Approved Professional Information for Medicines for Human Use: BIMAGAM FORT

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BIMAGAM FORT eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL eye drops, solution contains:

Bimatoprost 0,3 mg and timolol maleate 6,83 mg equivalent to 5 mg timolol.

Preservative: Benzalkonium chloride 0,005 % (*m/v*).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

BIMAGAM FORT is a colourless solution that is practically clear and free of particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to a topical beta-blocker or prostaglandin analogue(s) given alone.

4.2 Posology and method of administration

Posology

Recommended dosage in adults (including the elderly)

The recommended dose is one drop of BIMAGAM FORT in the affected eye(s) once daily, administered either in the morning or in the evening.

If one dose is missed, treatment should continue with the next dose as planned. The dose should not exceed one drop in the affected eye(s) daily.

If more than one topical ophthalmic product is to be used, the different products should be instilled at least 5 minutes apart.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced.

Special populations

Renal and hepatic impairment

BIMAGAM FORT has not been studied in patients with hepatic or renal impairment. Therefore, caution should be used in treating such patients.

Paediatric population

BIMAGAM FORT has only been studied in adults and therefore its use is not recommended in children or adolescents.

Method of administration

For ophthalmic use.

4.3 Contraindications

- Hypersensitivity to bimatoprost, timolol or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with a pace-maker, overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

The active substances (timolol/ bimatoprost) in BIMAGAM FORT may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed with BIMAGAM FORT. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions (ADRs) as seen with systemic betablockers may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders

Patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and receiving hypotension therapy with beta-blockers should be critically assessed and therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to the negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma, have been reported following administration of some ophthalmic beta-blockers.

BIMAGAM FORT should be used with caution in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Endocrine disorders

Beta-adrenergic blocking medicinal products should be administered with caution in patients subject to spontaneous hypoglycaemia or in patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Other beta-blocking medicines

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to patients already receiving a systemic beta-blocking] medicine. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking medicines is not recommended (see section 4.5).

Anaphylactic reactions

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy such as timolol after filtration procedures.

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving BIMAGAM FORT.

Hepatic

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 had no adverse reactions on liver function over

24 months. There are no known adverse reactions of ocular timolol, as in BIMAGAM FORT, on liver function.

Ocular

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, and periorbital skin hyperpigmentation since these have been observed during treatment with BIMAGAM FORT. Increased brown iris pigmentation has also been observed during treatment with BIMAGAM FORT. Increased iris pigmentation is likely to be permanent and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of BIMAGAM FORT, pigmentation of iris may be permanent. After 12 months of treatment with bimatoprost and timolol eye drops the incidence of iris pigmentation was 0,2 %. After 12 months of treatment with bimatoprost eye drops alone, the incidence was 1,5 % and did not increase following 3 years of treatment. 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 iridial pigmentation are not known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Neither nevi nor freckles of the iris appear to be affected by treatment. Periorbital tissue pigmentation has been reported to be reversible in some patients.

Macular oedema, including cystoid macular oedema has been reported with bimatoprost and timolol eye drops. Therefore, BIMAGAM FORT single-dose should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular

oedema (e.g. intraocular surgery, retinal vein occlusions, ocular inflammatory disease and diabetic retinopathy).

BIMAGAM FORT should be used with caution in patients with active intraocular inflammation (e.g. uveitis) because the inflammation may be exacerbated.

Skin

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

Other conditions

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

In studies of bimatoprost 0,3 mg/mL in patients with glaucoma or ocular hypertension, it has been shown that more frequent exposure of the eye to more than 1 dose of bimatoprost daily may decrease the IOP-lowering effect. Patients using BIMAGAM FORT with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

Excipient: Benzalkonium chloride

BIMAGAM FORT contains 0,05 mg benzalkonium chloride (a preservative) in each millilitre eye drop solution which is equivalent to 0,005 % (*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.

Benzalkonium chloride is known to discolour soft contact lenses.
Contact with soft contact lenses must be avoided.

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 specific interaction studies have been performed with the bimatoprost/timolol fixed combination.

There is a potential for additive effects resulting in hypotension, and/or marked bradycardia when ophthalmic betablocker solution is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking

medicines, parasympathomimetics, anti-dysrhythmics (including amiodarone) and digoxin.

Timolol as in BIMAGAM FORT can mask the signs and symptoms of and the body's reaction to hypoglycaemia (see section 4.8).

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers such as in BIMAGAM FORT.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine, selective serotonin reuptake inhibitors (SSRIs)) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of the bimatoprost / timolol fixed combination in pregnant women. BIMAGAM FORT should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Bimatoprost

No adequate clinical data in exposed pregnancies are available. Animal studies have shown reproductive toxicity at high maternotoxic doses.

Timolol

Signs and symptoms of beta-blockade (e.g., bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If BIMAGAM FORT is administered until delivery, the neonate should be carefully monitored during the first days of life.

Lactation

Timolol

Beta-blockers are excreted in breast milk. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

Bimatoprost

It is not known if bimatoprost is excreted in human breast milk.
BIMAGAM FORT should not be used by breastfeeding women.

Fertility

There are no data on the effects of BIMAGAM FORT on human fertility.

4.7 Effects on ability to drive and use machines

Transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machines.

4.8 Undesirable effects

a) Summary of the safety profile

The adverse reactions reported in the clinical study using bimatoprost and timolol eye drops, solution were limited to those earlier reported for the single active substances bimatoprost or timolol. No new adverse reactions specific for bimatoprost and timolol eye drops, solution have been observed in clinical studies. The majority of adverse reactions reported with bimatoprost and timolol eye drops, solution were ocular, mild in severity and none were serious. Based on a 12-week study of bimatoprost and timolol eye drops, solution administered once daily, the most commonly reported adverse reaction with bimatoprost and timolol eye drops, solution was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature).

b) Tabulated list of adverse reactions

Table 1 below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with bimatoprost and timolol eye drops, solution.

Table 1

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Immune system disorders			hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy
Psychiatric disorders			insomnia, nightmare
Nervous system disorders		headache	dysgeusia, dizziness
Eye disorders	conjunctival hyperaemia, punctuate keratitis, corneal erosion, burning sensation, conjunctival irritation, eye pruritus, stinging sensation in the eye, foreign body sensation, dry eye,	iritis, eye irritation, conjunctival oedema, blepharitis, epiphora, eyelid oedema, eyelid pain, visual acuity worsened, abnormal sensation in the eye,	cystoid macular oedema, eye swelling, vision blurred, ocular discomfort

	erythema of eyelid, eye pain, photophobia, eye discharge, visual disturbance, eyelid pruritus, blepharal pigmentation, lacrimation increased, growth of eyelashes	asthenopia, trichiasis, iris hyperpigmentation, deepening of eyelid sulcus (enophthalmos), eyelid retraction, eyelash discolouration (darkening)	
Cardiac disorders			bradycardia
Vascular disorders			hypertension
Respiratory, thoracic and mediastinal disorders		rhinitis	bronchospasm (predominantly in patients with pre-existing bronchospastic disease), asthma, dyspnoea

Skin and subcutaneous tissue disorders	skin hyperpigmentation (periocular)	hirsutism	alopecia, skin discolouration (periocular)
General disorders and administration site conditions			fatigue

Additional adverse reactions that have been seen with either of the active substances (bimatoprost or timolol), and may potentially occur also with BIMAGAM FORT are listed below in Table 2:

Table 2

System Organ Class	**Adverse reaction**
Infection and infestations	infection (primary colds and upper respiratory symptoms)[2]
Immune system disorders	systemic allergic reactions including urticarial, localised and generalised rash, pruritis, anaphylaxis[1]
Endocrine disorders	hypoglycaemia (in diabetic patients)[1]
Metabolism and nutrition	hypoglycaemia[1]

Psychiatric disorders	behavioural changes and psychic disturbances including anxiety, confusion, depression, disorientation, hallucination, nervousness, somnolence[1], memory loss[1],
Nervous system disorders	syncope[1], cerebrovascular accident[1], increase in signs and symptoms of myasthenia gravis[1], paraesthesia[1], cerebral ischaemia[1]
Eye disorders	decreased corneal sensitivity[1], diplopia[1], ptosis[1], choroidal detachment following filtration surgery (see section 4.4)[1], refractive changes (due to withdrawal of miotic therapy in some cases)[1], keratitis[1], pseudopemphigoid[1], signs and symptoms of ocular irritation including conjunctivitis[1], allergic conjunctivitis[2], eyelash darkening[2],

	blepharospasm[2], retinal haemorrhage[2], uveitis[2]
Ear and labyrinth disorders	tinnitus[1]
Cardiac disorders	atrioventricular block[1], cardiac arrest[1], dysrhythmia[1], cardiac failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1], pulmonary oedema[1], worsening of angina pectoris[1]
Vascular disorders	hypotension[1], claudication[1], Raynaud's phenomenon[1], cold hands and feet[1]

Respiratory, thoracic and mediastinal disorders	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)[1], cough[1], nasal congestion[1], respiratory failure[1], upper respiratory infection[1], asthma exacerbation[2], COPD exacerbation[2]
Gastrointestinal disorders	nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1], anorexia[1], vomiting[1]
Skin and subcutaneous tissue disorders	psoriasiform rash[1], exacerbation of psoriasis[1], skin rash[1], abnormal hair growth[2]

Musculoskeletal and connective tissue disorders	myalgia[1], systemic lupus erythematosus[1]
Reproductive system and breast disorders	sexual dysfunction[1], decreased libido[1], Peyronie's disease[1], retroperitoneal fibrosis[1]
General disorders and administration site conditions	asthenia[1,2], peripheral oedema[2]
Investigations	liver function tests (LFT) abnormal[2]

[1] adverse reactions observed with Timolol

[2] adverse reactions observed with Bimatoprost

c. Description of selected adverse reactions

Beta-blocker side effects

Like other topically applied ophthalmic medicines, BIMAGAM FORT (bimatoprost/timolol) is absorbed into the systemic circulation. Absorption of timolol may cause similar undesirable effects as seen with systemic beta-blocking agents. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

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 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

In overdose, side-effects may be exacerbated and exaggerated (see section 4.8). Symptoms of systemic timolol overdose include bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. Timolol does not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification: A.15.4 Ophthalmic Preparations. Other

Pharmacotherapeutic group: Ophthalmological, beta-blocking agents

ATC Code: S01ED51

Mechanism of action

The two active substances, bimatoprost and timolol maleate, decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone. The onset of action is rapid.

Bimatoprost is an 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 biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. Bimatoprost reduces intraocular pressure by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent. Timolol lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

5.2 Pharmacokinetic properties

Bimatoprost

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 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 drug concentration was reached during the first week of ocular dosing.

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 %.

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

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.

Special populations

After twice daily dosing the mean $AUG_{0\text{-}24hrs}$ 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.

Timolol

After ocular administration of 0,5 % eye drop solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/mL in the aqueous humour at one hour post-dose. Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 hours.

Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney. Timolol is not extensively bound to plasma proteins.

Paediatric population

The safety and efficacy of BIMAGAM FORT in children aged less than 18 years has not been established.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Citric acid monohydrate

Dibasic sodium phosphate heptahydrate

Sodium chloride

Sodium hydroxide or hydrochloric acid (for pH-adjustment).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

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.

Keep container tightly closed when not in use.

6.5 Nature and contents of container

BIMAGAM FORT eye drops, 3 mL solution is filled in a 5 mL white LDPE bottles with dark blue, tamper-proof HDPE screw cap and white LDPE dropper insert. The closed bottles are packed into 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.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: +27860287835

8. REGISTRATION NUMBER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT