SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE HUMAN MEDICINAL PRODUCT

BEMATORIN 0.03% eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of solution contains:

Active ingredient:

Bimatoprost	0.3 mg

Excipients:

Benzalkonium chloride	0.05 mg
Disodium hydrogen phosphate heptahydrate	2.68 mg
Sodium chloride	8.30 mg
Sodium hydroxide	(pH 6.5–7.5)

See Section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Sterile eye drops, solution.
Clear, colorless solution free of visible particles

4. CLINICAL CHARACTERISTICS

4.1 Therapeutic indications

BEMATORIN is indicated as a monotherapy agent for the reduction of elevated intraocular pressure (IOP) in patients with chronic open-angle glaucoma and ocular hypertension, or as an adjunct to beta-blockers in patients whose condition is not adequately controlled with topical beta-blockers.

4.2 Dosage and administration

Dosage/frequency and duration of administration:

When used as monotherapy or as adjunctive therapy, the recommended dose is one drop in the affected eye(s) once daily in the evening. The dose should not exceed once daily, as more frequent administration may reduce the IOP-lowering effect.

Administration:

If more than one topical ophthalmic medication is used, the medications should be administered at least 5 minutes apart.

To prevent contamination of the dropper tip and the solution, care must be taken to ensure the dropper tip of the bottle does not come into contact with the eyelids, the surrounding area, or other surfaces.

Keep the bottle tightly closed when not in use.

Additional information for specific populations:
Renal/Hepatic impairment:
Bimatoprost has not been studied in patients with renal impairment or moderate to severe hepatic impairment. Therefore, it should be used with caution in these patients. In patients with mild liver disease at baseline or a history of abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or bilirubin levels, BEMATORIN had no adverse effects on liver function over a 24-month period.

Pediatric population:
Due to insufficient data on the efficacy and safety of BEMATORIN, its use is not recommended in children under 18 years of age.

Geriatric population:
No dosage adjustment is required in elderly patients.

4.3 Contraindications
Contraindicated in cases of hypersensitivity to the active ingredient bimatoprost or any of the excipients.

BEMATORIN is contraindicated in patients with a history of a suspected adverse reaction to benzalkonium chloride that led to discontinuation of the medication.

4.4 Special warnings and precautions for use
Ocular
Before starting treatment with BEMATORIN, patients should be informed of the possibility of eyelash growth, darkening of the eyelid color, and increased iris pigmentation, as these events have been observed during bimatoprost therapy. Some of these changes may be permanent and, in cases where only one eye is treated, may result in a difference in appearance between the two eyes. Pigmentation in the iris is likely to be permanent. The cause of the pigmentation change is an increase in melanin content within the melanocytes rather than an increase in the number of melanocytes. The long-term effects of increased pigmentation are unknown. The color change in the iris observed with ophthalmic bimatoprost application may not be noticeable for months or years. Typically, the brown pigmentation forming around the pupil spreads concentrically toward the periphery of the iris, causing the entire iris or a portion of it to take on a more brownish hue. It has been observed that colored spots or patches in the iris are not affected by treatment. The incidence of iris pigmentation at 12 months with BEMATORIN is 1.5%, and it has not increased during 3 years of treatment follow-up (see Section 4.8). In some patients, periorbital tissue pigmentation has been reported to be reversible. Cystoid macular edema has been reported at an uncommon frequency (>1/1000 to <1/100) following bimatoprost treatment. Therefore, BEMATORIN should be used with caution in patients known

to be at risk for macular edema (e.g., aphakic patients, pseudophakic patients with a torn posterior lens capsule).

Rare reports of sudden reactivation of previous spontaneous corneal infiltrates or ocular infections have been associated with bimatoprost. BEMATORIN should be used with caution in patients with a history of severe ocular viral infections (e.g., herpes simplex) or uveitis/iritis.

BEMATORIN has not been studied in patients with inflammatory ocular conditions, neovascular glaucoma, inflammatory glaucoma, angle-closure glaucoma, congenital glaucoma, or narrow-angle glaucoma.

Skin

There is a potential for hair growth in areas where BEMATORIN comes into repeated contact with the skin surface. Therefore, it is important to apply BEMATORIN as recommended and prevent it from running onto the cheeks or other skin areas.

Respiratory

BEMATORIN has not been studied in patients with impaired respiratory function. Limited information is available regarding patients with a history of asthma or
COPD, but postmarketing experience has reported asthma, dyspnea, and exacerbation of COPD. The frequency of these symptoms is unknown. Patients with COPD, asthma, or impaired respiratory function due to other causes should be treated with caution.

Cardiovascular

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

Other Information

In studies of BEMATORIN in patients with glaucoma or ocular hypertension, it has been shown that exposure of the eye to more than one daily dose of bimatoprost may reduce the intraocular pressure-lowering effect (see Section 4.5). Patients using BEMATORIN in combination with other prostaglandin analogs should be monitored for changes in intraocular pressure.

BEMATORIN contains benzalkonium chloride, a preservative that can be absorbed by soft contact lenses. This may cause eye irritation and discoloration of the soft contact lens. Contact lenses should be removed before application and reinserted 15 minutes after application.

Benzalkonium chloride, commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since

BEMATORIN contains benzalkonium chloride, frequent or prolonged use in patients with dry eye or corneal damage should be monitored.

There have been reports of bacterial keratitis associated with the use of multi-dose topical ophthalmic products. These products were often accidentally contaminated by patients with concurrent ocular conditions . Patients with compromised ocular epithelial surfaces are at greater risk of developing bacterial keratitis.

This medical product contains sodium; however, due to the route of administration, no specific warnings are required.

4.5 Interactions with other medical products and other forms of interaction

No interaction studies have been conducted.

Since systemic concentrations of bimatoprost are extremely low (below 0.2 ng/mL) following ocular administration of BEMATORIN, interactions in humans are not expected. Bimatoprost undergoes biotransformation via multiple enzymes and pathways, and in preclinical studies, no effect on any of the drug-metabolizing enzymes in the liver has been observed.

In clinical trials, bimatoprost has been used in combination with various other ophthalmic beta-blockers, and no drug interactions have been identified.

The use of BEMATORIN in combination with antiglaucoma agents other than topical beta-blockers has not been evaluated in adjuvant glaucoma therapy.

When used in combination with other prostaglandin analogs, there is a possibility that the intraocular pressure-lowering effect of prostaglandin analogs (e.g., BEMATORIN) may be reduced in patients with glaucoma or ocular hypertension (see Section 4.4).

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: C

Women of childbearing potential/Contraception

Women of childbearing potential should use an appropriate contraceptive method during treatment.

Pregnancy

BEMATORIN should not be used during pregnancy unless absolutely necessary.

Animal studies are insufficient regarding effects on pregnancy and/or embryonic/fetal development and/or labor and/or postnatal development. The potential risk to humans is unknown.

Lactation
It is unknown whether bimatoprost passes into human breast milk. Animal studies indicate that bimatoprost passes into milk. The risk to the nursing infant cannot be ruled out. A decision regarding whether to continue lactation or continue/ BEMATORIN treatment should be made after evaluating the benefit of breastfeeding to the child and the benefit of BEMATORIN treatment to the mother.

Fertility
No effects on human fertility have been reported with topical ophthalmic use. However, reproductive toxicity has been observed in animal studies at high maternotoxic doses.

4.7 Effects on the ability to drive and use machines
BEMATORIN has a negligible effect on the ability to drive and use machines. As with any ocular treatment, if temporary blurred vision occurs after administration of the medication, the patient should wait until vision clears before driving and using machines.

4.8 Adverse effects
Over 1,800 patients have been treated with bimatoprost in clinical trials. Based on data from the combination of Phase III bimatoprost monotherapy and adjuvant data, the most common treatment-related adverse effects reported are: Eyelash growth, with an incidence of up to 45% in the first year, 7% in the second year, and 2% in the third year, conjunctival hyperemia (generally considered to be mild to moderate and non-inflammatory) with an incidence of up to 44% in the first year, with new reports of 13% in the second year and 12% in the third year, and ocular pruritus in up to 14% of patients in the first year, with new reports of 3% in the second year and 0% in the third year. Less than 9% of patients discontinued treatment due to adverse effects in the first year. The incidence of treatment discontinuation was 3% in both the second and third years.

The following adverse effects have been reported during clinical trials with bimatoprost. Most are ocular, mild to moderate in severity, and none are serious.

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), not known (cannot be estimated from available data).

Immune system disorders
Not known: Hypersensitivity reaction involving signs and symptoms of eye allergy and allergic dermatitis

Nervous system disorders
Common: Headache
Uncommon: Dizziness

Eye conditions

Very common:	Conjunctival hyperemia, eyelash growth, and ocular itching
Common:	Allergic conjunctivitis, asthenopia, blepharitis, conjunctival edema, corneal erosion, darkening of eyelashes, eye pain, foreign body sensation, iris- increased pigmentation, ocular burning, ocular dryness, ocular irritation, photophobia, superficial punctate keratitis, tearing, visual disturbances and decreased visual acuity, ocular discharge, erythema of the eyelid, itching of the eyelid
Uncommon:	Blepharospasm, cystoid macular edema, eyelid retraction, iritis, uveitis, and retinal hemorrhage, periorbital erythema, eyelid edema
Not known:	Changes in the periorbital area and eyelids, including deepening of the eyelid sulcus

Vascular disorders

Common:	Hypertension

Respiratory, chest, and mediastinal diseases

Not known:	Asthma, exacerbation of asthma, exacerbation of COPD, dyspnea

Gastrointestinal diseases

Uncommon:	Nausea

Skin and subcutaneous tissue disorders

Common:	Periorbital skin pigmentation
Uncommon:	Hirsutism

General disorders and conditions related to the application site

Uncommon:	Asthenia

Investigations

Common:	Abnormal liver function test

Adverse effects reported with phosphate-containing eye drops:
In patients with severe corneal damage, cases of corneal calcification associated with the use of phosphate-containing eye drops have been reported very rarely.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the national reporting system.

4.9 Overdose

No cases of overdose have been reported, and an overdose is unlikely.

If an overdose occurs, symptomatic and supportive treatment should be administered. If BEMATORIN is accidentally ingested, the following information may be helpful:
In a two-week study conducted on rats and mice, doses up to 100 mg/kg/day showed no toxic effects. When expressed as mg/m², this dose is 70 times higher than the amount that would result from a 10-kg child swallowing an entire bottle of BEMATORIN.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic Group: Ophthalmic drugs—prostaglandin analogs
ATC Code: S01EE03

The mechanism by which bimatoprost reduces intraocular pressure in humans is to increase the outflow of aqueous humor through the trabecular meshwork and uveoscleral outflow. The reduction in intraocular pressure begins approximately 4 hours after the first application and reaches its maximum effect within approximately 8 to 12 hours. The duration of action is at least 24 hours.

Bimatoprost is a potent ocular hypotensive agent. It is a synthetic prostamide structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and does not interact with any known prostaglandin receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthetic compounds known as prostamides. However, the prostamide receptor has not yet been structurally characterized.

During a 12-month comparative monotherapy study of bimatoprost versus timolol in adults, the mean change in intraocular pressure at 8:00 AM compared to baseline ranged from -7.9 to -8.8 mm Hg. At any visit, the diurnal average intraocular pressure values measured over 12 months did not differ by more than 1.3 mm Hg throughout the day and were never higher than 18.0 mm Hg.

In a 6-month study comparing bimatoprost with latanoprost, a statistically superior reduction in morning mean intraocular pressure was observed at all visits throughout the study (ranging from -7.6 to -8.2 mm Hg for bimatoprost, compared to -6.0 to -7.2 mm Hg for latanoprost). Conjunctival hyperemia, eyelash growth, and ocular pruritus are statistically significantly higher with bimatoprost compared to latanoprost; however, discontinuation rates due to adverse events are low and not significantly different.

Compared to beta-blocker monotherapy, combined beta-blocker and bimatoprost therapy reduced the mean morning (8:00 AM) intraocular pressure by -6.5 to -8.1 mmHg.

Data on its use in patients with open-angle glaucoma with pseudoexfoliative and pigmentary glaucoma and in patients with chronic angle-closure glaucoma who have undergone iridotomy are limited.

In clinical studies, no clinically significant effect on heart rate or blood pressure was observed.

5.2 Pharmacokinetic properties

General characteristics

Absorption:

Bimatoprost penetrates human cornea and sclera well *in vitro*. Following ocular administration, the systemic effect of bimatoprost is very low, and no accumulation occurs over time. Following ocular administration of one drop of 0.03% bimatoprost to both eyes once daily for a total of two weeks, blood concentrations reached peak levels within 10 minutes after dosing and fell below the lower limit of detection (0.025 ng/ml) within 1.5 hours after dosing. The mean C_{max} and $AUC_{0-24\,h}$ values were approximately 0.08 ng/mL and 0.09 µg/mL, respectively, on days 7 and 14. This indicates that a steady-state bimatoprost concentration is achieved within the first week of ocular dosing.

Distribution:

Bimatoprost distributes moderately into body tissues, and the systemic volume of distribution in humans at steady state is 0.67 L/kg. In human blood, bimatoprost is primarily found in plasma. The plasma protein binding rate of bimatoprost is approximately 88%.

Biotransformation:

Following ocular administration, bimatoprost is the primary substance entering the systemic circulation. Subsequently, bimatoprost undergoes oxidation, N-deethylation, and glucuronidation to form various metabolites.

Elimination:

Bimatoprost is primarily excreted via the renal route. In healthy volunteers, 67% of an intravenous dose was excreted in the urine and 25% in the feces. The elimination half-life observed after intravenous administration is approximately 45 minutes, and the total blood clearance is 1.5 L/h/kg.

Characteristics in Patients

Following twice-daily administration of bimatoprost, the mean $AUC_{0-24\ hours}$ value of 0.0634 ng·h/mL achieved in the elderly (volunteers aged 65 years or older) is significantly higher than the 0.0218 ng·h/mL value achieved in young healthy adults. However, this finding is not clinically significant, as systemic exposure remains very low in both elderly and young adults due to ocular administration.

Bimatoprost does not accumulate in the blood over time, and the safety profile is similar in both young and elderly patients.

5.3 Preclinical safety data

Effects in nonclinical studies have been observed only at exposures sufficiently higher than the maximum human exposure and have little relevance to clinical use.

In monkeys, daily ocular administration of bimatoprost at concentrations of ≥0.3 mg/mL for 1 year caused dose-related, reversible periocular effects characterized by increased iris pigmentation and the accentuation of the superior and/or inferior sulcus and widening of the palpebral fissure . The increase in iris pigmentation appears to result from increased stimulation of melanin production in melanocytes rather than an increase in the number of melanocytes. No functional or microscopic changes associated with the periocular effects have been observed, and the mechanism of the periocular changes is not known.

Bimatoprost was not mutagenic or cytogenic in a series of *in vitro* and *in vivo* studies.

Bimatoprost did not impair fertility in rats at doses up to 0.6 mg/kg/day (approximately 103 times the intended human dose). In embryo/fetal development studies, no effects on development were observed in mice and rats at doses 860 to 1,700 times higher than the human dose. These doses resulted in systemic exposure equivalent to at least 33 to 97 times the intended human dose, respectively. In peri/postnatal studies in rats, doses of ≥ 0.3 mg/kg/day (at least 41 times the intended human exposure) administered to female rats caused a reduction in gestation duration, fetal death, and decreased pup body weight. The pups' neurobehavioral functions were not affected.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Benzalkonium chloride
Disodium hydrogen phosphate heptahydrate
Citric acid monohydrate
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at a room temperature below 25°C.

Must be used within 28 days of first opening.

6.5 Nature and contents of container

It is supplied as a 3 mL solution in a package consisting of a dropper-tipped, transparent, low-density polyethylene bottle and a white polypropylene screw-cap.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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