SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BEMATORIN 0.01% eye drops, solution
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL solution contains:
Active substance:
Bimatoprost.....0.1 mg
Excipient(s) with known effect:
Benzalkonium chloride.....0.08 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the reduction of elevated intraocular pressure (IOP) in patients with chronic open-angle glaucoma or ocular hypertension, as monotherapy or as adjunctive therapy to topical beta-blockers.

4.2 Posology and method of administration

Posology/frequency and duration of administration
When used as monotherapy or as an adjunctive treatment, the recommended dose is one drop of BEMATORIN in the affected eye(s) once daily in the evening. The dose should not exceed one drop per day, as frequent administration may reduce the IOP-lowering effect.

Method of administration
It is applied by instillation into the eye. To prevent contamination of the dropper tip and the solution, care should be taken to ensure that the dropper tip of the bottle does not touch the eyelids, the surrounding area or other surfaces. The bottle should be kept tightly closed when not in use.

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

Additional information on special populations
Renal / Hepatic impairment
Bimatoprost 0.1 mg/ml eye drops have not been studied in patients with renal or moderate to severe hepatic impairment. Therefore, it should 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 0.3 mg/ml eye drops had no adverse effect on liver function over 24 months.

Pediatric population
The efficacy and safety of bimatoprost 0.1 mg/ml eye drops in pediatric patients under 18 years

of age have not yet been established. The use of BEMATORIN is not recommended for patients under 18 years of age.

Geriatric population
No dose adjustment is required in elderly patients.

4.3 Contraindications
It is contraindicated in case of hypersensitivity to bimatoprost or to any of the excipients.
It 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 starting treatment, patients should be informed of the possibility of prostaglandin analog periorbital pathology (PAP) and increased iris pigmentation, as these conditions have been observed during bimatoprost treatment. Some of these changes may be permanent and, if only one eye is treated, may lead to visual field defects and differences in appearance between the two eyes. (see Section 4.8).

Cystoid macular edema has been uncommonly reported (≥1/1,000 to <1/100) following treatment with bimatoprost 0.3 mg/ml eye drops. Therefore, BEMATORIN should be used with caution in patients with known risk factors for macular edema (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 0.3 mg/ml eye drops. BEMATORIN 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 BEMATORIN comes repeatedly in contact with the skin surface. Thus, it is important to apply BEMATORIN as instructed and avoid it running onto the cheek or other skin areas.

Respiratory
Bimatoprost 0.1 mg/mL eye drops have not been studied in patients with impaired respiratory function. While limited information is available in patients with a history of asthma or COPD, postmarketing experience has reported asthma, dyspnea, and exacerbations of COPD, as well as asthma. The frequency of these symptoms is unknown. Caution is advised when using this medication in patients with impaired respiratory function due to other conditions, asthma, or COPD.

Cardiovascular
Bimatoprost 0.1 mg/ml eye drops have 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 0.3 mg/ml eye drops.

Therefore, BEMATORIN should be used with caution in patients predisposed to low heart rate or low blood pressure.

Other information
In studies of bimatoprost 0.3 mg/ml 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 intraocular pressure lowering effect (see section 4.5). Patients using BEMATORIN with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

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 BEMATORIN contains 0.08 mg benzalkonium chloride, it should be used with caution in patients with dry eye or in cases where the cornea is compromised and in patients taking more than one medicine containing benzalkonium chloride. Patients should be monitored for prolonged use.

There have been reports of bacterial keratitis associated with the use of multiple dose topical ophthalmic products. These products are often inadvertently contaminated by patients who have a concurrent ocular disease. Patients with a disruption of the ocular epithelial surface are at greater risk of developing bacterial keratitis.

To avoid solution contamination, the tip of the bottle should not be allowed to contact the eye, surrounding tissues, fingers or any other surface.

BEMATORIN contains benzalkonium chloride. Benzalkonium chloride may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses before use and wait at least 15 minutes before reinserting them. It is known to cause discoloration of soft contact lenses.

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 0.3 mg/ml eye drops. Bimatoprost is bio-transformed by any of multiple enzymes and pathways, and no effects on hepatic medicine metabolizing enzymes were observed in preclinical studies.

In clinical studies, bimatoprost 0.3 mg/ml eye drops were used concomitantly with a number of different ophthalmic beta-blocking agents without evidence of interactions.

Concomitant use of bimatoprost 0.1 mg/ml eye drops and antiglaucomatous agents other than topical beta-blockers has not been evaluated during adjunctive glaucoma therapy.

There is a potential for the intraocular pressure lowering effect of prostaglandin analogues (e.g. BEMATORIN) to be reduced in patients with glaucoma or ocular hypertension when used with other prostaglandin analogues (see section 4.4).

If more than one topical ophthalmic drug is being used, the drugs should be administered at

least 5 minutes apart.

Additional information for specific populations:
None reported.

Pediatric population:
Not reported.

Geriatric population:
Not reported.

4.6 Pregnancy, lactation and fertility
General advice
Pregnancy category is C.

Women of childbearing potential/Birth control (Contraception)
There are no data on use in women of childbearing potential. Women of childbearing potential should use an appropriate contraceptive method during treatment.

Pregnancy
There is insufficient data on the use of 0.3 mg/mL bimatoprost eye drops in pregnant women. Animal studies have shown reproductive toxicity at high maternotoxic doses (see Section 5.3). The potential risk to humans is unknown.

Breastfeeding
It is unknown whether bimatoprost is excreted in human breast milk. Animal studies have shown excretion of bimatoprost in breast milk. The decision whether to continue treatment or breastfeeding should be based on the risks/benefits of the treatment for the mother and the breastfeeding for the baby.
BEMATORIN is not recommended for use in nursing mothers.

Fertility
There are no data on the effects of bimatoprost on human fertility. However, animal studies have shown reproductive toxicity at high maternotoxic doses.

4.7 Effects on ability to drive and use machines
BEMATORIN has negligible influence on the ability to drive and use machines. As with any ocular medicines, 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 a 12-month Phase III clinical study with bimatoprost 0.1 mg/ml, 38% of patients reported adverse reactions. The most frequently reported adverse event was conjunctival hyperemia (mostly trace to mild and thought to be of a non-inflammatory nature) occurring in 29% of patients. Approximately 4% of patients discontinued treatment with bimatoprost 0.1 mg/ml eye drops due to conjunctival hyperemia.

The following adverse reactions were reported during clinical trials with bimatoprost 0.1 mg/ml or in the post-marketing period. Most were ocular, mild and none were serious.

Adverse reactions are presented according to System Organ Class in order of decreasing seriousness within each frequency grouping. 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); not known (cannot be estimated from available data).

Immune system disorders
Not known: Symptoms and signs of hypersensitivity reactions, including eye allergies and allergic dermatitis and findings

Nervous system disorders
Uncommon: Headache
Not known: Dizziness

Eye disorders
Very common: Conjunctival hyperemia, prostaglandin analog periorbital syndrome
Common: Punctate keratitis, eye irritation, eye pruritus, growth of eyelashes, eye pain, erythema of eyelid, eyelid pruritus
Uncommon: Asthenopia, blurred vision, conjunctival disorder, conjunctival edema, iris hyperpigmentation, madarosis, eyelid edema
Not known: Blepharal pigmentation, macular edema, dry eye, eye discharge, eye edema, foreign body sensation in the eye, increased tear production, eye discomfort, photophobia

Vascular disorders
Not known: Hypertension

Respiratory, chest disorders, and mediastinal diseases
Not known: Asthma, asthma exacerbation, COPD exacerbation, and dyspnea

Gastrointestinal disorders
Uncommon: Nausea

Skin and subcutaneous tissue disorders
Common: Skin hyperpigmentation, hypertrichosis
Uncommon: Dry skin, eyelid margin crusting, pruritus
Not known: Skin discoloration (around the eyes)

General disorders and administration site conditions
Common: Instillation site irritation

Definition of selected side effects
Prostaglandin Analog Periorbitopathy (PAP)
Prostaglandin analogs, including bimatoprost, may cause periorbital lipodystrophic changes that can lead to deepening of the eyelid sulcus, ptosis, enophthalmos, eyelid retraction, involutional dermatochalasis, and exposure of the inferior sclera. These changes are generally mild, may appear approximately one month after starting bimatoprost treatment, and may cause visual field impairment even if not noticed by the patient. PAP is also associated with periocular

skin hyperpigmentation or discoloration and hypertrichosis. It has been noted that all changes may be partially or completely reversible upon discontinuation of treatment or switching to alternative therapies.

Iris Hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change stems from increased melanin content within melanocytes rather than an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are unknown. Changes in iris color observed with the ophthalmic application of bimatoprost may go unnoticed for several months to years. Typically, as the brown pigmentation around the pupil spreads concentrically toward the periphery of the iris, causing the entire iris or parts of it to become more brownish. Nevi or spots on the iris are not affected by treatment. The incidence of iris hyperpigmentation with bimatoprost 0.1 mg/mL eye drops, solution, is 0.5% over 12 months. The incidence with bimatoprost 0.3 mg/mL eye drops, solution, is 1.5% over 12 months (see Section 4.8, Table 2) and has not increased after 3 years of treatment

In clinical studies, over 1800 patients have been treated with bimatoprost 0.3 mg/ml. On combining the data from phase III monotherapy and adjunctive bimatoprost 0.3 mg/ml usage, the most frequently reported adverse events were:

- Growth of eyelashes in up to 45% in the first year with the incidence of new reports decreasing to 7% at year 2 and 2% at year 3.
- Conjunctival hyperemia (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 year 2 and 12% at year 3.
- Ocular pruritus in up to 14% of patients in the first year with the incidence of new reports decreasing to 3% at year 2 and 0% at year 3. Less than 9% of patients discontinued due to any adverse event in the first year. The incidence of treatment discontinuation is 3% in the 2nd and 3rd years.

The following adverse reactions were reported with bimatoprost 0.3 mg/ml. These included adverse reactions that occurred with both formulations but with different frequencies. Most were ocular, mild to moderate, and none were serious: Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders

Common:	Headache
Uncommon:	Dizziness

Eye disorders

Very common:	Ocular pruritus, growth of eyelashes
Common:	Corneal erosion, ocular burning, allergic conjunctivitis, blepharitis, worsening of visual acuity, asthenopia, conjunctival edema, foreign body sensation, ocular dryness, eye pain, photophobia, tearing, eye discharge, visual disturbance/blurred vision, increased iris pigmentation, eyelash darkening
Uncommon:	Retinal hemorrhage, uveitis, cystoid macular edema, iritis, blepharospasm, eyelid retraction, periorbital erythema

Vascular disorders

Common: Hypertension

Skin and subcutaneous tissue disorders
Uncommon: Hirsutism

General disorders and administration site conditions
Uncommon: Asthenia

Investigations
Common: Liver function test abnormal

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 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 case of overdose has been reported, and is unlikely to occur after ocular administration.
If overdose occurs, treatment should be symptomatic and supportive. In case of accidental ingestion, 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/m^2 is at least 210-times higher than the accidental dose of one bottle of BEMATORIN for a child weighing 10 kg.

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

Mechanism of action
Bimatoprost reduces intraocular pressure in humans by increasing the outflow of aqueous humor 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 action is maintained for at least 24 hours.

Bimatoprost is a potent ocular hypotensive agent. It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that does not act through any known prostaglandin receptor. Bimatoprost selectively mimics the effects of newly discovered biosynthesized substances called prostamides. The prostamide receptor, however, has not yet been structurally identified.

During a 12-month preliminary study in adults with bimatoprost 0.1 mg/ml, the mean diurnal intraocular pressure values measured at any visit over the 12-month study period differed by no more than 1.1 mmHg throughout the day and were never greater than 17.7 mmHg.

BEMATORIN contains benzalkonium chloride at a concentration of 0.008% (w/v).

Limited experience is available with the use of bimatoprost 0.1 mg/ml in patients with open-angle glaucoma with pseudoexfoliative and pigmentary glaucoma, and chronic angle-closure glaucoma with patent iridotomy.

No clinically relevant effects on heart rate and blood pressure were observed in clinical trials.

Pediatric population
The efficacy and safety of BEMATORIN in pediatric patients younger than 18 years of age have not been established.

5.2 Pharmacokinetic properties

General 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 0.3 mg/ml 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 C_{max} and AUC_{0-24h} values were approximately 0.08 ng/ml and 0.09 ng•hr/ml on days 7 and 14, respectively. This suggests 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 volunteers was excreted in the urine and 25% in feces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes and the total blood clearance was 1.5 L/hr/kg.

Characteristics in patients

Geriatric patients
After twice-daily dosing with bimatoprost 0.3 mg/ml eye drops, the mean AUC_{0-24hr} value of 0.0634 ng•hr/ml in elderly subjects (65 years and older) was significantly higher than the value of 0.0218 ng•hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure associated with elderly and young subjects is extremely low in ocular dosing. 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 characterized 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. 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 male and female rats up to doses of 0.6 mg/kg/day (at least 103-times the intended human exposure). In embryo/fetal 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 peri/postnatal studies in rats, females given doses of ≥ 0.3 mg/kg/day (at least 41-times the intended human exposure) showed reduced gestation time, fetal death and decreased offspring body weights. Neurobehavioral functions of offspring were not affected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

None reported.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at room temperature below 25 ºC.
The solution should be used within 4 weeks after the bottle is first opened.

6.5 Nature and contents of container

The product is available as 2.5 mL solution in a package consisting of a transparent, low-density polyethylene bottle with a dropper 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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2017/946

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization : 21.12.2017
Renewal of the authorization :

10. DATE OF REVISION OF THE TEXT