SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bimatoprost/Timolol 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container

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).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution, in single-dose container. (eye drops)

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 single-dose 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 (multi-dose formulation) 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).

The single-dose container is for single use only; one container is sufficient to treat both eyes. Any unused solution should be discarded immediately after use. 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 single-dose 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 single-dose in children aged less than 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 single-dose may be absorbed systemically. No enhancement of the systemic absorption of the individual active substances has been observed with Bimatoprost/Timolol (multi-dose formulation). Due to the beta-adrenergic component, timolol, the same types of

cardiovascular, pulmonary and other adverse reactions (ADRs) 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 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.

Bimatoprost/Timolol single-dose 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 hypoglycemia.

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 agents

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 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

Beta-blocking ophthalmological preparations may block systemic beta-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 eye drops 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 prostaglandin analogue periobitopathy (PAP), during treatment with Bimatoprost/Timolol single-dose. Increased brown iris pigmentation has also been observed during treatment with Bimatoprost/Timolol (multi-dose formulation). 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).

Macular oedema, including cystoid macular oedema has been reported with Bimatoprost/Timolol (multi-dose formulation). Therefore, Bimatoprost/Timolol 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).

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.

Other conditions

Bimatoprost/Timolol single-dose 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 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-blocker 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 single-dose 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).

T*imolol*

Epidemiological studies have not revealed malformative effects but have 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 single-dose 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 single-dose should not be used by breast-feeding women.

Fertility

There are no data on the effects of Bimatoprost/Timolol single-dose on human fertility.

4.7 Effects on ability to drive and use machines

Bimatoprost/Timolol single-dose has negligible influence on the ability to drive and use machines. As with any topical 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 single-dose

Summary of the safety profile

The adverse reactions reported in the clinical study using Bimatoprost/Timolol single-dose were limited to those earlier reported for either Bimatoprost/Timolol (multi-dose formulation) or for the single active substances bimatoprost or timolol. No new adverse reactions specific for Bimatoprost/Timolol single-dose have been observed in clinical studies.

The majority of adverse reactions reported with Bimatoprost/Timolol single-dose were ocular, mild in severity and none were serious. Based on a 12-week study of Bimatoprost/Timolol single-dose administered once daily, the most commonly reported adverse reaction with Bimatoprost/Timolol single-dose was conjunctival hyperaemia (mostly trace to mild and thought to be of a non-inflammatory nature) in approximately 21% of patients and led to discontinuation in 1.4% of patients.

Tabulated list of adverse reactions

Table 1 presents the adverse reactions that were reported during clinical studies of both Bimatoprost/Timolol single-dose and Bimatoprost/Timolol multi-dose formulations (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,

		prostaglandin analogue periorbitopathy
	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, 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 and subcutaneous 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 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]
Metabolism and nutrition disorders	hypoglycaemia[1]
Psychiatric disorders	depression[1], memory loss[1], hallucination (frequency not known) [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

Description of selected adverse reactions:

Prostaglandin analogue periorbitopathy (PAP)
Prostaglandin analogues including bimatoprost 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/Timolol single-dose 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, and may lead to differences in appearance between the eyes if only one eye is treated. After discontinuation of this medicine, pigmentation of iris may 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 iridial 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. Periorbital tissue pigmentation has been reported to be reversible in some patients. At 12 months, the incidence of iris hyperpigmentation with bimatoprost 0.1 mg/ml eye drops, solution was 0.5%. After 12 months treatment with bimatoprost / timolol fixed combination, the incidence of iris pigmentation was 0.2%. 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.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store).

4.9 Overdose

A topical overdose with Bimatoprost/Timolol single-dose is not likely to occur or to be associated with toxicity.

Bimatoprost

If Bimatoprost/Timolol single-dose is accidentally ingested, the following information may be useful: in 2-week oral mice and rats studies, doses of bimatoprost up to 100 mg/kg/day did not produce any toxicity; this corresponds to a human equivalent dose of 8.1 and 16.2 mg/kg, respectively. These

doses are at least 7.5 times higher than the amount of bimatoprost in an accidental dose of the entire contents of a carton of Bimatoprost/Timolol single-dose (90 single-dose containers x 0.4 mL; 36 mL) in a 10 kg child [(36 mL*0.3 mg/mL bimatoprost)/10 kg; 1.08 mg/kg].

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 single-dose 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 single-dose 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

A 12-week (double-masked, randomized, parallel group) clinical study compared the efficacy and safety of Bimatoprost/Timolol single-dose with bimatoprost/timolol (multi-dose formulation) in patients with glaucoma or ocular hypertension. Bimatoprost/Timolol single-dose achieved noninferior IOP-lowering efficacy to bimatoprost/timolol (multi-dose formulation): the upper limit of the 95% CI of the between-treatment difference was within the pre-defined 1.5 mm Hg margin at each timepoint evaluated (hours 0, 2, and 8) at week 12 (for the primary analysis), and also at weeks 2 and 6, for mean worse eye IOP change from baseline (worse eye IOP refers to the eye with the higher mean diurnal IOP at baseline). In fact, the upper limit of the 95% CI did not exceed 0.14 mm Hg at week 12.

Both treatment groups showed statistically and clinically significant mean decreases from baseline in worse eye IOP at all follow up timepoints throughout the study ($p < 0.001$). Mean changes from baseline worse eye IOP ranged from -9.16 to -7.98 mm Hg for Bimatoprost/Timolol (single-dose) group, and from -9.03 to -7.72 mm Hg for the bimatoprost/timolol (multi-dose formulation) group across the 12-week study.

Bimatoprost/Timolol single-dose also achieved equivalent IOP-lowering efficacy to bimatoprost/timolol (multi-dose formulation) in average eye and worse eye IOP at each follow-up timepoint at weeks 2, 6 and 12.

Based on studies of bimatoprost/timolol (multi-dose formulation), 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 (multi-dose formulation) 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 single-dose in children aged less than 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 (multi-dose formulation) 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 of bimatoprost/timolol (multi-dose formulation) in which systemic absorption was measured, no accumulation was observed of 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 $_{0\text{-}24hrs}$ 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 1/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 of bimatoprost 0.3 mg/ml, 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 of bimatoprost/timolol (multi-dose formulation) 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 $\geq$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

Sodium chloride

Sodium phosphate dibasic heptahydrate

Citric acid monohydrate

Hydrochloric acid or sodium hydroxide (to adjust pH)

Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Once the sachet is opened, use the single-dose containers within 7 days. Discard the opened single-dose container immediately after use.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions. Keep the single-dose containers in the sachet and place the sachet back in carton in order to protect against light and moisture.

6.5 Nature and contents of container

Clear, single-dose low density polyethylene (LDPE) containers with a twist-off tab.

Each single-dose container contains 0.4 ml solution. Each strip of 5 single-dose containers is enclosed within a PET/Al/PE sachet.

The following pack sizes are available:

Carton containing 5 single-dose containers in aluminium foil sachet.

Carton containing 30 or 90 single-dose containers in six or eighteen aluminium foil sachets respectively. Each sachet contains 5 single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aspire Pharma Limited

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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