NOVARTIS

Regulatory Affairs

TRAVATAN®

(travoprost)
40 µg/mL Eye Drops, Solution

Summary of Product Characteristics (SmPC)

TRAVATAN®

Ophthalmological-antiglaucoma preparations and miotics-prostaglandin analogs.

DESCRIPTION AND COMPOSITION

Pharmaceutical form(s)

Eye drops, solution.

Colorless to light yellow solution.

Certain dosage strengths and dosage forms may not be available in all countries.

Active substance(s)

One mL of solution contains 40 micrograms of travoprost.

Excipients

Mannitol, polyoxyethylene hydrogenated castor oil 40 (HCO-40), propylene glycol, sodium chloride, boric acid, polyquaternium-1, sodium hydroxide and/or hydrochloric acid (to adjust pH); purified water.

INDICATIONS

Adults

Travatan eye drops is indicated for the decrease of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

Pediatrics (2 months to < 18 years)

Travatan eye drops is also indicated for the decrease of elevated IOP in pediatric patients aged 2 months to < 18 years with ocular hypertension or pediatric glaucoma.

Indication and patient population may vary between countries.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Adults and Children (2 months to < 18 years)

- The recommended dose is 1 drop of Travatan in the conjunctival sac of the affected eye(s) once daily.
- Optimal effect is obtained if the dose is administered in the evening.
- Travatan may be used concomitantly with other topical ophthalmic drug products to lower IOP.

Special populations

Renal impairment

- Travatan has been studied in patients with mild to severe renal impairment (creatine clearance as low as 14 mL/min).
- No dosage adjustment is necessary in these patients

Hepatic impairment

- Travatan has been studied in patients with mild to severe hepatic impairment.
- No dosage adjusment is necessary in these patients

Pediatric population

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

Elderly population

- No differences were seen between elderly patients and younger patients with Travatan.

Method of administration

- Travatan is for ocular use.
- Nasolacrimal occlusion or gently closing the eyelid(s) for 2 minutes 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 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, since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP lowering effect.
- When substituting another ophthalmic antiglaucoma agent with Travatan, the other agent should be discontinued and Travatan should be started the following day.
- If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.
- The patient should remove the protective overwrap immediately prior to initial use. [Only applicable to markets where a pouch is used].
- After cap is removed, if tamper evident snap collar is loose, it should be removed before using the product.
- 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. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Eye Color Changes

Travatan may gradually change the eye color 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 color. The change in iris color occurs slowly and may not be noticeable for months to years.

Periorbital and eye lid changes

Periorbital and/or eyelid skin darkening has been reported in association with the use of Travatan.

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

Travatan may gradually change eyelashes in the treated eye(s); these changes include increased length, thickness, pigmentation, and/or number of lashes.

Iritis/Uveitis

Travatan should be used with caution in patients with active intraocular inflammation, as well as patients with predisposing risk factors for uveitis.

Aphakic Patients

Macular oedema has been reported during treatment with prostaglandin F2a analogues. Use Travatan with caution in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema.

Contact lenses

Patients must be instructed to remove contact lenses prior to application of Travatan and wait at least 15 minutes before reinsertion.

ADVERSE DRUG REACTIONS

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 1 Adverse drug reactions from clinical trials with Travatan

System Organ Classification	Adverse drug reactions
Immune system disorders	Uncommon: hypersensitivity
Nervous system disorders	Uncommon: headache Rare: dizziness, dysgeusia
Eye disorders	Very common: ocular hyperaemia Common: eye pain, eye pruritus, dry eye, eye irritation, iris hyperpigmentation, ocular discomfort Uncommon: corneal erosion, punctate keratitis, keratitis, iritis, cataract, visual acuity

System Organ Classification	Adverse drug reactions
	reduced, conjunctivitis, anterior chamber inflammation, blepharitis, vision blurred, photophobia, periorbital oedema, eyelids pruritus, eye discharge, eyelid margin crusting, lacrimation increased, erythema of eyelid, growth of eyelashes Rare: uveitis, iridocyclitis, ophthalmic herpes simplex, conjunctival follicles, conjunctival oedema, hypoaesthesia eye, eye inflammation, trichiasis, anterior chamber pigmentation, asthenopia, eye allergy, eczema eyelids, eyelid irritation, eyelash hyperpigmentation, eyelash thickening
Cardiac disorders	Rare: heart rate decreased, palpitations
Vascular disorders	Rare: hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Rare: asthma, dyspnoea, dysphonia, cough, rhinitis allergic, oropharyngeal pain, nasal discomfort, nasal dryness.
Gastrointestinal disorders	Rare: dry mouth, constipation
Skin and subcutaneous tissue disorders	Uncommon: skin hyperpigmentation, hypertrichosis Rare: skin discolouration, madarosis, erythema, hair colour changes, rash
Musculoskeletal and connective tissue disorders	Rare: arthralgia, musculoskeletal pain
General disorders and administration site conditions	Rare: asthenia

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

Additional adverse reactions have been derived from post-marketing experience with travoprost via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System Organ Classification	Adverse drug reactions
Psychiatric disorders	depression, anxiety, insomnia
Eye disorders	macular oedema, lid sulcus deepened
Ear and labyrinth disorders	tinnitus
Cardiac disorders	arrhythmia, tachycardia, chest pain
Respiratory, thoracic and mediastinal disorders	epistaxis
Gastrointestinal disorders	diarrhoea, vomiting, nausea, abdominal pain
Skin and subcutaneous tissue disorders	pruritus
Renal and urinary disorders	dysuria, urinary incontinence
Investigations	prostatic specific antigen increased

INTERACTIONS

No clinically relevant interactions have been described.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary

There are no adequate well- controlled studies in pregnant women to inform a drug- associated risk. Studies in rats and mice with subcutaneous (s.c.) administration of travoprost during organogenesis have shown reproductive toxicity at the dose of 20 times and 1 time, respectively, the maximum recommended ocular human dose (MROHD) based on body surface area (BSA).

Travatan should not be used during pregnancy unless clearly necessary.

Animal data

An embryo-fetal study was conducted in pregnant mice administered travoprost once daily by subcutaneous injection during the period of organogenesis. At 1 microgram/kg/day (1 times the MROHD, based on BSA), travoprost caused post-implantation loss and decreased fetal weight. The no-observed-effect-level (NOEL) for embryofetal toxicity was 0.3 micrograms/kg/day (0.3 times the MROHD, based on BSA). The maternal NOEL was 1 microgram/kg/day.

An embryo-fetal study was conducted in pregnant rats administered travoprost once daily by s.c. injection during the period of organogenesis. At 10 micrograms/kg/day (20 times the MROHD, based on BSA), travoprost was teratogenic in rats, as evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, including fused sternebrae, domed head and hydrocephaly. Travoprost caused post-implantation loss, lower numbers of live fetuses, and lower fetal body weight at 10 micrograms/kg/day. The NOEL for embryofetal toxicity was 3 micrograms/kg/day (6 times the MROHD, based on BSA).

Pre and postnatal development studies were conducted in rats administered with travoprost once daily by s.c. injection during organogenesis and lactation. The number of dams delivering litter and with live pup was significantly decreased at 0.72 micrograms/kg/day. At doses of ≥0.12 micrograms/kg/day (0.24 times the MROHD, based on BSA), adverse pregnancy outcomes (embryofetal lethality, increased still births, abortion, early delivery), low birth weight and developmental delays were observed for F_1 offspring. The NOEL for F_2 offspring development was 0.36 micrograms/kg/day (0.7 times the MROHD, based on BSA). In subsequent study carried out at lower doses, the NOAEL for maternal function, adverse pregnancy outcomes, low birth weight and developmental delay was 0.1 micrograms/kg/day (0.23 times the MROHD, based on BSA).

Lactation

Risk Summary

There is a limited amount of data from the use of Travatan Eye Drops, Solution in breast-feeding women. It is not known whether travoprost/metabolites are transferred into human milk after topical ocular administration.

An animal study has shown transfer excretion of travoprost and/or metabolites into breast milk following subcutaneous administration (see Animal data). The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Travatan and any potential adverse effects on the breast-fed child from Travatan.

Animal data

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk following subcutaneous administration with highest concentrations of travoprost and/or metabolites observed 6 hours post dose with a milk to plasma ratio of 11.

Females and males of reproductive potential

Fertility

There are no data on the effects of Travatan on human fertility. Fertility studies in rats showed no effect of travoprost on fertility at doses up to 6 times the MRHOD, based on BSA (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

• A topical overdose is not likely to be associated with toxicity.

• Treatment of an accidental ingestion is symptomatic and supportive.

CLINICAL PHARMACOLOGY

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 is believed to reduce IOP by increasing the outflow of aqueous humor via trabecular meshwork and uveoscleral pathways. Reduction of IOP in humans starts approximately 2 hours after administration and maximum IOP reduction

is reached within 12 hours. Significant lowering of IOP can be maintained for periods exceeding 24 hours with a single dose.

As primary therapy, Travatan eye drops, dosed once-daily, reduced IOP 7 to 9 mmHg. Stable diurnal IOP reductions were achieved as early as 2 weeks after initiation of therapy and were maintained over 6 to 12 month treatment periods in 3 well-controlled studies.

Pharmacodynamics (PD)

In addition to reducing IOP, travoprost has been shown to increase optic nerve head blood flow, and decrease tear film stability and tear secretion. Travoprost does not affect respiration rate/volume or systolic blood pressure during exercise and recovery. Prostaglandin F2α analogs can induce the anagen phase in hair follicles and stimulate melanogenesis in the skin. Travatan eye drops 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.

Pediatric population

See Section DOSAGE REGIMEN AND ADMINISTRATION.

Pharmacokinetics (PK)

Absorption

Travoprost is an isopropyl ester prodrug. It is absorbed through the cornea where the ester is hydrolyzed to the active free acid. Studies in rabbits have shown maximum concentrations of approximately 20 ng/mL of travoprost free acid in aqueous humor were achieved within 1 to 2 hours of topical ocular dosing. Aqueous humor concentrations of travoprost free acid declined with a half-life of approximately 1.5 hours. Low concentrations of travoprost free acid are also found in plasma following topical dosing.

Distribution

Following topical ocular administration to humans, low systemic exposure to active free acid was observed, with peak plasma concentrations of approximately 20 pg/mL or less observed between 10 and 20 minutes post-dose. Plasma concentrations declined rapidly to below the 10 pg/mL assay quantitation limit within 1 hour of administration. Trace plasma concentrations of travoprost may be present immediately following dosing in some subjects.

Biotransformation/metabolism

Metabolism is the major route of clearance for both travoprost and its free acid in nonclinical species. The systemic metabolic pathways parallel those of endogenous prostaglandin F2α which are characterized by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl to a ketone and β oxidative cleavages of the carboxylic acid side chain.

Elimination

Following administration of radiolabelled travoprost to rats, approximately 95% of the dose was eliminated within 24 hours. Approximately, 75% of the dose was eliminated in the feces and the remainder was excreted in urine.

Linear/non-linear pharmacokinetics

Travoprost exhibits linear pharmacokinetics in both ocular tissues and plasma after topical ocular administration.

Pharmacokinetic/pharmacodynamic relationship(s)

The pharmacokinetic and pharmacodynamics relationship has not been established for travoprost after topical ocular administration.

Special populations

Pediatric patients

The systemic pharmacokinetics of travoprost after topical ocular administration in patients between the ages of 2 months to less than 18 years of age showed a similar concentration range to that of adults, with most plasma samples below the limit of quantitation of 10 pg/mL.

Renal impairment

The systemic pharmacokinetics of Travoprost 0.004% eye drops has been studied in patients with mild to severe renal impairment (creatine clearance as low as 14 mL/minute). No dose adjustment is required in these populations.

Hepatic impairment

The systemic pharmacokinetics of Travoprost 0.004% eye drops has been studied in patients with mild to severe hepatic impairment. No dose adjustment is required in these populations.

CLINICAL STUDIES

Travatan is a well established product.

Data from clinical trials

Travoprost 0.004% eye drops

In a clinical trial, patients with open-angle glaucoma or ocular hypertension who were treated with Travoprost 0.004% eye drops (polyquaternium-preserved) dosed QD in the evening demonstrated 8-9 mmHg reductions (approximately 33%) in IOP from a baseline range of 24-36 mmHg. Data on adjunctive administration of Travoprost 0.004% eye drops with timolol 0.5% and limited data with brimonidine 0.2% collected during clinical trials showed an additive effect of Travoprost 0.004% eye drops with these concomitant medications. No clinical data are available on adjunctive use with other ocular hypotensive medications.

Travoprost 0.004% eye drops is generally well-tolerated. The most common side effect is hyperemia, as observed with other ophthalmic prostaglandin analogs.

NON-CLINICAL SAFETY DATA

Non-clinical data for travopost reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated-dose toxicity, genotoxicity, and carcinogenic potential and topical ocular irritation studies. Adverse reproductive and developmental toxicity was observed in animals at exposure levels of travoprost similar to clinical exposure levels and is possibly relevant to clinical use.

For details on reproductive studies, see Section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Fertility studies in rats dosed with travoprost subcutaneously resulted in significant reductions in the number of corpora lutea, viable fetuses, and an increased early post-implantation loss as well as resorption rate at 10 micrograms/kg/day (20 times the MROHD, based on BSA). The NOEL was set at 3 micrograms/kg/day (6 times the MROHD, based on BSA).

PHARMACEUTICAL INFORMATION

INCOMPATIBILITIES

None known.

Specific *in vitro* interaction studies were performed with travoprost and medicinal products containing thiomersal. No evidence of precipitation was observed.

STORAGE

See folding box.

Travatan should not be used after the date marked “EXP” on the pack.

Travatan must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

No special requirements.

Special precautions for disposal

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

Manufacturer:

S.A. Alcon-Couvreur N.V.

Rijksweg 14, Puurs, B 2870, Belgium

Marketing Authorization Holder:

Novartis Nigeria Limited

Landmark Building,

52-54, Isaac John Street,

Ikeja G.R.A

Lagos.