1. NAME OF THE MEDICINAL PRODUCT

Zimed® Preservative Free 0.3 mg/mL, eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 0.3 mg bimatoprost.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless solution, practically free from particles.

The solution has a pH of about 7.3. The osmolality of the solution is approximately 300 mOsml/kg.

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, a multi-dose formulation of bimatoprost 0.3 mg/mL containing benzalconium chloride as a preservative 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.

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) 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 multi-dose formulations of bimatoprost 0.3 mg/mL eye drops, solution containing benzalkonium chloride as a preservative. 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 multi-dose formulations of bimatoprost 0.3 mg/mL eye drops, solution containing benzalkonium chloride as a preservative. 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 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 multi-dose formulations of bimatoprost 0.3 mg/mL eye drops, solution containing benzalkonium chloride as a preservative.
Bimatoprost 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 eye drops, solution 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.

Patients with a history of contact hypersensitivity to silver should not use this product as dispensed drops may contain traces of silver.

Bimatoprost has not been studied in patients wearing contact lenses. Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration.

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 multi-dose formulations of bimatoprost 0.3 mg/mL containing benzalkonium chloride as a preservative. Bimatoprost is biotransformed by any of multiple enzymes and pathways, and no effects on hepatic drug metabolising enzymes were observed in preclinical studies.

In clinical studies, a multi-dose formulation of bimatoprost 0.3 mg/mL containing benzalkonium chloride as a preservative 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 (see section 4.4).

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 (see section 5.3).

Bimatoprost should not be used during pregnancy unless clearly necessary.

Breast-feeding

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 breast-feeding or to discontinue from bimatoprost therapy taking into account the benefit of breast feeding 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 a 3 month clinical study, approximately 29% of patients treated with a formulation of bimatoprost 0.3 mg/mL eye drops, solution without preservative experienced adverse reactions. The most frequently reported adverse reactions were conjunctival hyperaemia (mostly trace to mild and of a non-inflammatory nature) occurring in 24% of patients, and eye pruritis occurring in 4% of patients. Approximately 0.7% of patients in the formulation of bimatoprost 0.3 mg/mL eye drops, solution without preservative group discontinued due to any adverse event in the 3 month study.

The following adverse reactions were reported during clinical trials with a formulation of bimatoprost 0.3 mg/mL eye drops, solution without preservative or in the post-marketing period. Most were ocular, mild 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.

Table 1

System Organ class	**Frequency**	**Adverse reaction**
Nervous system disorders	uncommon	headache
	not known	dizziness
Eye disorders	very common	conjunctival hyperaemia, prostaglandin analogue periorbitopathy
	common	punctate keratitis, eye irritation, foreign body sensation, dry eye, eye pain, eye pruritus, growth of eyelashes, eyelid erythema
	uncommon	asthenopia, conjunctival oedema, photophobia, lacrimation increased, iris hyperpigmentation, blurred vision, eyelid pruritus, eyelid oedema
	not known	eye discharge, ocular discomfort
Respiratory, thoracic and mediastinal disorders	not known	asthma, asthma exacerbation, COPD exacerbation and dyspnoea
Skin and subcutaneous tissue disorders	Common	skin hyperpigmentation (periocular)
	uncommon	hair growth abnormal
	not known	skin discoloration (periocular)
Immune system disorders	not known	Hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis
Vascular disorders	not known	hypertension

Description of selected adverse reactions:

Prostaglandin analogue periorbitopathy (PAP)
Prostaglandin analogues including Zimed® Preservative Free 0.3 mg/mL, eye drops, solution 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 Zimed® Preservative Free 0.3 mg/mL, eye drops, solution, 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 appear to be affected by the treatment. At 12 months, the incidence of iris hyperpigmentation with bimatoprost 0.1 mg/ml eye drops, solution was 0.5%. At 12 months, the incidence with bimatoprost 0.3 mg/ml eye drops, solution was 1.5% (see section 4.8 Table 2) and did not increase following 3 years treatment.

In clinical studies, over 1800 patients have been treated with a multi-dose formulation of bimatoprost 0.3 mg/mL eye drops, solution containing benzalkonium chloride as a preservative. On combining the data from phase III monotherapy and adjunctive multi-dose formulations of bimatoprost 0.3 mg/mL eye drops, solution containing benzalkonium chloride as a preservative usage, the most frequently reported adverse reactions 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% at 3 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
- 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.

Table 2 lists adverse reactions that were seen in a 12 month clinical study with a multi-dose formulation of bimatoprost 0.3 mg/mL eye drops, solution containing benzalkonium chloride as a preservative but were reported at a higher frequency than with a formulation of bimatoprost 0.3 mg/mL eye drops, solution without preservative. Most were ocular, mild to moderate, and none were serious.

Table 2

System Organ class	Frequency	Adverse Reaction
Nervous system disorders	common	headache
Eye disorders	very common	ocular pruritus, growth of eyelashes
	common	asthenopia, conjunctival oedema, photophobia, tearing, increased iris pigmentation; blurred vision

Skin and subcutaneous tissue disorders	common	eyelid pruritus

In addition to the adverse reactions seen with bimatoprost 0.3 mg/mL eye drops, solution without preservative, Table 3 lists additional adverse reactions that were seen with multi-dose formulations of bimatoprost 0.3 mg/mL eye drops, solution containing benzalkonium chloride as a preservative. Most were ocular, mild to moderate, and none were serious.

Table 3

System Organ class	**Frequency**	**Adverse Reaction**
Nervous system disorders	uncommon	dizziness
Eye disorders	common	corneal erosion, ocular burning, allergic conjunctivitis, blepharitis, worsening of visual acuity, eye discharge, visual disturbance, eyelash darkening
	uncommon	retinal haemorrhage, uveitis, cystoid macular oedema, iritis, blepharospasm, eyelid retraction
Vascular disorders	common	hypertension
Gastrointestinal disorders	uncommon	nausea
Skin and subcutaneous tissue disorders	not known	periobital erythema
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 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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No information is available on overdose in humans; overdose 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 short term oral (by gavage) mouse and rat studies, doses up to 100 mg/kg/day of bimatoprost did not produce any toxicity. This dose is at least 22 times higher than an accidental dose of the entire content of 4 bottles of Zimed® Preservative Free 0.3 mg/mL, 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.

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 receptors. Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified.

Clinical efficacy

A 12 week (double-masked, randomized, parallel group) clinical study compared the efficacy and safety of bimatoprost 0.3 mg/mL without preservative with a multi-dose formulation of bimatoprost 0.3 mg/mL containing benzalkonium chloride as a preservative. Bimatoprost 0.3 mg/mL without preservative achieved non-inferior IOP-lowering efficacy to the multi-dose formulation of bimatoprost 0.3 mg/mL containing benzalkonium chloride as a preservative for worse eye IOP change from baseline in patients with glaucoma or ocular hypertension. Bimatoprost 0.3 mg/mL without preservative also achieved equivalent IOP lowering efficacy with a multi-dose formulation of bimatoprost 0.3 mg/mL containing benzalkonium chloride as a preservative in average eye IOP at each follow-up timepoint at weeks 2, 6 and 12.

During 12 months' monotherapy treatment with a multi-dose formulation of bimatoprost 0.3 mg/mL containing benzalkonium chloride as a preservative in adults, versus timolol, mean change from baseline in morning (08:00) intraocular pressure ranged from -7.9 to -8.8 mmHg. At any visit, the mean diurnal IOP values measured over the 12-month study period differed by no more than 1.3 mmHg throughout the day and were never greater than 18.0 mmHg.

In a 6-month clinical study with a multi-dose formulation of bimatoprost 0.3 mg/mL containing benzalkonium chloride as a preservative versus latanoprost, a statistically superior reduction in morning mean IOP (ranging from -7.6 to -8.2 mmHg for bimatoprost versus –6.0 to -7.2 mmHg for latanoprost) was observed at all visits throughout the study.

Conjunctival hyperaemia, growth of eyelashes, and eye pruritus were statistically significantly higher with bimatoprost than with latanoprost, however, the discontinuation rates due to adverse events were low with no statistically significant difference.

Compared to treatment with beta-blocker alone, adjunctive therapy with beta-blocker and a multi-dose formulation of bimatoprost 0.3 mg/mL containing benzalkonium chloride as a preservative lowered mean morning (08:00) intraocular pressure by -6.5 to -8.1 mmHg.

Limited experience is available 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 have been observed in clinical trials.

Paediatric population

The safety and efficacy of bimatoprost in children aged 0 to 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 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 $_{0\text{-}24hrs}$ 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.

Characteristics in elderly patients

After twice daily dosing of bimatoprost 0.3 mg/mL, the mean $AUC_{0\text{-}24hr}$ value of 0.0634 ng•hr/ml bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng•hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure for both elderly and young subjects remained very low from 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 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 were 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). Neurobehavioural functions of offspring were not affected.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Disodium hydrogen phosphate heptahydrate

Citric acid monohydrate

Hydrochloric acid or sodium hydroxide (for pH-adjustment)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months
28 days after first opening.

6.4 Special precautions for storage

Store below 25ºC. Store in the original bottle and keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Novelia® system Low Density Polyethylene bottle closed with a white nozzle and cap subassembly (High Density Polyethylene and silicone). Silicone also comes into contact with the solution as part of the components.

Each bottle contains 3 mL of solution.

Each pack contains one bottle.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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