Summary of Product Characteristics

1. Name of the finished pharmaceutical product

TRAVATAN 40 µg/mL Eye Drops, Solution

2. Qualitative and quantitative composition

Active substance

Travatan: One mL of solution contains 40 micrograms of travoprost.

Izba: One mL of solution contains 30 micrograms of travoprost.

For full list of excipients, see section 6.1

3. Pharmaceutical form

Eye drops, solution. Colorless to light yellow.

4. Clinical particulars

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

4.2 Posology and method of administration

Posology

Adults and Children (2 months to < 18 years)

The recommended dose is 1drop 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 adjustment is necessary in these patients.

Pediatric population

The IOP-lowering of Izba in pediatric patients (2 months to < 18 years) was comparable to adult patients with Travatan. However, data in the age group 2 months to < 3 years (9 patients) is limited.

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.

Patients must be instructed to remove soft contact lenses prior to application of Travatan and wait 15 minutes after instillation of the dose before reinsertion [only applicable for Travatan formulation containing benzalkonium chloride]

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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.

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.

Iritis/Uveitis

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

Contact lenses

Travatan contains benzalkonium chloride which may cause irritation and is known to discolor soft contact lenses. Avoid contact with soft contact lenses. Patients must be instructed to remove contact lenses prior to application of Travatan and wait at least 15 minutes before reinsertion.

4.5 Interactions with other pharmaceutical products and other forms of interaction

No clinically relevant interactions have been described.

4.6 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 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 MROHD, based on BSA (see Section 13 Non-clinical safety data).

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) 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 4-1 Adverse drug reactions from clinical trials with 40 µg/mL 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 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, paplpitations
Vascular disorders	*Rare:* hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	*Rare:* astma, 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

System Organ Classification	**Adverse drug reactions**
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 4-2 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	epitaxis
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

* To be included as an ADR from post-marketing experience in Travatan only. This ADR is already listed for Izba (from clinical trials – frequency uncommon).

Reporting of suspected adverse reactions
Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdosage

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

Treatment of an accidental ingestion is symptomatic and supportive.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Ophthalmologicals-antiglaucoma preparations and miotics- prostaglandin analogs. ATC code: S01E E04

Mechanism of action (MOA)

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. Travoprost 0.004% 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 4 Dosage Regimen and Administration.

5.2 Pharmacokinetic properties

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 1-2 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 travaprost 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.

Linearity/non-linearity

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

Pharmacokinetic/pharmacodynamic relationship(s)

Pharmacokinetic and pharmacodynamics relationship has not been established for travaprost 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.

5.3 Pre-clinical safety data

Non-clinical data for travoprost 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 9 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).

6 Pharmaceutical information

6.1 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.

6.2 Incompatibilities

None known.

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.

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

6.5 Nature and contents of container

2.5 ml solution in a LDPE plastic bottle

6.6 Special precautions for disposal and other handling

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

7 Merketing authorization holder and manufacturing site addresses

Novartis Pharma AG

Lichtstrasse 35,

CH-4056 Basel,

Switzerland

Manufacturer

Novartis Manufacturing NV

Rijksweg 14,

2870 Puurs-Sint-

Amands Belgium

8 Marketing authorization number

Kenya: H2004/027

9 Date of first registration/ renewal of the registration

Kenya: 18 February 2004

Latest: June 2022

10 Date of revision of the text

June 2022