1.3.1. SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. **Name of the medicinal product**

Vitaprost-T Ophthalmic Solution (Travoprost USP 0.04mg, Timolol Maleate BP equivalent to Timolol 5mg/ml)

2. **Qualitative and quantitative composition**

Each ml of solution contains: Travoprost USP 0.04mg, Timolol Maleate BP equivalent to Timolol 5mg/ml)

Excipients with known effect

Each ml of solution contains 150 micrograms of benzalkonium chloride and 5 mg of macrogolglycerol hydroxystearate 40 (see section 4.4).

For the full list of excipients, see section 6.1.

3. **Pharmaceutical form**

Eye drops, solution (eye drops).

Clear, colourless, aqueous solution, practically free from particles.

pH: 5.5 - 7.0

Osmolality: 252 – 308 mOsmol/kg

4. Clinical particulars
4.1 Therapeutic indications

Vitaprost-T is indicated in adults for the decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (see section 5.1).

4.2 Posology and method of administration

Posology

Use in adults, including the elderly

The dose is one drop of Vitaprost-T in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. It should be administered at the same time each day.

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

Special populations

Hepatic and renal impairment

No studies have been conducted with Vitaprost-T (travoprost/timolol 40 micrograms/ml + 5 mg/ml) eye drops, solution or with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment.

Travoprost has been studied in patients with mild to severe hepatic impairment and in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dose adjustment was necessary in these patients.

Patients with hepatic or renal impairment are unlikely to require dose adjustment with Vitaprost-T (see section 5.2).

Paediatric population

The safety and efficacy of Vitaprost-T (travoprost/timolol 40 micrograms/ml + 5 mg/ml) eye drops, solution in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

For ocular use.

The patient should remove the protective sachet immediately prior to initial use. To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle.

When nasolacrimal occlusion is used or the eyelids are closed for 2 minutes, systemic absorption is reduced. This may result in a decrease in systemic adverse reactions and an increase in local activity (see section 4.4).

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart (see section 4.5).

When substituting another ophthalmic antiglaucoma medicinal product with Vitaprost-T, the other medicinal product should be discontinued and Vitaprost-T should be started the following day.

Patients must be instructed to remove soft contact lenses prior to application of Vitaprost-T and wait 15 minutes after instillation of the dose before reinsertion (see section 4.4).

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

- Hypersensitivity to other beta-blockers.

- Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease.

- Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second- or third-degree atrioventricular block not controlled with pacemaker. Overt cardiac failure, cardiogenic shock.

- Severe allergic rhinitis and corneal dystrophies.

4.4 Special warnings and precautions for use

Systemic effects

Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking medicinal products may occur. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. For information on how to reduce systemic absorption, see section 4.2.

Cardiac disorders

In 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 their 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.

Vitaprost-T 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.

Hypoglycaemia/diabetes

Beta-blockers 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.

Muscle weakness

Beta-adrenergic blocking medicinal products have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalised weakness).

Corneal diseases

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

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

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 medicinal product. 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).

Surgical anaesthesia

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

Hyperthyroidism

Beta-blockers may mask the signs of hyperthyroidism.

Skin contact

Prostaglandins and prostaglandin analogues are biologically active substances that may be absorbed through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In the unlikely event of coming in contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately.

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.

Concomitant therapy

Timolol may interact with other medicinal products (see section 4.5).

The use of two local prostaglandins is not recommended.

Ocular effects

Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. The long-term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e. blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported.

Periorbital and lid changes, including deepening of the eyelid sulcus, have been observed with prostaglandin analogues.

Travoprost may gradually change eyelashes in the treated eye(s); these changes were observed in about half of the patients in clinical trials and include: increased length, thickness, pigmentation and/or number of lashes. The mechanism of eyelash changes and their long-term consequences are currently unknown.

Travoprost has been shown to cause slight enlargement of the palpebral fissure in studies in the monkey. However, this effect was not observed during the clinical trials and is considered to be species specific.

There is no experience of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution in inflammatory ocular conditions, nor in neovascular, angle-closure, narrow-angle or congenital glaucoma, and only limited experience in thyroid eye disease, in open-angle glaucoma of pseudophakic patients and in pigmentary or pseudoexfoliative glaucoma.

Macular oedema has been reported during treatment with prostaglandin F2α analogues. Caution is recommended when using Vitaprost-T in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for cystoid macular oedema.

In patients with known predisposing risk factors for iritis/uveitis, and in patients with active intraocular inflammation, Vitaprost-T can be used with caution.

Excipients

Vitaprost-T contains benzalkonium chloride which is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided.

Patients must be instructed to remove contact lenses prior to application of Vitaprost-T and wait at least 15 minutes after instillation of the dose before reinsertion (see section 4.2).

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised.

Patients should be monitored in case of prolonged use.

Vitaprost-T contains macrogolglycerol hydroxystearate 40, which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed with travoprost or timolol.

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, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or guanethidine.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

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.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic medicinal products.

Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception

Vitaprost-T must not be used in women of child-bearing age/potential unless adequate contraceptive measures are in place (see section 5.3).

Pregnancy

Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/newborn child.

There are no or limited amount of data from the use of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution or the individual components in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.

Epidemiological studies have not revealed malformative effects but show a risk for intrauterine 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 Vitaprost-T is administered until delivery, the neonate should be carefully monitored during the first days of life.

Vitaprost-T should not be used during pregnancy unless clearly necessary. For information on how to reduce systemic absorption, see section 4.2.

Breast-feeding

It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. Timolol is excreted in breast milk and has the potential to cause serious adverse reactions in the breast-fed infant. 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. For information on how to reduce systemic absorption, see section 4.2.

The use of Vitaprost-T by breast-feeding women is not recommended.

Fertility

There are no data on the effects of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution on human fertility. Animal studies showed no effect of travoprost on fertility at doses up to 75 times the maximum recommended human ocular dose, whereas no relevant effect of timolol was noted at this dose level.

4.7 Effects on ability to drive and use machines

Vitaprost-T has no or negligible influence on the ability to drive and use machines.

As with any eye drops, temporary blurred vision or other visual disturbances may occur. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In clinical studies involving 2,170 patients treated with travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution the most frequently reported treatment-related adverse reaction was ocular hyperaemia (12.0%).

Tabulated summary of adverse reactions

The adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to 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), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Uncommon	hypersensitivity
Psychiatric disorders	Rare	nervousness
	Not known	depression
Nervous system disorders	Uncommon	dizziness, headache
	Not known	cerebrovascular accident, syncope, paraesthesia
Eye disorders	Very common	ocular hyperaemia
	Common	punctate keratitis, eye pain, visual disturbance, vision blurred, dry eye, eye pruritus, ocular discomfort, eye irritation
	Uncommon	keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes, eye allergy, conjunctival oedema, eyelid oedema

	Rare	corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis
	Not known	macular oedema, eyelid ptosis, lid sulcus deepened, iris hyperpigmentation, corneal disorder
Cardiac disorders	Uncommon	bradycardia
	Rare	arrhythmia, heart rate irregular
	Not known	cardiac failure, tachycardia, chest pain, palpitations
Vascular disorders	Uncommon	hypertension, hypotension
	Not known	oedema peripheral
Respiratory, thoracic and mediastinal disorders	Uncommon	dyspnoea, postnasal drip
	Rare	dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort
	Not known	asthma
Gastrointestinal disorders	Not known	dysgeusia
Hepatobiliary disorders	Rare	alanine aminotransferase increased, aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Uncommon	dermatitis contact, hypertrichosis, skin hyperpigmentation (periocular)
	Rare	urticaria, skin discolouration, alopecia
	Not known	rash
Musculoskeletal and connective tissue disorders	Rare	pain in extremity
Renal and urinary disorders	Rare	chromaturia
General disorders and administration site conditions	Rare	thirst, fatigue

Additional adverse reactions that have been seen with one of the active substances and may potentially occur with Vitaprost-T:

Travoprost

System Organ Class	**Adverse Reactions**
Immune system disorders	seasonal allergy
Psychiatric disorders	anxiety, insomnia
Eye disorders	uveitis, conjunctival follicles, eye discharge,

	periorbital oedema, eyelids pruritus, ectropion, cataract, iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids, halo vision, hypoaesthesia eye, anterior chamber pigmentation, mydriasis, eyelash hyperpigmentation, eyelash thickening, visual field defect
Ear and labyrinth disorders	vertigo, tinnitus
Vascular disorders	blood pressure diastolic decreased, blood pressure systolic increased
Respiratory, thoracic and mediastinal disorders	asthma aggravated, rhinitis allergic, epistaxis, respiratory disorder, nasal congestion, nasal dryness
Gastrointestinal disorders	peptic ulcer reactivated, gastrointestinal disorder, diarrhoea, constipation, dry mouth, abdominal pain, nausea, vomiting
Skin and subcutaneous tissue disorders	skin exfoliation, hair texture abnormal, dermatitis allergic, hair colour changes, madarosis, pruritus, hair growth abnormal, erythema
Musculoskeletal and connective tissue disorders	musculoskeletal pain, arthralgia
Renal and urinary disorders	dysuria, urinary incontinence
General disorders and administration site conditions	asthenia
Investigations	prostatic specific antigen increased

Timolol

Like other topically applied ophthalmic medicinal products, timolol is absorbed into the systemic circulation. This may cause undesirable effects similar to those seen with systemic beta-blocking agents. Additional listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. For information on how to reduce systemic absorption, see section 4.2.

System Organ Class	**Adverse Reactions**
Immune system disorders	systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis
Metabolism and nutrition disorders	hypoglycaemia
Psychiatric disorders	Insomnia, nightmares, memory loss, hallucination
Nervous system disorders	cerebral ischaemia, increases in signs and symptoms of myasthenia gravis
Eye disorders	signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness),

	choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, diplopia
Cardiac disorders	oedema, congestive heart failure, atrioventricular block, cardiac arrest
Vascular disorders	Raynaud's phenomenon, cold hands and feet
Gastrointestinal disorders	nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	psoriasiform rash or exacerbation of psoriasis
Musculoskeletal and connective tissue disorders	myalgia
Reproductive system and breast disorders	sexual dysfunction, decreased libido
General disorders and administration site conditions	asthenia

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 (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 Vitaprost-T is not likely to occur or to be associated with toxicity.

In case of accidental ingestion, symptoms of overdose from systemic beta-blockade may include bradycardia, hypotension, bronchospasm and heart failure.

If overdose with Vitaprost-T occurs, treatment should be symptomatic and supportive. Timolol does not dialyse readily.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma preparations and miotics, ATC code: S01ED51.

Mechanism of action

Vitaprost-T contains two active substances: travoprost and timolol maleate. These two components lower intraocular pressure by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Travoprost, a prostaglandin F2α analogue, is a full agonist which is highly selective and has a high affinity for the prostaglandin FP receptor and reduces the intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in man starts within approximately 2 hours after administration and maximum effect is reached after 12 hours. Significant lowering of intraocular pressure can be maintained for periods exceeding 24 hours with a single dose.

Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Secondary pharmacology

Travoprost significantly increased optic nerve head blood flow in rabbits following 7 days of topical ocular administration (1.4 micrograms once daily).

Pharmacodynamic effects

Clinical effects

In a twelve-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution dosed once daily in the morning was 8 to 10 mmHg. The non-inferiority of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution as compared to latanoprost 50 micrograms/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all visits.

In a three-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 27 to 30 mmHg the mean IOP-lowering effect of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution dosed once daily in the morning was 9 to 12 mmHg and was up to 2 mmHg greater than that of travoprost 40 micrograms/ml dosed once daily in the evening and 2 to 3 mmHg greater than that of timolol 5 mg/ml dosed twice daily. A statistically superior reduction in morning mean IOP (8 AM-24 hours after the last dose of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution) was observed compared to travoprost at all visits throughout the study.

In two three-month, controlled clinical studies in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 23 to 26 mmHg, the mean IOP-lowering effect of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution dosed once daily in the morning was 7 to 9 mmHg. Mean IOP reductions were non-inferior, although numerically lower, to those achieved by concomitant therapy with travoprost 40 micrograms/ml dosed once daily in the evening and timolol 5 mg/ml dosed once daily in the morning.

In a 6-week, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 24 to 26 mmHg, the mean IOP-lowering effect of

travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution (polyquaternium-1-preserved) dosed once daily in the morning was 8 mmHg and equivalent to that of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution (benzalkonium chloride-preserved).

Inclusion criteria were common across the studies, with the exception of the IOP entry criteria and response to previous IOP therapy. The clinical development of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution included both patients naive and on therapy. Insufficient responsiveness to monotherapy was not an inclusion criterion.

Existing data suggest that evening dosing might have some advantages as regards mean IOP reduction. Consideration should be given to patient convenience and their likely compliance when recommending morning vs. evening dosing.

5.2 Pharmacokinetic properties

Absorption

Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes rapid ester hydrolysis in the cornea to the active free acid. Following once-daily administration of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution PQ in healthy subjects (N=22) for 5 days, travoprost free acid was not quantifiable in plasma samples from the majority of subjects (94.4%) and generally was not detectable one hour after dosing. When measurable (≥ 0.01 ng/ml, the assay limit of quantitation), concentrations ranged from 0.01 to 0.03 ng/ml. The mean timolol steady-state Cmax was 1.34 ng/ml and Tmax was approximately 0.69 hours after once-daily administration of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution.

Distribution

Travoprost free acid can be measured in the aqueous humour during the first few hours in animals and in human plasma only during the first hour after ocular administration of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution. Timolol can be measured in human aqueous humour after ocular administration of timolol and in plasma for up to 12 hours after ocular administration of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution.

Biotransformation

Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin F2α which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and β - oxidative cleavages of the upper side chain.

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other gives an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma $t_{1/2}$ of

timolol is 4 hours after ocular administration of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution.

Elimination

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Less than 2% of an ocular dose of travoprost was recovered in urine as free acid. Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites.

5.3 Preclinical safety data

In monkeys, administration of travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution twice daily was shown to induce increased palpebral fissure and to increase iris pigmentation similar to that observed with ocular administration of prostanoids.

Travoprost/timolol 40 micrograms/ml + 5 mg/ml eye drops, solution preserved with polyquaternium-1 induced minimal ocular surface toxicity, compared to eye drops preserved with benzalkonium chloride, on cultured human corneal cells and following topical ocular administration in rabbits.

Travoprost

Topical ocular administration of travoprost to monkeys at concentrations of up to 0.012% to the right eye twice daily for one year resulted in no systemic toxicity.

Reproduction toxicity studies with travoprost have been undertaken in rats, mice and rabbits using the systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss and foetotoxicity. In pregnant rats, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic fluid and foetal tissues of pregnant rats administered ^{3}H-travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/ml and 30 pg/ml plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/ml).

Timolol

Non-clinical data reveal no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse reactions on postnatal development (7,000 times the clinical dose) and increased foetal resorptions in rabbits (14,000 times the clinical dose).

6. Pharmaceutical particulars

6.1 List of excipients

Benzalkonium chloride

Macrogolglycerol hydroxystearate 40

Trometamol

Edetate disodium

Boric acid (E284)

Mannitol (E421)

Sodium hydroxide (for pH adjustment)

Water for injections or Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Discard 4 weeks after first opening.

6.4 Special precautions for storage

Before opening, this medicinal product does not require any special temperature storage conditions. Keep the bottle in the sachet in order to protect from light.

After first opening, this medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polypropylene bottle of 5 ml with colourless LDPE nozzle and a white opaque HDPE/LDPE cap with tamper proof seal. Each bottle contains 3 ml solution.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Aristopharma Ltd

Plot #14-22, Road # 11 & 12, Shampur-Kadamtali I/A,

Dhaka-1204, Bangladesh

Tel.: +8802222221692, +8809606332211

Fax: +880-2-8317005