ICH CTD
MODULE 1.3

1.3 PRODUCT INFORMATION

1.3.1 Summary of product characteristics (SmPC)

Provided in the following pages.

Product Name: Vitaprost Ophthalmic Solution
(Travoprost Ophthalmic Solution USP, 0.004% w/v)

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

1.1 Product Name: Vitaprost Ophthalmic Solution

1.2 Strength: Travoprost USP 0.004% w/v

1.3 Pharmaceutical Dosage Form: Ophthalmic Solution

2. Quality and Quantitative Composition:

2.1 Qualitative Declaration

2.2 Quantitative Declaration

Name of the Ingredient	Specifications	Quantity/100 ml	Overage	Function
Active Ingredient				
Travoprost	USP	0.004 g	5%	Active Pharmaceutical Ingredient
Excipients				
Polyoxyl 40 Hydrogenated Castor oil	USP NF	0.100 g	-	Solubilizing Agent
Sodium Chloride [For sterile]	BP	0.250 g	-	Tonicity agent
Mannitol [Injectable Grade]	BP	1.500 g	-	
Boric Acid	BP	0.500 g	-	Ionic buffer as Preservative
Propylene Glycol	BP/USP	0.500 g	-	
Sorbitol Solution (70%)	BP	0.200g (equivalent to 0.156 ml)	-	
Zinc Chloride	USP	0.010 g	-	
Sodium Hydroxide or Hydrochloric acid	BP	q.s. to adjust pH	-	For pH adjustment
Water for Injections	BP	q.s. to 100.00 ml	-	Solvent

3. Pharmaceutical Form :

Pharmaceutical form: A clear and colorless solution.

4. Clinical Particulars:

4.1 Therapeutic indications:

Decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma (see section 5.1).
Decrease of elevated intraocular pressure in paediatric patients aged 2 months to < 18 years with ocular hypertension or paediatric glaucoma (see section 5.1).

4.2 Posology and method of administration:

Posology:

Use in adults, including elderly population:

The dose is one drop of Travoprost in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening.

Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

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).

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.

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

Hepatic and 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 dosage adjustment is necessary in these patients (see section 5.2).

Paediatric population:

Travoprost can be used in paediatric patients from 2 months to < 18 years at the same posology as in adults. However, data in the age group 2 months to < 3 years (9 patients) is limited (see section 5.1).

The safety and efficacy of Travoprost in children below the age of 2 months have not been established. No data are available.

Method of Administration:

For ocular use

For patients who wear contact lenses, please refer to section 4.4.

The patient should remove the protective overwrap 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.

4.3 Contraindications:

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

4.4 Special warning and precautions for use:

Eye colour change:

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 be become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

Periorbital and eye lid changes:

In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of Travoprost has been reported in 0.4% of patients. Periorbital and lid changes including deepening of the eyelid sulcus have also 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 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. Travoprost should therefore be used with caution in patients with active intraocular inflammation.

Aphakic patients:

Macular oedema has been reported during treatment with prostaglandin F2a analogues. Caution is recommended when using Travoprost 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.

Iritis/uveitis:

In patients with known predisposing risk factors for iritis/uveitis, Travoprost should be used with caution.

Contact with the skin:

Skin contact with Travoprost must be avoided as transdermal absorption of Travoprost has been demonstrated in rabbits.

Prostaglandins and prostaglandin analogues are biologically active materials 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.

Contact lenses:

Patients must be instructed to remove contact lenses prior to application of Travoprost and wait 15 minutes after instillation of the dose before reinsertion.

Excipients:

Vitaprost contains propylene glycol which may cause skin irritation.
Vitaprost contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.

Paediatric population:

Efficacy and safety data in the age group 2 months to < 3 years (9 patients) is limited (see section 5.1). No data are available for children below the age of 2 months.

In children < 3 years old that mainly suffer from PCG (primary congenital glaucoma), surgery (e.g. trabeculotomy/goniotomy) remains the first line treatment.

No long-term safety data are available in the paediatric population.

4.5 Undesirable effects:

Summary of the safety profile:

In clinical trials with Travoprost, the most common adverse reactions were ocular hypearemia and iris hyperpigmentation, occurring in approximately 20% and 6% of patient respectively.

Tabulated list of adverse reactions:

The following adverse reactions are classified according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), rare (≥1/1/10,000 available data). Within each frequency group, adverse reactions are presented in decreasing order of seriousness. The adverse reactions were obtained from clinical studies and post-marketing data with Travoprost.

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Uncommon	hypersensitivity, seasonal allergy
Psychiatric disorders	Not known	depression, anxiety, insomnia
Nervous system disorder	Uncommon	headache
	Rare	dizziness, visual field defect, dysgeusia
Eye disorders	Very common	ocular hyperaemia
	Common	iris hyperpigmentation, eye pain, ocular discomfort, dry eye, eye pruritus, eye irritation
	Uncommon	corneal erosion, uveitis, iritis, anterior chamber inflammation, keratitis, punctate keratitis, photophobia, eye discharge , blepharitis, erythema of eyelid, periorbital oedema, eyelids pruritus, visual acuity reduced, vision blurred, lacrimation increased, conjunctivitis, ectropion, cataract, eyelid margin crusting, growth of eyelashes
	Rare	iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids, conjunctival oedema, halo vision, conjunctival follicles, hypoaesthesia eye, trichiasis, meibomianitis, anterior chamber pigmentation, mydriasis, asthenopia, eyelash hyperpigmentation, eyelash thickening
	Not known	macular oedema, lid sulcus deepened
Ear and labyrinth disorders	Not known	vertigo, tinnitus
Cardiac disorders	Uncommon	palpitations
	Rare	heart rate irregular, heart rate decreased
	Not known	chest pain, bradycardia, tachycardia, arrhythmia
Vascular disorders	Rare	blood pressure diastolic decreased, blood pressure systolic increased, hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	cough, nasal congestion, throat irritation
	Rare	dyspnoea, asthma, respiratory disorder, oropharyngeal pain, dysphonia, rhinitis allergic, nasal dryness
	Not known	asthma aggravated, epistaxis
Gastrointestinal disorders	Rare	peptic ulcer reactivated, gastrointestinal disorder, constipation, dry mouth
	Not known	diarrhoea, abdominal pain, nausea, vomiting
Skin and subcutaneous tissue disorders	Uncommon	skin hyperpigmentation (periocular), skin discolouration, hair texture abnormal, hypertrichosis
	Rare	dermatitis allergic, dermatitis contact, erythema, rash, hair colour changes, madarosis
	Not known	pruritus, hair growth abnormal

Musculoskeletal and connective tissue disorders	Rare	musculoskeletal pain, arthralgia
Renal and urinary disorders	Not known	dysuria, urinary incontinence
General disorders and administration site conditions	Rare	asthenia
Investigations	Not known	prostatic specific antigen increased

Paediatric population:

In a 3 month phase 3 study and a 7 days pharmacokinetic study, involving 102 paediatric patients exposed to Travoprost, the types and characteristics of adverse reactions reported were similar to what has been observed in adult patients. The short-term safety profiles in the different paediatric subsets were also similar (see section 5.1). The most frequent adverse reactions reported in the paediatric population were ocular hyperaemia (16.9%) and growth of eyelashes (6.5%). In a similar 3 month study in adult patients, these events occurred at an incidence of 11.4% and 0.0%, respectively.

Additional adverse drug reactions reported in paediatric patients in the 3 month paediatric study (n=77) compared to a similar trial in adults (n=185) included erythema of eyelid, keratitis, lacrimation increased, and photophobia all reported as single events with an incidence of 1.3% versus 0.0% seen in adults.

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 national reporting system listed in Appendix V.

4.6 Overdose:

No cases of overdose have been reported. A topical overdose is not likely to occur or to be associated with toxicity. A topical overdose of Travoprost may be flushed from the eye(s) with lukewarm water. Treatment of a suspected oral ingestion is symptomatic and supportive.

4.7 Fertility, pregnancy and lactation

Women of child-bearing potential/contraception:

Travoprost 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 fetus/new-born child. Vitaprost should not be used during pregnancy unless clearly necessary.

Breastfeeding:

It is unknown whether travoprost from the eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. The use of Avatan by breast-feeding mothers is not recommended.

Fertility:

There are no data on the effects of Vitaprost on human fertility. Animal studies showed no effect of travoprost on fertility at doses more than 250 times the maximum recommended human ocular dose.

4.8 Effects on ability to drive and use machines

Vitaprost has no or negligible influence on the ability to drive and use machines, however as with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines

5. Pharmacological Properties:

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group:
Ophthalmologicals-antiglaucoma preparations and miotics-prostaglandin analogues, ATC code: S01E E04

Mechanism of action:
Travoprost, a prostaglandin F2α analogue, is a highly selective full agonist which 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 the intraocular pressure in man starts about 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

5.2 Pharmacokinetic Properties:
Absorption:

Travoprost is an ester prodrug. It is absorbed through the cornea where the isopropyl ester is hydrolysed to the active free acid. Studies in rabbits have shown peak concentrations of 20 ng/mL of the free acid in aqueous humour one to two hours after topical dosing of Travoprost. Aqueous humour concentrations declined with a half-life of approximately 1.5 hours.

Distribution:

Following topical ocular administration of Travoprost to healthy volunteers, low systemic exposure to active free acid was demonstrated. Peak active free acid plasma concentrations of 25 pg/mL or less were observed between 10 and 30 minutes post-dose. Thereafter, plasma

levels declined rapidly to below the 10 pg/mL assay quantitation limit before 1 hour post-administration. Due to the low plasma concentrations and rapid elimination following topical dosing, the elimination half-life of active free acid in man could not be determined.

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.

Elimination:

Travoprost free acid and its metabolites are mainly excreted by the kidneys. 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 dosage adjustment is necessary in these patients.

Paediatric population:

A pharmacokinetic study in paediatric patients aged 2 months to < 18 years demonstrated very low plasma exposure to travoprost free acid, with concentrations ranging from below the 10 pg/mL assay limt of quantitation (BLQ) to 54.5 pg/mL. In 4 previous systemic pharmacokinetic studies in adult populations, travoprost free acid plasma concentrations ranged from BLQ to 52.0 pg/mL. While most of the plasma data across all studies was non-quantifiable, making statistical comparisons of systemic exposure across age groups unfeasible, the overall trend shows that plasma exposure to travoprost free acid following topical administration of Travoprost is extremely low across all age groups evaluated.

5.3 Preclinical Safety Data:

In ocular toxicity studies in monkeys, administration of travoprost at a dose of 0.45 microgram, twice a day, was shown to induce increased palpebral fissure. 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.

6. Pharmaceutical Particulars :

6.1 List of excipients:

- Polyoxyl 40 Hydrogenated Castor Oil
- Sodium Chloride BP (For sterile)
- Mannitol BP (Injectable Grade)
- Boric Acid BP
- Propylene Glycol BP/USP
- Sorbitol Solution (70%) BP
- Zinc Chloride USP
- Sodium Hydroxide BP
- Hydrochloric Acid BP
- Water for injections BP

6.2 Incompatibilities:

None known.

6.3 Shelf life:

Two years from manufacture date.

6.4 Special precautions for storage:

- Store between 2°C and 25°C, dry place away from light.
- Discard 30 days after opening.
- Keep out of the reach of children.
- Close the bottle immediately after use.

6.5 Nature and contents of container:

Low Density Polyethylene (LDPE) white opaque dropper bottle with a LDPE white opaque dropper tip and High Density Polyethylene (HDPE) white opaque closure.
Pack size: 3 ml

7. Marketing Authorization Holder :

Name	:	Aristopharma Ltd.
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8. Marketing Authorization Numbers: 143–366–052

9. Date of first authorization / renewal of the authorization: 17–01–2008

10. Date of revision of the text: - To be given after approval of the product.