SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bimatoprost/Timolol 0.3 mg/ml + 5 mg/ml eye, drops solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate).

Excipient with known effect

Each ml of solution contains 0.05 mg of benzalkonium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

4.2 Posology and method of administration

Posology

Recommended dosage in adults (including older people)

The recommended dose is one drop of Bimatoprost/Timolol in the affected eye(s) once daily, administered either in the morning or in the evening. It should be administered at the same time each day.

Existing literature data for bimatoprost/timolol suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing (see section 5.1).

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.

Renal and hepatic impairment

Bimatoprost/Timolol has not been studied in patients with hepatic or renal impairment. Therefore caution should be used in treating such patients.

Paediatric population

The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established. No data are available.

Method of administration

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

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

4.3 Contraindications

- Hypersensitivity to the active substances 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 pace-maker. Overt cardiac failure, cardiogenic shock.

4.4 Special warnings and precautions for use

Like other topically applied ophthalmic medicinal products, the active substances (timolol/ bimatoprost) in Bimatoprost/Timolol may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions as seen with systemic beta-blockers 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 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 its 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.

Bimatoprost/Timolol 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 hypoglycemia or to patients with labile diabetes as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Beta-blockers may also mask the signs of hyperthyroidism.

Corneal diseases

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

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents 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 (e.g. timolol, acetazolamide) after filtration procedures.

Surgical anaesthesia

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

Hepatic

In patients with a history of mild liver disease or abnormal alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin at baseline, bimatoprost had no adverse reactions on liver function over 24 months. There are no known adverse reactions of ocular timolol on liver function.

Ocular

Before treatment is initiated, patients should be informed of the possibility of eyelash growth, darkening of the eyelid or periocular skin and increased brown iris pigmentation since these have been observed during treatment with bimatoprost and bimatoprost/timolol. 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 bimatoprost/timolol, pigmentation of iris may be permanent. After 12 months treatment with bimatoprost/timolol, the incidence of iris pigmentation was 0.2%. After 12 months treatment with bimatoprost eye drops alone, the incidence was 1.5% and did not increase following 3 years 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/timolol. Therefore, Bimatoprost/Timolol 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). Bimatoprost/Timolol 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 bimatoprost/timolol solution comes repeatedly in contact with the skin surface. Thus, it is important to apply Bimatoprost/Timolol as instructed and avoid it running onto the cheek or other skin areas.

Excipients

The preservative in Bimatoprost/Timolol, benzalkonium chloride, may cause eye irritation. Contact lenses must be removed prior to application, with at least a 15-minute wait before reinsertion. Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses must be avoided.

Benzalkonium chloride has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Therefore monitoring is required with frequent or prolonged use of Bimatoprost/Timolol in dry eye patients or where the cornea is compromised.

Other conditions

Bimatoprost/Timolol has not been studied in patients with inflammatory ocular conditions, neovascular, inflammatory, angle-closure glaucoma, congenital glaucoma 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 Bimatoprost/Timolol with other prostaglandin analogues should be monitored for changes to their intraocular pressure.

4.5 Interaction with other medicinal products 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 beta-blockers solution is administered concomitantly with oral calcium channel blockers, guanethidine, beta-adrenergic blocking agents, parasympathomimetics, anti-arrhythmics (including amiodarone) and digitalis glycosides.

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of the bimatoprost/timolol fixed combination in pregnant women. Bimatoprost/Timolol 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 (see section 5.3).

Timolol

Epidemiological studies have not revealed malformative effects but shown a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, 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 Bimatoprost/Timolol is administered until delivery, the neonate should be carefully monitored during the first days of life. Animal studies with timolol have shown reproductive toxicity at doses significantly higher than would be used in clinical practice (see section 5.3).

Breast-feeding

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 but it is excreted in the milk of the lactating rat. Bimatoprost/Timolol should not be used by breast-feeding women.

Fertility

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

4.7 Effects on ability to drive and use machines

Bimatoprost/Timolol 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

Bimatoprost/Timolol

Summary of the safety profile

The adverse reactions reported in clinical studies using bimatoprost/timolol were limited to those earlier reported for either of the single active substances bimatoprost and timolol. No new adverse reactions specific for bimatoprost/timolol have been observed in clinical studies.

The majority of adverse reactions reported in clinical studies using bimatoprost/timolol were ocular, mild in severity and none were serious. Based on 12-month clinical data, the most commonly reported adverse reaction was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 26% of patients and led to discontinuation in 1.5% of patients.

Tabulated list of adverse reactions

Table 1 presents the adverse reactions that have been reported during clinical studies with all bimatoprost/timolol formulations (multi-dose and single-dose) (within each frequency grouping, adverse reactions are presented in order of decreasing seriousness) or in the post-marketing period.

The frequency of possible adverse reactions listed below is defined using the following convention:

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	Frequency cannot be estimated from available data

Table 1

System Organ class	Frequency	Adverse reaction
Immune system disorders	Not known	hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy
Psychiatric disorders	Not known	Insomnia[2], nightmare[2]
Nervous system disorders	Common	headache
	Not known	Dysgeusia[2], dizziness
Eye disorders	Very common	conjunctival hyperaemia.
	Common	punctuate keratitis, corneal erosion[2], burning sensation[2], conjunctival irritation[1], eye pruritus, stinging sensation in the eye[2], foreign body sensation, dry eye, erythema of eyelid, eye pain,

System Organ class	Frequency	Adverse reaction
		photophobia, eye discharge, visual disturbance[2], eyelid pruritus, visual acuity worsened[2], blepharitis[2], eyelid oedema, eye irritation, lacrimation increased, growth of eyelashes.
	Uncommon	iritis[2], conjunctival oedema[2], eyelid pain[2], abnormal sensation in the eye[1], asthenopia, trichiasis[2], iris hyperpigmentation[2], periorbital and lid changes associated with periorbital fat atrophy and skin tightness resulting in deepening of eyelid sulcus, eyelid ptosis, enophthalmos, lagophthalmos and eyelid retraction[1&2], eyelash discolouration (darkening)[1].
	Not known	cystoid macular oedema[2], eye swelling, vision blurred[2], ocular discomfort
Cardiac disorders	Not known	Bradycardia
Vascular disorders	Not known	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Rhinitis[2]
	Uncommon	Dyspnoea
	Not known	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)[2], asthma
Skin andsubcutaneous tissue disorders	Common	blepharal pigmentation[2], hirsutism[2], skin hyperpigmentation (periocular).
	Not known	Alopecia, skin discolouration (periocular)
General disorders and administration site conditions	Not known	fatigue

[1]adverse reactions only observed with bimatoprost/timolol single-dose formulation

[2] adverse reactions only observed with bimatoprost/timolol multi-dose formulation

Like other topically applied ophthalmic drugs, Bimatoprost/Timolol (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.

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

Table 2

System Organ class	Adverse reaction
Immune system disorders	systemic allergic reactions including anaphylaxis[1]

System Organ class	Adverse reaction
Metabolism and nutrition disorders	Hypoglycaemia[1]
Psychiatric disorders	depression[1], memory loss[1], hallucination[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], keratitis[1], blepharospasm[2], retinal haemorrhage[2], uveitis[2],
Cardiac disorder	atrioventricular block[1], cardiac arrest[1], arrhythmia[1], cardiac failure[1], congestive heart failure[1], chest pain[1], palpitations[1], oedema[1]
Vascular disorders	hypotension[1], Raynaud's phenomenon[1], cold hands and feet[1]
Respiratory, thoracic and mediastinal disorders	Asthma exacerbation[2], COPD exacerbation[2],cough[1]
Gastrointestinal disorders	nausea[1,2], diarrhoea[1], dyspepsia[1], dry mouth[1], abdominal pain[1], vomiting[1]
Skin and subcutaneous tissue disorders	psoriasiform rash[1] or exacerbation of psoriasis[1], skin rash[1]
Musculoskeletal and connective tissue disorders	Myalgia[1]
Reproductive system and breast disorders	sexual dysfunction[1], decreased libido[1]
General disorders and administration site conditions	asthenia[1,2]
Investigations	liver function tests (LFT) abnormal[2]

[1] adverse reactions observed with timolol

[2] adverse reactions observed with bimatoprost

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 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

4.9 Overdose

A topical overdose with bimatoprost/timolol is not likely to occur or to be associated with toxicity.

Bimatoprost

If Bimatoprost/Timolol is accidentally ingested, the following information may be useful: in two-week oral rat and mouse studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity. This dose expressed as mg/m^2 is at least 70-times higher than the accidental dose of one bottle of bimatoprost/timolol in a 10 kg child.

Timolol

Symptoms of systemic timolol overdose include: bradycardia, hypotension, bronchospasm, headache, dizziness, shortness of breath, and cardiac arrest. A study of patients with renal failure showed that timolol did not dialyse readily.

If overdose occurs treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmological,– beta-blocking agents – ATC code: S01ED51

Mechanism of action

Bimatoprost/Timolol consists of two active substances: bimatoprost and timolol. These two components 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. Bimatoprost/Timolol has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance. 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. The mechanism of action by which bimatoprost reduces intraocular pressure in man is 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 that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. 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.

Clinical effects

The IOP-lowering effect of bimatoprost/timolol is non-inferior to that achieved by adjunctive therapy of bimatoprost (once daily) and timolol (twice daily).

Existing literature data for bimatoprost/timolol suggest that evening dosing may be more effective in IOP lowering than morning dosing. However, consideration should be given to the likelihood of compliance when considering either morning or evening dosing.

Paediatric population

The safety and efficacy of bimatoprost/timolol in children aged 0 to 18 years has not been established.

5.2 Pharmacokinetic properties

Bimatoprost/Timolol medicinal product

Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to bimatoprost/timolol treatment in healthy subjects. Systemic absorption of the individual components was minimal and not affected by co-administration in a single formulation.

In two 12-month studies where systemic absorption was measured, no accumulation was observed with either of the individual components.

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 $AUC_{0\text{-}24\ hrs}$ 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-deethylation 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 1/hr/kg.

Characteristics in older people

After twice daily dosing, the mean $AUC_{0\text{-}24hrs}$ 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 a 0.5% eye drops 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.

5.3 Preclinical safety data

Bimatoprost/Timolol medicinal product

Repeated dose ocular toxicity studies on bimatoprost/timolol showed no special hazard for humans. The ocular and systemic safety profile of the individual components is well established.

Bimatoprost

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential. Studies in rodents produced species-specific abortion at systemic exposure levels 33- to 97-times that achieved in humans after ocular administration.

Monkeys administered ocular bimatoprost concentrations of ≥0.03% 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 have been observed, and the mechanism of action for the periocular changes is unknown.

Timolol

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride solution

Sodium chloride

Sodium phosphate dibasic heptahydrate

Citric acid monohydrate

Hydrochloric acid or sodium hydroxide (to adjust pH)

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Shelf life after first opening: 28 days.

Chemical and physical in-use stability has been demonstrated for 28 days at 25°C.

From a microbiological point of view, the in-use storage times and conditions are the responsibility of the user and would normally not be longer than 28 days at 25°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

White opaque low-density polyethylene bottles with polystyrene screw cap. Each bottle has a fill volume of 3 ml.

The following pack size is available:
1 or 3 bottles of 3 ml fill in 5 ml 3-piece LDPE S-design bottle with white LDPE S open nozzle and turquoise color HDPE S cap with TSTR -Tear off Ring in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Brown & Burk UK Limited
Micro House
Bury street
Ruislip, H4A 7TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 25298/0382

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/11/2024

10 DATE OF REVISION OF THE TEXT

22/11/2024