

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Bimiduo 0.3 mg/ml + 5 mg/ml eye drops, solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each bottle contains 3 ml or 9 ml solution.

Excipient with known effect: phosphates.

Each ml of solution contains 0.95 mg phosphates equivalent to 3.58 mg disodium phosphate dodecahydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, solution

Colourless, transparent solution

pH: 6.8 to 7.4

osmolality: 270 to 320 mOsmol/kg

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 Bimiduo 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.

Bimiduo eye drops solution is a sterile solution that does not contain any preservatives.

Renal and hepatic impairment

Bimiduo 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 Bimiduo in children aged less than 18 years has not been established. No data are available.

Method of administration

For ocular use only.

Bimiduo eye drops have not been studied in patients wearing contact lenses. Contact lenses should be removed prior to instillation and may be reinserted 15 minutes following administration.

Do not use more than once a day as the effectiveness of treatment may be reduced.

Do not allow the tip of the multidose container to touch the eye or areas around the eye. It could cause injury to your eye. The eye drops solution may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision.

To avoid possible contamination of the multidose container, keep the tip of the dropper away from contact with any surface.

Instructions for use:

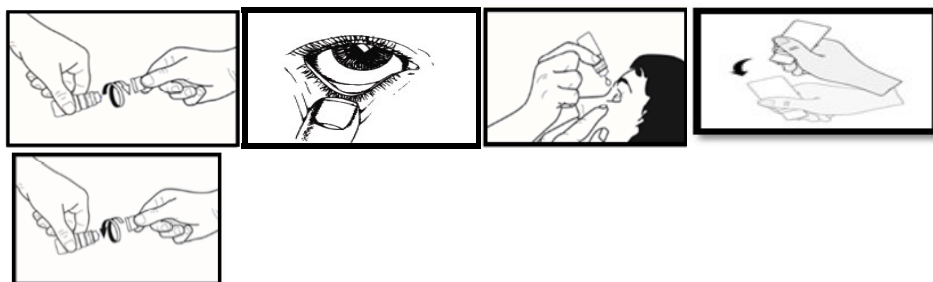
Before instillation of the eye drops:

- Wash your hands before opening the bottle.
- Do not use if you notice that the tamper-proof seal on the bottle neck is broken before first use.

- When using for the first time, before delivering a drop to the eye, you should firstly practice using the dropper bottle by squeezing it slowly to deliver one drop into the air to get used to the pressure and time required to deliver one drop. In case of difficulties of delivering one drop at a time, this step may be repeated.
- When you are confident that you can deliver one drop at a time, you should choose the position that you find most comfortable for the instillation of the drops (you can sit down, lie on your back, or stand in front of a mirror).

Instillation:

1. Hold the bottle directly below the cap and turn the cap to open the bottle (*see picture 1*). Do not touch anything with the tip of the bottle to avoid contamination of the solution.
2. Tilt your head back and gently pull down your lower eyelid to form a pouch between your eye and eyelid (*see picture 2*). Avoid contact between the tip of the bottle and your eye, eyelids or fingers.
3. Instil one drop into the pouch by pressing slowly on the bottle (*see picture 3*). Squeeze the bottle gently in the middle and let a drop fall into your eye. There might be a few seconds delay between squeezing and the drop coming out. Do not squeeze too hard. If you are not sure how to administer your medicine, ask your doctor, pharmacist or nurse.
4. Compress the tear duct for about 2 minutes (by pressing a finger against the corner of the eye by the nose) and close your eye(s) and keep it/them closed during this time. This ensures that the drop is absorbed by the eye and that the amount of medicine draining through the tear duct to the nose will probably be reduced.
5. Repeat steps 2, 3 and 4 in your other eye if your doctor has told you to do this.
6. If a drop misses your eye, try again.
7. After use and prior to recapping, the bottle should be shaken once in a downwards direction, without touching the dropper tip, in order to remove any residual liquid on the tip (*see picture 4*). This is necessary in order to ensure delivery of subsequent drops. Then screw the cap on the bottle (*see picture 5*).
8. After you have used all doses there will be some Bimiduo left in the bottle. You should not be concerned since an extra amount of formulation has been added and you will get the full amount that your doctor prescribed. Do not attempt to use the excess medicine remaining in the bottle after you have completed the course of treatment.



Picture 1.

Picture 2.

Picture 3.

Picture 4.

Picture 5.

Do not use the eye drops for longer than 90 days after first opening the bottle.

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.

If more than one topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart. Eye ointments and eye gels should be administered last.

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 (bimatoprost/timolol) in Bimiduo 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 (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.

Bimiduo 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 periorbitopathy (PAP) 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 impaired field of vision and differences in appearance between the eyes if only one eye is treated (see section 4.8).

Macular oedema, including cystoid macular oedema has been reported with bimatoprost/timolol fixed combination. Therefore, Bimiduo 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).

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

Other conditions

Bimatoprost/timolol 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 Bimiduo with other prostaglandin analogs should be monitored for changes to their intraocular pressure.

Bimiduo is preservative-free and has not been studied in patients wearing contact lenses. Contact lenses should be removed prior to application, with at least a 15-minute wait before reinsertion.

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. Bimiduo 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).

Breastfeeding

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. Bimiduo 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

Bimiduo 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

Summary of the safety profile

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

The majority of adverse reactions reported with bimatoprost/timolol were ocular, mild in severity and none were serious. Based on a 12-week study 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 were reported during clinical studies of both bimatoprost/timolol single-dose preservative-free formulation and bimatoprost/timolol multi-dose formulations with preservative (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	$\geq 1/10$
Common	$\geq 1/100$ to $< 1/10$
Uncommon	$\geq 1/1,000$ to $< 1/100$
Rare	$\geq 1/10,000$ 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
<i>Immune system disorders</i>	Not known	hypersensitivity reactions including signs or symptoms of allergic dermatitis, angioedema, eye allergy
<i>Psychiatric disorders</i>	Not known	insomnia ² , nightmare ²
<i>Nervous system disorders</i>	Common	headache
	Not known	dysgeusia ² , dizziness ²
<i>Eye disorders</i>	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 ² ,

		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 , eyelid retraction ² , eyelash discolouration (darkening) ¹
	Not known	cystoid macular oedema ² , eye swelling, vision blurred ² , ocular discomfort
<i>Cardiac disorders</i>	Not known	bradycardia
<i>Vascular disorders</i>	Not known	hypertension
<i>Respiratory, thoracic and mediastinal disorders</i>	Common	rhinitis ²
	Uncommon	dyspnoea
	Not known	bronchospasm (predominantly in patients with pre-existing bronchospastic disease) ² , asthma
<i>Skin and subcutaneous tissue disorders</i>	Common	blepharal pigmentation ² , hirsutism ² , skin hyperpigmentation (periocular)
	Not known	alopecia ² , skin discolouration (periocular)
<i>General disorders and administration site conditions</i>	Not known	fatigue

¹adverse reactions only observed with bimatoprost/timolol preservative-free formulation

²adverse reactions only observed with bimatoprost/timolol formulation with preservative (benzalkonium chloride)

Description of selected adverse reactions

Prostaglandin analogue periorbitopathy (PAP)

Prostaglandin analogues including Bimiduo 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 Bimiduo, and may cause impaired field of vision even in the absence of patient recognition. PAP is also associated with periocular skin hyperpigmentation or discoloration and hypertrichosis. All changes have been noted to be partially or fully reversible upon discontinuation or switch to alternative treatments.

Iris hyperpigmentation

Increased iris pigmentation is likely to be permanent. The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. The long-term effects of increased iris pigmentation are not

known. Iris colour changes seen with ophthalmic administration of bimatoprost may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts become more brownish. Neither naevi nor freckles of the iris appear to be affected by the treatment. After 12 months of treatment with bimatoprost/timolol fixed combination, the incidence of iris pigmentation was 0.2%. After 12 months of treatment with bimatoprost eye drops 0.3 mg/ml alone, the incidence was 1.5% (see section 4.8 Table 1) and did not increase following 3 years of treatment.

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
<i>Immune system disorders</i>	systemic allergic reactions including anaphylaxis ¹
<i>Metabolism and nutrition disorders</i>	hypoglycaemia ¹
<i>Psychiatric disorders</i>	depression ¹ , memory loss ¹ , hallucination ¹
<i>Nervous system disorders</i>	syncope ¹ , cerebrovascular accident ¹ , increase in signs and symptoms of myasthenia gravis ¹ , paraesthesia ¹ , cerebral ischaemia ¹
<i>Eye disorders</i>	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
<i>Cardiac disorder</i>	atrioventricular block ¹ , cardiac arrest ¹ , arrhythmia ¹ , cardiac failure ¹ , congestive heart failure ¹ , chest pain ¹ , palpitations ¹ , oedema ¹
<i>Vascular disorders</i>	hypotension ¹ , Raynaud's phenomenon ¹ , cold hands and feet ¹
<i>Respiratory, thoracic and mediastinal disorders</i>	asthma exacerbation ² , COPD exacerbation ² , cough ¹
<i>Gastrointestinal disorders</i>	nausea ^{1,2} , diarrhoea ¹ , dyspepsia ¹ , dry mouth ¹ , abdominal pain ¹ , vomiting ¹
<i>Skin and subcutaneous tissue disorders</i>	psoriasiform rash ¹ or exacerbation of psoriasis ¹ , skin rash ¹
<i>Musculoskeletal and connective tissue disorders</i>	myalgia ¹
<i>Reproductive system and breast disorders</i>	sexual dysfunction ¹ , decreased libido ¹
<i>General disorders and administration site conditions</i>	asthenia ^{1,2}
<i>Investigations</i>	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 to Yellow Card Scheme via 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 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/m² 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

Bimiduo 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 β_1 and β_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 in single-dose preservative-free formulation with bimatoprost/timolol multi-dose formulation with preservative (benzalkonium chloride) in patients with glaucoma or ocular hypertension. Bimatoprost/timolol single dose preservative-free formulation achieved noninferior IOP-lowering efficacy to bimatoprost/timolol multi-dose formulation with preservative (benzalkonium chloride): 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 preservative-free formulation group, and from -9.03 to -7.72 mm Hg for the bimatoprost/timolol multi-dose formulation with preservative group across the 12-week study.

Bimatoprost/timolol in single-dose preservative-free formulation also achieved equivalent IOP-lowering efficacy to bimatoprost/timolol multi-dose formulation with preservative 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 with preservative, 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 with preservative 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 less than 18 years has not been established.

5.2 Pharmacokinetic properties

Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to bimatoprost/timolol multi-dose formulation with preservative 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 with preservative 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 $AUC_{0-24\text{hrs}}$ 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 l/hr/kg.

Characteristics in older people

After twice daily dosing of bimatoprost 0.3 mg/ml, the mean $AUC_{0-24\text{hrs}}$ 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 multi-dose formulation with preservative 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.

6.1 List of excipients

Disodium phosphate dodecahydrate

Citric acid monohydrate

Sodium chloride
Sodium hydroxide or hydrochloric acid, diluted (for pH-adjustment)
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Before opening: 2 years
Discard 90 days after the first opening.

For storage conditions of the product after the first opening of the bottle, see section 6.4.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
After first opening of the bottle, store below 25°C.

6.5 Nature and contents of container

The packaging consists of 5 ml or 11 ml white LDPE bottle with multidose HDPE dropper applicator that prevents content back contamination thanks to a silicon valve system and filtering air return into the bottle and tamper-proof HDPE screw-cap and the carton box.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 ml solution or 1 bottles of 9 ml solution.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Zakłady Farmaceutyczne POLPHARMA S.A.
ul. Pelplińska 19, 83-200 Starogard Gdański, Poland

8 MARKETING AUTHORISATION NUMBER(S)

PL 29556/0002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

20/05/2022

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