SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

[PRODUCT NAME] Preservative-free 40 micrograms/mL eye drops solution, multi dose container

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 40 micrograms of travoprost.

Excipient(s) with known effect:
Each mL of solution contains 2 mg of macrogol glycerol hydroxyl stearate 40 (see section 4.4.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.
Clear, colourless aqueous 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).

4.2 Posology and method of administration

Posology
Use in adults, including elderly population
The dose is one drop of [PRODUCT NAME] Preservative-free 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 [PRODUCT NAME] Preservative-free, the other medicinal product should be discontinued and [PRODUCT NAME] Preservative-free should be started the following day.

Hepatic and renal impairment
[PRODUCT NAME] Preservative-free 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
The efficacy and safety of [PRODUCT NAME] Preservative-free in children below the age of 18 years have not been established and its use is not recommended in these patients until further data become available.

Method of Administration

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

[PRODUCT NAME] preservative-free eye drops solution, multidose container is a sterile solution that does not contain a preservative. The solution from the multi-dose container is to be used for 28 days after opening for administration to the affected eye(s). Since sterility can be maintained after the multi- dose container is opened, the remaining content must not be discarded before the 28 days after opening.

Patients should be instructed to wash their hands before use and avoid allowing the container to come into contact with the eye or surrounding structures as this could cause injury to the eye.

The patient should remove the protective overwrap (if there is one) immediately prior to initial use. After cap is removed, [PRODUCT NAME] preservative-free eye drops solution, multi-dose container is ready for 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 warnings 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 [PRODUCT NAME] Preservative-free and wait 15 minutes after instillation of the dose before reinsertion.

Excipients
[PRODUCT NAME] Preservative-free contains macrogol glycerol hydroxyl stearate 40 which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 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 foetus/new-born child. [PRODUCT NAME] Preservative-free 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 [PRODUCT NAME] Preservative-free by breast-feeding mothers is not recommended.

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

4.7 Effects on ability to drive and use machines

Travoprost 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.

4.8 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 2 0 % and 6 % of patients respectively.

Tabulated list of adverse reactions
The following adverse reactions are classified according to the following convention: very common (>1 /1 0), common (>1 / 1 0 0 to <1 /1 0), uncommon (>1 /1 , 0 0 0 to <1 /1 0 0), rare (>1 /1 0 , 0 0 0 to<1 /1 ,0 0 0), very rare <1 /1 0 ,0 0 0), or not known (frequency cannot be estimated from the 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
Infections and infestations	Rare	herpes simplex, keratitis herpetic
Immune system disorders	Uncommon	hypersensitivity, seasonal allergy
Psychiatric disorders	Not known	depression, anxiety
Nervous system disorder	Uncommon	headache, dizziness, visual field defect
	Rare	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, eyelash discolouration, asthenopia
	Rare	iridocyclitis, eye inflammation, photopsia, eczema eyelids, conjunctival oedema, halo vision,

		conjunctival follicles, hypoaesthesia eye, meibomianitis, anterior chamber pigmentation, mydriasis, eyelash thickening
	Not known	macular oedema, sunken eyes
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
Vascular disorders	Rare	blood pressure diastolic decreased, blood pressure systolic increased, hypotension, hypertension
Respiratory, thoracic and mediastinal disorders	Uncommon	dyspnoea, asthma, nasal congestion, throat irritation
	Rare	respiratory disorder, oropharyngeal pain, cough, dysphonia
	Not known	asthma aggravated
Gastrointestinal disorders	Rare	peptic ulcer reactivated, gastrointestinal disorder, constipation, dry mouth
	Not known	diarrhoea, abdominal pain, nausea
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
	Not known	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

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.

4.9 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.

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 F_{2a} 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.

Clinical efficacy and safety
Data on adjunctive administration of travoprost with timolol 0.5% and limited data with brimonidine 0.2% were collected during clinical trials that showed an additive effect of travoprost with these glaucoma medications. No clinical data are available on adjunctive use with other ocular hypotensive medications.

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/g 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 F_{2a} 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.

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.

Reproduction toxicity studies have been undertaken in rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Macrogolglycerol hydroxystearate 40
Boric acid
Mannitol
Sodium chloride
Propylene glycol
Sodium hydroxide (for pH-adjustment)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

1 year

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

Before opening, keep bottle in overwrap pouch (if available) in order to protect from moisture.

[PRODUCT NAME] Preservative-Free eye drops solution, multi-dose container should be used no longer than 28 days after first opening of the multi – dose container.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

In a cardboard box is included a 5 ml white multi dose ophthalmic container containing 2.5ml of the ophthalmic solution.
The multi – dose container can be available in an overwrap, inside the carton box.

[PRODUCT NAME] Preservative-free eye drops solution, multi-dose container is available in the following packaging configurations:
1 x 2.5 ml (single 2.5-ml multi dose container)
3 x 2.5 ml (three 2.5-ml multi dose containers)
Cartons containing 1 or 3 number of bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBERS

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT