1. NAME OF THE MEDICINAL PRODUCT

TRAVATAN® C 30 micrograms/ml eye drops, solution (travoprost)

2. DESCRIPTION AND COMPOSITION

1 ml of solution contains 30 micrograms of travoprost.

Preservative: 1 ml of solution contains 10 micrograms of polyquaternium-1.

Excipients with known effect: 1 ml of solution contains 7.5 mg propylene glycol and 2 mg polyoxyethylene hydrogenated castor oil 40 (HCO-40) (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Clear, colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRAVATAN C® eye drops contains travoprost, a prostaglandin analogue.

TRAVATAN C eye drops is indicated for the 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 patients

The dose is 1 drop of TRAVATAN C eye drops in the conjunctival sac of the affected eye(s) once daily. Optimal effect is obtained if the dose is administered in the evening.

TRAVATAN C eye drops may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure.

Use in patients with renal impairment

Travoprost 30 µg/ml has not been studied in patients with renal impairment. However, travoprost 40 µg/ml has been studied 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).

Therefore, no need for dose adjustment at the lower concentration of active ingredient is anticipated.

Use in patients with hepatic impairment

Travoprost 30 µg/ml has not been studied in patients with hepatic. However, travoprost 40 µg/ml has been studied in patients with mild to severe hepatic impairment.No dosage adjustment is necessary in these patients (see section 5.2).

Therefore, no need for dose adjustment at the lower concentration of active ingredient is anticipated.

Use in children and adolescents

The safety and efficacy of TRAVATAN C eye drops in children and adolescents below the age of 18 years has 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. Keep the bottle tightly closed when not in use. The dropper tip should also not come into contact with the eye as this may cause injury to the eye.

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 1 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 medicinal product with TRAVATAN C eye drops, the other medicinal product should be discontinued and TRAVATAN C eye drops 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.

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 0.2% of patients.

- Periorbital and lid changes including deepening of the eyelid sulcus have 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.

- 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.

Aphakic patients

- Macular oedema has been reported during treatment with prostaglandin F2α 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 active intraocular inflammation, as well as patients with known predisposing risk factors for iritis / uveitis, travoprost can 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 TRAVATAN C eye drops and wait at least 15 minutes after instillation of the dose before reinsertion.

Excipients

- TRAVATAN C eye drops contains propylene glycol which may cause skin irritation.

- TRAVATAN C eye drops contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. However, no clinically relevant interactions are expected to occur.

4.6 Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk Summary

Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child.

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 C eye drops should not be used during pregnancy unless clearly necessary.

Animal data

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 C 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 C eye drops and any potential adverse effects on the breast-fed child from TRAVATAN C eye drops.

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

TRAVATAN C eye drops must not be used in women of child bearing age/potential unless adequate contraceptive measures are in place (see section 5.3).

Fertility

There are no data on the effects of TRAVATAN C eye drops 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 5.3 Preclinical safety data).

4.7 Effects on ability to drive and use machines

TRAVATAN C eye drops has no or negligible influence on the ability to drive and use machines.

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 a clinical trial of 3 months duration (N = 442) involving TRAVATAN C eye drops as monotherapy, the most common adverse reaction observed was hyperaemia of the eye (ocular or conjunctival) reported in approximately 12% of the patients.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1 and Table 2) 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 30 micrograms/ml eye drops, solution (TRAVATAN C eye drops)

System Organ class	Frequency	Adverse drug reactions
Eye disorders	Very common	ocular hyperaemia
	Common	eye pruritus, dry eye, ocular discomfort, eye irritation
	Uncommon	punctate keratitis, conjunctivitis, anterior chamber inflammation, blepharitis, visual impairment, vision blurred, photophobia, eye pain, eye discharge, eyelid margin crusting, eyelid oedema, foreign body sensation in eyes, growth of eyelashes, eyelash thickening, dark circles under eyes
Skin and subcutaneous tissue disorders	Uncommon	rash, pruritus

Table 2: Adverse drug reactions from a clinical trial with Travoprost 40 micrograms/ml eye drops, solution

System Organ class	Frequency	Adverse drug reactions
Immune system disorders	Uncommon	hypersensitivity, seasonal allergy
Psychiatric disorders	Not known	depression, anxiety, insomnia
Nervous system disorder	Uncommon	Headache. visual field defect
	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, ectropion, periorbital oedema, eyelids pruritus, eye discharge, eyelid margin crusting, lacrimation increased, erythema of eyelid, growth of eyelashes, eyelid margin crusting
	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, mydriasis
	Not known	macular oedema, lid sulcus deepened
Ear and labyrinth disorders	Not known	vertigo, tinnitus
Cardiac disorders	Rare	heart rate decreased , palpitations
	Not known	arrhythmia, chest pain, tachycardia, bradycardia
Vascular disorders	Rare	hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	nasal congestion, throat irritation
	Rare	asthma, dyspnoea, dysphonia, cough, rhinitis allergic, oropharyngeal pain, nasal discomfort, nasal dryness
	Not known	asthma aggravated, epistaxis
Gastrointestinal disorders	Rare	dry mouth, constipation
	Not known	diarrhoea, vomiting, nausea, abdominal pain
Skin and subcutaneous tissue disorders	Uncommon	skin hyperpigmentation (periocular), hypertrichosis, hair texture abnormal
	Rare	skin discolouration, madarosis, erythema, hair colour changes, rash
	Not known	pruritus, hair growth abnormal
Musculoskeletal and connective tissue disorders	Rare	arthralgia, musculoskeletal pain
Renal and urinary disorders	Not known	dysuria, urinary incontinence

General disorders and administrative site conditions	Rare	asthenia
Investigations	Not known	prostatic specific antigen increased

4.9 Overdose

A topical overdose of TRAVATAN C® eye drops may be flushed from the eye(s) with lukewarm water.

A topical overdose is not likely to occur or to be associated with toxicity. Treatment of a suspected oral ingestion is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, prostaglandin analogues. ATC code: S01EE04.

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 (IOP) by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in humans starts about 2 hours after administration and maximum effect is reached within 12 hours. Significant lowering of IOP can be maintained for periods exceeding 24 hours with a single dose.

Data from clinical trials

In a clinical trial, patients with open-angle glaucoma or ocular hypertension treated with TRAVATAN C eye drops dosed once-daily in the evening, demonstrated IOP lowering equivalent to Travoprost 40 micrograms / ml eye drops, solution at all on-therapy visits and time points (95% CI within ±1.0 mmHg). The mean reduction from baseline in IOP ranged from 7.1 to 8.2 mmHg as summarised in Table 3. The mean percent reductions in IOP from baseline to each study visit and assessment time point ranged from 28.4% to 30.7%.

Table 3: IOP Change from Baseline (mmHg) for TRAVATAN C eye drops

Visit		8 AM	10 AM	4 PM
Week 2	Mean	-8.0	-7.3	-7.1
(N=442)	95% CI	(-8.3, -7.7)	(-7.6, -7.0)	(-7.4, -6.8)
Week 6	Mean	-8.1	-7.4	-7.2
(N=440**)	95% CI	(-8.4, -7.9)	(-7.6, -7.1)	(-7.5, -6.9)
Month 3	Mean	-8.2	-7.5	-7.1
(N=432**)	95% CI	(-8.6, -7.9)	(-7.9, -7.2)	(-7.4, -6.8)

** One subject had missing data at 8 AM at Week 6; one had missing data at 4 PM at Month 3.

An improved safety profile has been observed for TRAVATAN C eye drops when compared to the marketed Travoprost 40 micrograms / ml eye drops, solution (benzalkonium chloride preserved or polyquaternium-1 preserved). The most common adverse reaction associated with both TRAVATAN C eye drops and Travoprost 40 µg/ml eye drops, solution is hyperaemia. Hyperaemia (ocular or conjunctival) was observed in 11.8% of patients (N = 442) exposed to TRAVATAN C eye drops compared with 14.5% observed for patients exposed to Travoprost 40 µg/ml eye drops, solution, benzalkonium chloride preserved.

Based on the review of adverse events, no major difference was observed on comparison to Travoprost 0.004%. Travoprost 0.003% treatment was found to be associated with numerically less hyperemia than Travoprost 0.004% treatment.

Pharmacodynamic effects

In addition to reducing IOP, travoprost has been shown to increase optic nerve head blood flow, based on data in rabbits following 7 days of topical ocular administration (1.4 micrograms, once-daily), 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 analogues can induce the anagen phase in hair follicles and stimulate melanogenesis in the skin.

Travoprost 40 µg/ml eye drops, solution 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.

5.2 Pharmacokinetic properties

Absorption

Travoprost is an isopropyl 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 approximately 20 ng/ml of travopost free acid in aqueous humour achieved within one to two hours after topical ocular dosing of Travoprost 40 micrograms/ml eye drops, solution. Aqueous humour concentrations of travopost 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 of Travoprost 40 micrograms/ml eye drops, solution to humans, 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 20 minutes post-dose. Thereafter, plasma levels declined rapidly to below the 10 pg/ml assay quantitation limit before 1 hour post-administration. Trace plasma concentrations of travoprost may be present immediately following dosing in some subjects. 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 in non-clinical species. The systemic metabolic pathways parallel those of endogenous prostaglandin F2α which are characterised by reduction of the double bond in position C13-C14, oxidation of the 15-hydroxyl to a ketone and β-oxidative cleavages of the carboxylic acid side chain.

EliminationFollowing administration of radiolabelled travoprost to rats, approximately 95% of the dose was eliminated with 24 hours. Approximately 75% of the dose was eliminated in the faeces 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)

Pharmacokinetic and pharmacodynamic relationship has not been established for travoprost after topical ocular administration.

Pharmacokinetics in special populations

Renal impairment

The systemic pharmacokinetics of travoprost 40 micrograms/ml eye drops, solution has been studied in patients with mild to severe renal impairment (creatinine clearance as low as 14 ml/min). No dosage adjustment is necessary in these patients.

Hepatic impairment

The systemic pharmacokinetics of travoprost 40 micrograms/ml eye drops, solution has been studied in patients with mild to severe hepatic impairment. No dosage adjustment is necessary in these patients.

5.3 Preclinical 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. 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).

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.

Increased palpebral fissure observed in monkeys were not seen in rabbits or in the clinical trials with travoprost products and is considered to be species specific.

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 3H-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).

Data to evaluate a potential effect on the environment are currently limited.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

mannitol (E421), polyoxyethylene hydrogenated castor oil 40 (HCO-40), propylene glycol (E1520), sodium chloride, boric acid (E284), Polyquaternium-1, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Specific in vitro interaction studies were performed with travoprost and medicinal products containing thiomersal. No evidence of precipitation was observed.

6.3 Special precautions for storage

Do not store above 30°C

Do not use this medicine after the expiry date which is stated on the packaging.

Discard 28 days after first opening. Once opened, the bottle may be stored at not more than 30 °C. Keep this medicine out of the sight and reach of children.

6.4 Nature and contents of container

Plastic bottle with dispensing plug and closure, containing 1.5 ml or 2.5 ml, presented in an overwrap.

6.5 Special precautions for disposal

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

Novartis Pharma AG, Basel, Switzerland