SUMMARY OF RODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRAVAPRESS 40 microgram/ml oogdruppels, oplossing

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 40 micrograms of travoprost.

Excipient(s) with known effect:

Each mL of solution contains 10 microgram of polyquaternium-1, 7.5 mg of propylene glycol (E 1520), 2 mg of macrogolglycerol hydroxystearate 40 (see section 4.4.)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution. (Eye drops)
Clear, colourless solution.

pH 6.3 to 7.3;
osmolality 265 - 320 mOsmol/kg

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).

Decrease of elevated intraocular pressure in paediatric patients aged 2 months to < 18 years with ocular hypertension or paediatric 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 <TRAVOPROST> 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 travoprost eye drops, the other medicinal product should be discontinued and travoprost eye drops should be started the following day.

Patients with hepatic and renal impairment
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 (see section 5.2).

Paediatric population
Travoprost 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 (see section 5.1).

The safety and efficacy of Travoprost 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, please refer to section 4.4.

After cap is removed, if the tamper evident snap collar is loose, remove before using the medicinal 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.

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 F_{2a} 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 travoprost eye drops and wait 15 minutes after instillation of the dose before reinsertion.

Excipients
<TRAVOPROST> contains propylene glycol (E 1520) which may cause skin irritation.
<TRAVOPROST> contains macrogolglycerol hydroxystearate 40 which may cause skin reactions.

Paediatric population
Efficacy and safety data in the age group 2 months to < 3 years (9 patients) is limited (see section 5.1). 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.

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. Travoprost 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 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 eye drops, the most common adverse reactions were hyperaemia and iris hyperpigmentation, occurring in approximately 20% and 6% of patients respectively.

Tabulated list of adverse reactions
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 <1/1000), or 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.

System Organ Class	**Frequency**	**Adverse reactions**
Immune system disorders	Uncommon	hypersensitivity, seasonal allergy
Phychiatric disorders	Not known	depression, anxiety, insomnia
Nervous system disorder	Uncommon	headache
	Rare	dizziness, visual field defect, 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,

	Rare	iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids, conjunctival oedema, 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	vertigo, 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 disorder	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	Rare	peptic ulcer reactivated, gastrointestinal disorder, constipation, dry mouth
	Not known	diarrhoea, abdominal pain, nausea, vomiting
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, arthralgia
Renal and urinary disorders	Not known	dysuria, urinary incontinence

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

Paediatric Population
In a 3 month phase 3 study and a 7 days pharmacokinetic study, involving 102 paediatric patients exposed to travoprost, 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 (see section 5.1). 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.

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 - to be completed nationally].

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 $F_{2\alpha}$ 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 (polyquaternium preserved) 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 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.

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

Travoprost 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.

Paediatric population
The efficacy of travoprost 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 (see Table 1).

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.

Table 1: Comparison of Mean IOP Change from Baseline (mmHg) at Week 12

Travoprost		**Timolol**			
N	**Mean (SE)**	**N**	**Mean (SE)**	**Mean Difference[a]**	**(95% CI)**
53	-6.4 (1.05)	60	-5.8 (0.96)	-0.5	(-2.1, 1.0)

SE = Standard Error; CI = Confidence Interval;
[a]Mean difference is Travoprost – Timolol. Estimates based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where primary diagnosis and baseline IOP stratum are in the model.

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/mL 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 $F_{2\alpha}$ 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.

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 52.0 pg/mL. While most of the plasma data across all studies was non-quantifiable, 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 is extremely low across all age groups evaluated.

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

Boric acid (E 284)
Sodium chloride
Mannitol (E 421)
Macrogolglycerol hydroxystearate 40
Polyquaternium-1
Propylene glycol (E 1520)
Sodium hydroxide (E 524) and/or hydrochloric acid (E 507) (for pH adjustment)
Purified water

6.2 Incompatibilities

Not applicable.
Specific *in vitro* interaction studies were performed with travoprost and medicinal products containing thiomersal. No evidence of precipitation was observed.

6.3 Shelf life

2 years
Discard 4 weeks after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

Transparent LDPE bottles with transparent LDPE dropper insert and light blue, tamper-proof HDPE screw cap.

Pack sizes:
1 x 2.5 mL
3 x 2.5 mL
6 x 2.5 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

S.C. Rompharm Company S.R.L.
1A Eroilor Street
Otopeni 075100, Ilfov, Roemenië

8. MARKETING AUTHORISATION NUMBER(S)

RVG 114244

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum can eerste verlening van de vergunning: 21 februari 2015
Datum van laatste verlenging: 20 januari 2020

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 2, 4.1, 4.2, 4.4, 4.7, 4.8, 5.1, 5.2 en 9: 7 november 2020