Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

BIPROST (Bimatoprost Ophthalmic Solution 0.03 % w/v)

2. Qualitative and quantitative composition

Composition
Bimatoprost ..... 0.03 % w/v
Benzalkonium chloride BP .....0.005% w/v (As preservative)
Aqueous buffered vehicle .....Q.S. For a full list of excipients, see section 6.1.

3. Pharmaceutical form Eye drops, solution.

Colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to beta-blockers).

4.2 Posology and method of administration

Posology

The recommended dose is one drop in the affected eye(s) once daily, administered in the evening. The dose should not exceed once daily as more frequent administration may lessen the intraocular pressure lowering effect.

Paediatric population:
The safety and efficacy of bimatoprost in children aged 0 to 18 years has not yet been established.

Patients with hepatic and renal impairment:
Bimatoprost has not been studied in patients with renal or moderate to severe hepatic impairment and should therefore be used with caution in such patients.
In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, Bimatoprost eye drops, solution had no adverse effect on liver function over 24 months.

Method of administration
If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Bimatoprost is contraindicated in patients who have had a suspected previous adverse reaction to benzalkonium chloride that has led to discontinuation.

4.4 Special warnings and precautions for use
Ocular
Before treatment is initiated, patients should be informed of the possibility of prostaglandin analogue periorbitopathy (PAP): eyelash growth, darkening of the eyelid skin and increased iris pigmentation, since these have been observed during treatment with bimatoprost. Some of these changes may be permanent, and may lead to impaired field of vision and differences in appearance between the eyes when only one eye is treated (see section 4.8).
Cystoid macular oedema has been uncommonly reported (≥ 1/1,000 to <1/100) following treatment with bimatoprost 0.3 mg/ml eye drops. Therefore, bimatoprost should be used with caution in patients with known risk factors for macular oedema (e.g. aphakic patients, pseudophakic patients with a torn posterior lens capsule).
There have been rare spontaneous reports of reactivation of previous corneal infiltrates or ocular infections with Bimatoprost.
Bimatoprost should be used with caution in patients with a prior history of significant ocular viral infections (e.g. herpes simplex) or uveitis/iritis.
Bimatoprost has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle- closure glaucoma, congenital glaucoma or narrow- angle glaucoma.

Skin
There is a potential for hair growth to occur in areas where bimatoprost solution comes repeatedly in contact with the skin surface. Thus, it is important to apply bimatoprost as instructed and avoid it running onto the cheek or other skin areas.

Respiratory
Bimatoprost has not been studied in patients with compromised respiratory function. While there is limited information available on patients with a history

of asthma or COPD, there have been reports of exacerbation of asthma, dyspnoea and COPD, as well as reports of asthma, in post marketing experience. The frequency of these symptoms is not known. Patients with COPD, asthma or compromised respiratory function due to other conditions should be treated with caution.

Cardiovascular
Bimatoprost has not been studied in patients with heart block more severe than first degree or uncontrolled congestive heart failure. There have been a limited number of spontaneous reports of bradycardia or hypotension with Bimatoprost therefore should be used with caution in patients predisposed to low heart rate or low blood pressure.

Other Information
In studies of bimatoprost in patients with glaucoma or ocular hypertension, it has been shown that the more frequent exposure of the eye to more than one dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using bimatoprost with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

Bimatoprost solution contains the preservative benzalkonium chloride, which may be absorbed by soft contact lenses. Eye irritation and discolouration of the soft contact lenses may also occur because of the presence of benzalkonium chloride. Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since bimatoprost contains benzalkonium chloride, monitoring is required with frequent or prolonged use in dry eye patients or where the cornea is compromised.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures, to avoid eye injury and contamination of the solution.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.

No interactions are anticipated in humans, since systemic concentrations of bimatoprost are extremely low (less than 0.2 ng/ml) following ocular dosing with Bimatoprost solution. Bimatoprost is bio-transformed by any of multiple enzymes and pathways, and no effects on hepatic drug metabolising enzymes were observed in preclinical studies.
In clinical studies, bimatoprost was used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of interactions. Concomitant use of bimatoprost and antiglaucomatous agents other than topical beta- blockers has not been evaluated during adjunctive glaucoma therapy.
There is a potential for the IOP-lowering effect of prostaglandin analogues (e.g. Bimatoprost) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of bimatoprost in pregnant women. Animal studies have shown reproductive toxicity at high maternotoxic doses. Bimatoprost should not be used during pregnancy unless clearly necessary.

Breastfeeding

It is unknown whether bimatoprost is excreted in human breast milk. Animal studies have shown excretion of bimatoprost in breast milk. A decision must be made whether to discontinue breastfeeding or to discontinue from bimatoprost therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effects of bimatoprost on human fertility.

4.7 Effects on ability to drive and use machines

Bimatoprost has negligible influence on the ability to drive and use machines. As with any ocular treatment, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

In clinical studies, over 1800 patients have been treated with Bimatoprost solution. On combining the data from phase III monotherapy and adjunctive Bimatoprost eye drops usage, the most frequently reported treatment-related

adverse events were: growth of eyelashes in up to 45% in the first year with the incidence of new reports decreasing to 7% at 2 years and 2% at3 years, conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in up to 44% in the first year with the incidence of new reports decreasing to 13% at 2 years and 12% at 3 years and ocular pruritus in up to 14% of patients in the first year with the incidence of new reports decreasing to 3% at 2 years and 0% at 3 years. Less than 9% of patients discontinued due to any adverse event in the first year with the incidence of additional patient discontinuations being 3% at both 2 and 3 years. The following adverse reactions were reported during clinical trials with Bimatoprost 0.3 mg/ml eye drops, solution or in the post-marketing period. Most were ocular, mild to moderate, and none was serious:
Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000) and not known (cannot be estimated from available data) adverse reactions are presented according to System Organ Class in Table 1.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ class	Frequency	Adverse reaction
Nervous system disorders	common	headache
	uncommon	dizziness
Eye disorders	very common	conjunctival hyperaemia, ocular pruritus, growth of eyelashes, prostaglandin analogue periorbitopathy
	common	superficial punctate keratitis, corneal erosion, ocular burning, ocular irritation, allergic conjunctivitis, blepharitis, worsening of visual acuity,asthenopia, conjunctival oedema, foreign body sensation, ocular dryness, eye pain, photophobia, tearing, eye discharge, visual disturbance/blurred vision, increased iris pigmentation, eyelash darkening, eyelid erythema, eyelid pruritus

	uncommon	retinal haemorrhage, uveitis, cystoid macular oedema, iritis, blepharospasm, eyelid retraction, periorbital erythema, eyelid oedema
	not known	ocular discomfort
Vascular disorders	common	hypertension
Respiratory, thoracic and mediastinal disorders	not known	asthma, asthma exacerbation, COPD exacerbation and dyspnoea
Gastrointestinal disorders	uncommon	nausea
Skin and subcutaneous tissue disorders	common	pigmentation of periocular skin
	uncommon	hirsutism
	not known	skin discoloration (periocular)
General disorders and administration site conditions	uncommon	asthenia
Investigations	common	liver function test abnormal
Immune system disorders	not known	hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis

Description of selected adverse reactions Prostaglandin analogue periorbitopathy (PAP)
Prostaglandin analogues including bimatoprost can induce periorbital lipodystrophic changes which can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involution of dermatochalasis and inferior scleral show. Changes are typically mild, can occur as early as one month after initiation of treatment with bimatoprost, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevi nor freckles of the iris appears to be affected by the treatment. At 12 months, the incidence of iris pigmentation with bimatoprost was 1.5% and did not increase following 3 years treatment.

Adverse reactions reported in phosphate containing eye drops:

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

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 pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'.

4.9 Overdose
No case of overdose has been reported, and is unlikely to occur after ocular administration. If overdose occurs, treatment should be symptomatic and supportive. If bimatoprost is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m2 is at least 70-times higher than the accidental dose of one bottle of Bimatoprost eye drops, solution in a 10 kg child.

5. Pharmacological properties
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Ophthalmologicals, prostaglandin analogues, ATC code: S01EE03.

Mechanism of action

The mechanism of action by which bimatoprost reduces intraocular pressure in humans is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow. Reduction of the intraocular pressure starts approximately 4 hours after the first administration and maximum effect is reached within approximately 8 to 12 hours. The duration of effect is maintained for at least 24 hours.

Paediatric population
The safety and efficacy of bimatoprost in children aged 0 to less than 18 years has not been established.

5.2 Pharmacokinetic properties
Absorption
Bimatoprost penetrates the human cornea and sclera well *in vitro*. After ocular administration in adults, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/ml) within 1.5 hours after dosing. Mean Cmax and AUC 0-24hrs values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng» hr/ml respectively, indicating that a steady bimatoprost concentration was reached during the first week of ocular dosing.

Distribution
Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady- state was 0.67 l/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Biotransformation
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N- deethylation and glucuronidation to form a diverse variety of metabolites.

Elimination
Bimatoprost is eliminated primarily by renal excretion, up to 67% of an intravenous dose administered to healthy adult volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life,

determined after intravenous administration, was approximately 45 minutes; the total blood clearance was 1.5 l/hr/kg.

Elderly
There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.
Monkeys administered ocular bimatoprost concentrations of ≥ 0.3 mg/ml daily for 1 year had an increase in iris pigmentation and reversible dose-related periocular effects characterised by a prominent upper and/or lower sulcus and widening of the palpebral fissure. The increased iris pigmentation appears to be caused by increased stimulation of melanin production in melanocytes and not by an increase in melanocyte number. No functional or microscopic changes related to the periocular effects have been observed, and the mechanism of action for the periocular changes is unknown.
Bimatoprost was not mutagenic or carcinogenic in a series of *in vitro* and *in vivo* studies.
Bimatoprost did not impair fertility in rats up to doses of 0.6 mg/kg/day (at least 103- times the intended human exposure). In embryo/foetal developmental studies abortion, but no developmental effects were seen in mice and rats at doses that were at least 860-times or 1700-times higher than the dose in humans, respectively. These doses resulted in systemic exposures of at least 33- or 97-times higher, respectively, than the intended human exposure. In rat peri/postnatal studies, maternal toxicity caused reduced gestation time, foetal death, and decreased pup body weights at ≥ 0.3 mg/kg/day (at least 41-times the intended human exposure). Neuro behavioural functions of offspring were not affected.

6. Pharmaceutical particulars
6.1 List of excipients
Benzalkonium chloride
Sodium chloride
Citric acid monohydrate
Sodium phosphate dibasic heptahydrate
Sodium hydroxide
Hydrochloric acid

Water for injection

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Do not store above 30°C.
Do not freeze.

6.5 Nature and contents of container
3 ml plastic bottle

6.6 Special precautions for disposal and other handling
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder
Manufactured in India by:
MERCURY LABORATORIES LIMITED
Unit No. 2/13-2/14, Industrial estate,
Gorwa, Vadodara-390016. Gujarat, India
Manufactured For & Marketed by:
KRISHNA CHEMISTS LTD. P.O. BOX 3328-00506 Nairobi, Kenya.

8. Marketing authorisation number(s)

9. Date of first authorisation/renewal of the authorisation
13/12/2024

10. Date of revision of the text
13/12/2024