Approved Professional Information for Medicines for Human Use:

BIMAGAM 0,01 %

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BIMAGAM 0,01 % eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of sterile solution contains bimatoprost 0,1 mg.

Contains benzalkonium chloride 0,02 % (*m/v*) as preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

BIMAGAM 0,01 % Eye drops, solution

Colourless solution that is a practically clear and free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

When used as monotherapy or as adjunctive therapy, the recommended dose is one

drop of BIMAGAM 0,01 % eye drops 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.

Special populations

Elderly population

No dosage adjustment in elderly patients is necessary.

Hepatic and renal impairment

BIMAGAM 0,01 % eye drops 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 ALT, AST and/or bilirubin at baseline, BIMAGAM 0,01 % eye drops had no adverse effect on liver function over 24 months.

Paediatric population

BIMAGAM 0,01 % eye drops has only been studied in adults and therefore its use is not recommended in children or adolescents (under the age of 18).

Method of administration

BIMAGAM 0,01 % is for ocular use only**.**

To prevent contamination of the dropper tip and solution, care should be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

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

4.3 Contraindications

- Hypersensitivity to bimatoprost, benzalkonium chloride or to any of the other 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) eyelash growth, darkening of the eyelid skin and increased iris pigmentation, since these have been observed during treatment with bimatoprost as in BIMAGAM 0,01 %. Some of these changes may be permanent and may lead to differences in appearance between the eyes when only one eye is treated. 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. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Cystoid macular oedema has been less frequently reported following treatment with bimatoprost 0,3 mg/mL eye drops, solution. Therefore, BIMAGAM 0,01 % 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 less frequent spontaneous reports of reactivation of previous corneal infiltrates or ocular infections with bimatoprost 0,3 mg/mL eye drops, solution. BIMAGAM 0,01 % should be used with caution in patients with a prior history of significant ocular viral infections (e.g. herpes simplex) or uveitis/iritis.

BIMAGAM 0,01 % 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 BIMAGAM 0,01 % solution comes repeatedly in contact with the skin surface. Thus, it is important to apply BIMAGAM 0,01 % as instructed and avoid it running onto the cheek or other skin areas.

Respiratory

BIMAGAM 0,01 % 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

BIMAGAM 0,01 % 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 0,3 mg/mL eye drops, solution. BIMAGAM 0,01 % should be used with caution in patients predisposed to low heart rate or low blood pressure.

Other Information

Concomitant use with other prostaglandin analogues

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 IOP-lowering effect (see section 4.5). Patients using BIMAGAM 0,01 % with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

Bacterial keratitis

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

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.

Contact lenses

BIMAGAM 0,01 % eye drops contain the preservative benzalkonium chloride (200 ppm), 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.

Excipients: Benzalkonium chloride

BIMAGAM 0,01 % contains 0,2 mg benzalkonium chloride (a preservative) in each millilitre eye drop solution which is equivalent to 0,02 % (*m/v*).
As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations, cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the

use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.

Since BIMAGAM 0,01 % eye drops contains 200 ppm benzalkonium chloride (four times the concentration in bimatoprost 0,3 mg/mL eye drops), it should be used with caution in dry eye patients, in patients where the cornea may be compromised and in patients taking multiple BAK-containing eye drops. In addition, monitoring is required with prolonged use in such patients.

From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

4.5 Interaction with other medicines 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, solution (multi-dose formulation). Bimatoprost is biotransformed by any of multiple enzymes and pathways, and no effects on hepatic medicine metabolising enzymes were observed in preclinical studies.

In clinical studies, BIMAGAM 0,3 mg/mL (multi-dose formulation) was used concomitantly with a number of different ophthalmic beta-blocking medicines without evidence of interactions.

Concomitant use of BIMAGAM 0,01 % and antiglaucomatous medicines 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. BIMAGAM 0,01 %) 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

The safety of BIMAGAM 0,01 % during pregnancy and lactation has not been established.

Pregnancy

There are no adequate data from the use of bimatoprost in pregnant women. Animal studies have shown reproductive toxicity at high maternotoxic doses.

BIMAGAM 0,01 % 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. It is recommended that BIMAGAM 0,01 % not be used in breastfeeding mothers.

Fertility

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

4.7 Effects on ability to drive and use machines

BIMAGAM 0,01 % has negligible influence on the ability to drive and use machines. if transient blurred vision or dizziness occurs at instillation, the patient should wait until the vision clears or dizziness subsides before driving or using machines.

4.8 Undesirable effects

a. Summary of the safety profile

In a 12-month Phase III clinical study approximately 38 % of patients treated with bimatoprost 0,1 mg/mL eye drops, solution experienced adverse reactions. The most frequently reported adverse reaction was conjunctival hyperaemia (mostly trace to mild and of a non-inflammatory nature).

b. Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with bimatoprost 0,1 mg/mL eye drops, solution. Most were ocular, mild and none was serious.

Table 1.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Immune system disorders			Hypersensitivity reaction including signs and symptoms of eye allergy and allergic dermatitis

Nervous system disorders		Headache	Dizziness
Eye disorders	Conjunctival hyperaemia, prostaglandin analogue periorbitopathy, punctate keratitis, eye irritation, eye pruritus, growth of eyelashes, eye pain, erythema of eyelid, eyelid pruritus	Asthenopia, blurred vision, conjunctival disorder, conjunctival oedema, iris hyperpigmentation, madarosis, eyelid oedema	Blepharal pigmentation, macular oedema, periorbital and lid changes including deepening of the eyelid sulcus, dry eye, eye discharge, eye oedema, foreign body sensation in eyes, lacrimation increased, ocular discomfort, photophobia
Vascular disorders			Hypertension
Respiratory, thoracic and mediastinal disorders			Asthma, asthma exacerbation, COPD exacerbation and dyspnoea

Gastrointestinal disorders		Nausea	
Skin and subcutaneous tissue disorders	Skin hyperpigmentation, hypertrichosis (abnormal hair growth around the eyes)	Dry skin, eyelid margin crusting, pruritus	Skin discoloration (periocular)
General disorders and administration site conditions	Instillation site irritation		

In clinical studies, over 1800 patients have been treated with bimatoprost 0,3 mg/mL eye drops. On combining the data from phase III monotherapy and adjunctive bimatoprost 0,3 mg/mL eye drops usage, the most frequently reported adverse reactions were:

- growth of eyelashes in the first year with the incidence of new reports decreasing at 3 years
- conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in the first year with the incidence of new reports decreasing at 3 years
- ocular pruritus in the first year with the incidence of new reports decreasing at 3 years.

Additional adverse reactions reported with bimatoprost 0,3 mg/mL eye drops are presented in Table 2. The table also includes those adverse reactions which occurred with both formulations but at a different frequency. Most were ocular, mild to moderate, and none was serious: With each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2.

System Organ Class	**Frequency**	
	Frequent	**Less Frequent**
Nervous system disorders	Headache	Dizziness
Eye disorders	Ocular pruritus, growth of eyelashes, corneal erosion, ocular burning, allergic conjunctivitis, blepharitis, worsening of visual acuity, asthenopia, conjunctival oedema,	Retinal haemorrhage, uveitis, cystoid macular oedema, iritis, blepharospasm, eyelid retraction, periorbital erythema

	foreign body sensation, ocular dryness, eye pain, photophobia, tearing, eye discharge, visual disturbance/blurred vision, increased iris pigmentation, eyelash darkening, cataract	
Vascular disorders	Hypertension	
Skin and subcutaneous tissue disorders		Hirsutism, pigmentation of peri-ocular skin, abnormal hair growth
General disorders and administration site conditions		Asthenia, peripheral oedema
Investigations	Liver function test abnormal	

Infections and infestations		Infection (primarily colds and upper respiratory tract infections)

c. Description of selected adverse reactions

Prostaglandin analogue periorbitopathy (PAP)

Prostaglandin analogues including bimatoprost as in BIMAGAM 0,01 % 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 as in BIMAGAM 0,01 %, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discolouration 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 as in BIMAGAM 0,01 % 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 as in BIMAGAM 0,01 % eye drops, solution was 0,5 %. At 12 months, the incidence with bimatoprost 0,03 % eye drops, solution was 1,5 % (see section 4.8 Table 2) and did not increase following 3 years treatment.

Adverse reactions reported in phosphate containing eye drops

Cases of corneal calcification have been reported less frequently 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A. 15.4 Ophthalmological preparations. Others

Pharmacotherapeutic group: Ophthalmologicals, prostaglandin analogues, ATC Code: S01EE03

Mechanism of action

Bimatoprost is an ocular hypotensive medicine. It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ that does not act through any known prostaglandin receptors. Bimatoprost selectively mimics the effects of prostamides. The prostamide receptor, however, has not yet been structurally identified.

Bimatoprost reduces intraocular pressure (IOP) in humans 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 24 hours.

Limited experience is available with the use of bimatoprost in patients with open-angle glaucoma with pseudoexfoliative and pigmentary glaucoma, and chronic angle-closure glaucoma with patent iridotomy and no recommendation can be made.

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

5.2 Pharmacokinetic properties

Absorption

Bimatoprost penetrates the human cornea and sclera well *in vitro.* After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time.

After once daily ocular administration of one drop of 0,03 % bimatoprost to both eyes of 15 healthy subjects for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0,025 ng/ mL) in most subjects 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 medicine 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.

As the concentration of the active substance for BIMAGAM 0,01 % has been reduced three-fold it is considered that the systemic medicine exposure will not Increase compared with 0,03 % bimatoprost.

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In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88 %.

Biotransformation

Bimatoprost is not extensively metabolised in the human eye. Bimatoprost is the major circulating component 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, 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, 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Citric acid monohydrate

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Dibasic sodium phosphate heptahydrate

Purified water

Sodium chloride

Sodium hydroxide or hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

28 days (4 weeks) after first opening

6.4 Special precautions for storage

Store unopened container at or below 25 °C in the original carton, until required for use.

Opened container must be stored at or below 25 ºC. Do not use more than 28 days after opening.

6.5 Nature and contents of container

BIMAGAM 0,01 % eye drops, solution is filled in a white LDPE bottle with white LDPE dropper insert, and closed with a bluish green, tamper-proof HDPE screw cap. Each bottle has a fill volume of 3 mL. Subsequently, the bottle is packed into the respective folding carton together with the leaflet.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 mL solution. Not all pack sizes may be marketed.

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6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 October 2023

10. DATE OF REVISION OF THE TEXT