For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

Travoprost Eye Drops USP 0.004% w/v

TRAVASENZ®

For the use of Registered Medical Practitioner only

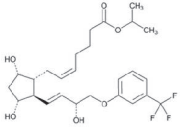
Composition

Travoprost USP …..... 0.004% w/v

Benzalkonium Chloride Solution USP …..... 0.02% v/v (as preservative)

Water for Injection USP ..... q.s

Chemical Structure & Name



C26H35F3O6

[1R - [1•(*Z*), 2•(1*E* ,3*R* *), 3•, 5•]] – 7 - [3, 5 – Dihydroxy – 2 - [3 – hydroxy – 4 - [3 - (trifluoromethyl)phenoxy]-1-butenyl] cyclopentyl]-5-heptenoic acid, 1-methylethyl ester.

Isopropyl (*Z*)-7-[(1*R* ,2*R*,3*R* ,5*S*)-3,5-dihydroxy-2-[(1*E* ,3*R*)-3-hydroxy-4-[(•,•,•-trifluorom- tolyl)oxy]-1-butenyl] cyclopentyl]-5-heptenoate.

Category

Pharmacotherapeutic group: Ophthalmologicals-antiglaucoma preparations and mioticsprostaglandin

analogues

ATC code: S01E E04

Description

A clear colourless solution filled in 5mL sterile gamma-irradiated white opaque LDPE bottle sealed with sterile gamma-irradiated natural transparent LDPE open nozzle and sterile gamma-irradiated white HDPE tamp safe cap.

Pharmacology

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.

Clinical efficacy and safety

In a clinical trial, patients with open-angle glaucoma or ocular hypertension who were treated with Travoprost Eye Drops USP 0.004% w/v dosed once-daily in the evening demonstrated 8 to 9 mmHg reductions (approximately 33%) in intraocular pressure from 24 to 26 mmHg baseline. Data on adjunctive administration of Travoprost Eye Drops USP 0.004% w/v with timolol 0.5% and limited data with brimonidine 0.2% were collected during clinical trials that showed an additive effect of Travoprost Eye Drops USP 0.004% w/v with these glaucoma medications. No clinical data are available on adjunctive use with other ocular hypotensive medications.

Secondary pharmacology

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

Paediatric population

The efficacy of Travoprost Eye Drops USP 0.004% w/v in paediatric patients from 2 months to less than 18 years of age was demonstrated in a 12-week, double-masked clinical study of travoprost compared with timolol in 152 patients diagnosed with ocular hypertension or paediatric glaucoma. Patients received either travoprost 0.004% once daily or timolol 0.5% (or 0.25% for subjects younger than 3 years old) twice daily. The primary efficacy endpoint was the intraocular pressure (IOP) change from baseline at Week 12 of the study. Mean IOP reductions in the travoprost and timolol groups were similar.

In the age groups 3 to < 12 years (n=36) and 12 to <18 years (n=26), mean IOP reduction at Week 12 in the travoprost group was similar to that in the timolol group. Mean IOP reduction at Week 12 in the 2 months to < 3 years of age group was 1.8 mmHg in the travoprost group and 7.3 mmHg in the timolol group. IOP reductions for this group were based on only 6 patients in the timolol group and 9 patients in the travoprost group where 4 patients in the travoprost group versus 0 patients in the timolol group had no relevant mean IOP reduction at Week 12. No data are available for children less than 2 months old.

The effect on IOP was seen after the second week of treatment and was consistently maintained throughout the 12 week period of study for all age groups.

Pharmacokinetic:

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 Eye Drops USP 0.004% w/v. Aqueous humour concentrations declined with a half-life of approximately 1.5 hours.

Distribution

Following topical ocular administration of Travoprost Eye Drops USP 0.004% w/v to healthy volunteers, low systemic exposure to active free acid was demonstrated. Peak active free acid plasma concentrations of 25pg/mL or less were observed between 10 and 30 minutes postdose.

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 F2□which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl and □- oxidative cleavages of the upper side chain.

Elimination

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Travoprost Eye Drops USP 0.004% w/v 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 limit 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 52.0pg/mL. While most of the plasma data across all studies was nonquantifiable,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 Eye Drops USP 0.004% w/v is extremely low across all age groups evaluated.

Indications

Travoprost Eye Drops USP 0.004% w/v is indicated to decrease elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma and decrease of elevated intraocular pressure in paediatric patients aged 2 months to < 18 years with ocular hypertension or paediatric glaucoma.

Dosage & Administration

Posology

Use in adults, including elderly population

The dose is one drop of Travoprost Eye Drops USP 0.004% w/v 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.

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 Eye Drops USP 0.004% w/v, the other medicinal product should be discontinued and Travoprost Eye Drops USP 0.004% w/v should be started the following day.

Hepatic and renal impairment

Travoprost Eye Drops USP 0.004% w/v 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

Travoprost Eye Drops USP 0.004% w/v 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.

The safety and efficacy of Travoprost Eye Drops USP 0.004% w/v 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: Patients must be instructed to remove contact lenses prior to application of Travoprost Eye Drops USP 0.004% w/v and wait 15 minutes after instillation of the dose before reinsertion.

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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warning and Precaution

Eye colour change

Travoprost Eye Drops USP 0.004% w/v 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, greybrown, 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 Eye Drops USP 0.004% w/v 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 Eye Drops USP 0.004% w/v 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 Eye Drops USP 0.004% w/v 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 Eye Drops USP 0.004% w/v in inflammatory ocular conditions; or 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 Eye Drops USP 0.004% w/v 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 Eye Drops USP 0.004% w/v 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 Eye Drops USP 0.004% w/v should be used with caution.

Contact with the skin

Skin contact with Travoprost Eye Drops USP 0.004% w/v 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 Eye Drops USP 0.004% w/v and wait 15 minutes after instillation of the dose before reinsertion. The preservative in Travoprost Eye Drops USP 0.004% w/v, benzalkonium chloride, may cause eye irritation. Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses must be avoided.

Paediatric population

Efficacy and safety data in the age group 2 months to < 3 years (9 patients) is limited. 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.

Travoprost Eye Drops USP 0.004% w/v 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.

Interactions

No interaction studies have been performed.

Pregnancy & Lactation

Pregnancy

Travoprost has harmful pharmacological effects on pregnancy and/or the fetus/new-born child. Travoprost Eye Drops USP 0.004% w/v 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 Travoprost Eye Drops USP 0.004% w/v by breast-feeding mothers is not recommended.

Women of child-bearing potential/contraception

Travoprost Eye Drops USP 0.004% w/v must not be used in women of child bearing age/potential unless adequate contraceptive measures are in place.

Fertility There are no data on the effects of Travoprost Eye Drops USP 0.004% w/v on human fertility. Animal studies showed no effect of travoprost on fertility at doses

more than 250 times the maximum recommended human ocular dose.

Adverse reaction

In clinical trials with Travoprost Eye Drops USP 0.004% w/v, the most common adverse reactions occurring were ocular hypearemia and iris hyperpigmentation. 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 (≥ 1/10,000 to<1/1,000), very rare <1/10,000), 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 Eye Drops USP 0.004% w/v.

System Organ Classification	Frequency	Adverse Reactions
Immune system disorders	Uncommon	Hypersensitivity, seasonal allergy
Psychiatric disorders	Not known	Depression, anxiety
Nervous system disorder	Uncommon	Headache
	Rare	Dizziness, visual field defect, Dysgeusia
Eye disorders	Common	Iris hyperpigmentation, eye pain, ocular discomfort, dry eye, eye pruritus, eye irritation Corneal erosion, uveitis, iritis, anterior chamber inflammation, keratitis, punctate keratitis, photophobia, eye discharge, blepharitis, erythema of eyelid, periorbitaloedema, 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, conjunctivaloedema, 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	Not known Vertigo, tinnitusVertigo, 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	Not known	Diarrhoea, abdominal pain, nausea, vomiting
Skin and subcutaneous tissue disorders	Unknown	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 andconnective tissue disorders	Rare	Musculoskeletal pain, Arthralgia
	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 studies and a 7 days pharmacokinetic study, involving 102 paediatric patients exposed to Travoprost Eye Drops USP 0.004% w/v, 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. 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.

Overdosage

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 Eye Drops USP 0.004% w/v may be flushed from the eye(s) with lukewarm water. Treatment of a suspected oral ingestion is symptomatic and supportive.

Storage

Store between 15°C - 30 °C. Protect from light

Keep out of reach of children.

Shelf life

24 Months from the date of manufacture.

Presentation

3mL clear colourless solution filled in 5mL sterile gamma-irradiated white opaque LDPE bottle sealed with sterile gamma-irradiated natural transparent LDPE open nozzle and sterile gamma-irradiated white HDPE tamp safe cap in printed carton along with leaflet.

Directions for use :

Turn the tamper proof cap anti-clockwise to break the seal.

Remove the cap, dispense drops with gentle pressure.

Replace the cap immediately after every use.

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