in vascular tissues. Presynaptic α_2-adrenoceptors act as a negative feedback mechanism; activation of these receptors inhibits the release of norepinephrine. Activation of post-synaptic α_2-adrenoceptors decreases intracellular cAMP leading to tissue specific effects, including vasoactive effects. Brimonidine has been shown to act on both pre- and post-synaptic α_2-adrenoceptors in the ciliary body to mediate intraocular pressure. The α_2-adrenoceptor mediated vasoconstriction appears to occur primarily on the venous-side.

In the eye, α_2-adrenergic receptor agonism has been shown to regulate intraocular pressure by modulating neurotransmitter release and ciliary blood vessel constriction in the ciliary body and increasing the uveoscleral outflow.
Alpha-2-adrenergic receptors have been identified in human conjunctival biopsy samples, supporting the vasoconstrictive (blanching) effects observed in the conjunctiva.

Pharmacodynamic effects
Lumobry 0.25 mg/ml eye drops medicinal product has a rapid onset of action for the relief of conjunctival hyperaemia within 1 minute and a lasting effect of up to 8 hours.

Clinical efficacy and safety
Clinical studies with Lumobry 0.25 mg/ml eye drops medicinal product used 4 times a day have shown superiority to placebo in reducing ocular hyperaemia with no significant tachyphylaxis. Subjects with isolated hyperaemia with no underlying condition were included in two randomized controlled studies. Subjects were 2:1 randomized to brimonidine 0.25 mg/ml (N=78) or vehicle (N=39). The duration of the studies was 28 days and 5 weeks respectively. The mean shift on ocular redness score was -1.36 points for subjects on brimonidine and -0.24 for subjects on vehicle, measured from 5 minutes post-intillation up to 240 minutes post-instillation.
The safety of brimonidine was evaluated in 475 subjects. The incidence of adverse events was comparable to placebo. No clinically significant intra-ocular pressure changes were observed in study participants.

5.2 Pharmacokinetic properties

Absorption
After ocular administration, intraocular absorption is rapid. After a single topical administration of 0.5% brimonidine in rabbits, measurable levels of brimonidine were observed in all ocular tissues assessed (conjunctiva, cornea, aqueous humor, iris, ciliary body and lens) as soon as 10 minutes post-dosing.
Following oral administration to man, brimonidine is well absorbed.
Following topical ocular dosing of Lumobry 0.25 mg/ml eye drops medicinal product in 14 healthy volunteers, systemic exposure was below the lower limit of quantification (LLOQ, i.e. < 0.0250 ng/mL) in all subjects but one who demonstrated a C_{max} of 0.0253 ng/mL.

Distribution
Brimonidine has been shown to be distributed to all ocular tissues after ocular dosing in rabbits. In humans, mean levels of brimonidine in aqueous humor samples obtained approximately 1 h after a single 30 µL drop of 0.1% or 0.15% brimonidine were 59.4 ng/mL or 95.5 ng/mL, respectively. Brimonidine binds to pigment resulting in higher levels in pigmented tissues (e.g., iris). However, long term clinical studies in humans suggest that there are no adverse effects associated with binding to pigmented tissues.
It is reported that after ocular administration of a 0.2% solution twice daily for 10 days, plasma concentrations are low (mean C_{max} 0.06 ng/ml). There is a slight accumulation in the blood after multiple instillations (twice daily for 10 days). AUC_{0-12h} at steady state is reported as 0.31 ng*hr/ml, compared to 0.23 ng*hr/ml after the initial dose. The mean apparent half-life in the systemic circulation after topical dosing in humans was approximately 3 hours. Plasma protein binding of brimonidine after topical dosing in humans is approximately 29%.

Biotransformation
In-vitro studies, using animal and human liver, indicate that the metabolism is mediated largely by aldehyde oxidase and cytochrome P450. Hence, the systemic elimination seems to be primarily hepatic metabolism.

Elimination
Following oral administration to man, brimonidine is rapidly eliminated. The major part of the dose (around 75%) is excreted as metabolites in urine within 5 days; no unchanged drug was detected in urine.

Linearity/non-linearity
There is limited data available for ocular applied brimonidine tartrate pharmacokinetics and no information about linearity or non-linearity are available.

5.3 Preclinical safety data

Published non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

There is no data available concerning the influence of ocularly applied brimonidine on animal pregnancy. It is also not known if brimonidine is excreted in animal milk after ocular administration.

In rabbits, brimonidine tartrate (p.o.), at plasma levels higher than are achieved during therapy in humans, has been shown to cause increased pre-implantation loss and postnatal growth reduction.The compound is excreted in the milk of the lactating rat.een perform

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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
Water for Injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years (unopened)
Discard 121 days after the first opening.

6.4 Special precautions for storage

Donot store above 25°C.

6.5 Nature and contents of container

7.5 mL fill volumes in 10 mL LDPE bottles using LLDPE dropper applicators (tips) and two-piece child-resistant PP/HDPE screw caps.

6.6 Special precautions for disposal

No special measures.

7 MARKETING AUTHORISATION HOLDER

Bausch + Lomb Ireland Limited
3013 Lake Drive
Citywest Business Campus
Dublin 24, D24 PPT3
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23259/024/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th June 2024

10 DATE OF REVISION OF THE TEXT