SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DRASOTER 0.004% Eye Drops, Solution
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains;
Active substance:
Travoprost ..... 0.04 mg

Excipient(s):
Propylene glycol ..... 7.5 mg
PEG-40 hydrogenated castor oil ..... 2 mg
Benzalkonium chloride ..... 0.020 mg

For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Eye drops
Clear and colorless solution, free from particles

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indicated for decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma (see section 5.1).

4.2 Posology and method of administration

Posology/frequency and duration of administration:
The dose of DRASOTER is one drop in the conjunctival sac of the affected eye(s) once a day. Optimal effect is achieved when 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 fewer systemic side effects.

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, the treatment should continue as planned with the next dose. The amount of the dose administered to the affected eye should not exceed one drop daily.

If switching from another anti-glaucoma agent to DRASOTER, discontinue the other agent and continue treatment with DRASOTER the following day.

Method of administration:
For ocular use only.

Patients should remove the sachet before the first use. To prevent contamination of the dropper

tip and the solution, care should be taken to avoid contact of the dropper tip with the eyelids, surrounding areas, or other surfaces.

Additional information on special populations:
Renal/Hepatic impairment:
DRASOTER 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 required in these patients.

Pediatric population:
The efficacy and safety of DRASOTER have not been established in patients under 18 years of age, and until more detailed data are available, the use of DRASOTER in pediatric population is not recommended.

Geriatric population:
No special usage recommendations.

4.3 Contraindications
Contraindicated in case of hypersensitivity to travoprost or any of the other substances of the medicine.

4.4 Special warnings and precautions for use
DRASOTER may change eye color over time by increasing the number of melanosomes (pigment granules) in melanocytes. Patients should be informed of the possibility of permanent changes in eye color before starting treatment. Unilateral treatment may result in permanent heterochromia. The long-term effects on melanocytes and the consequences are currently unknown. Changes in iris color occur gradually and may not be noticeable for months or even years. This change has been observed predominantly in patients with mixed-colored irises, such as blue-brown, gray-brown, yellow-brown, and green-brown irises, but 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. No further increase in brown iris pigment has been observed after discontinuation of treatment.

In controlled clinical studies, the use of travoprost has been associated with skin darkening around the eyes and/or eyelids in 0.4% of patients.

DRASOTER may cause changes in the eyelashes of the treated eye(s); these changes have been observed in approximately half of patients in clinical studies and include increased length, thickness, pigmentation, and/or number of lashes. The mechanism of eyelash changes and their long term consequences are currently unknown.

In monkey studies, travoprost has been shown to cause slight enlargement of the palpebral fissure. However, this effect was not observed in clinical studies and is assumed to be species-specific.

There is no experience of DRASOTER 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. DRASOTER should therefore be used with caution in patients with active intraocular inflammation.

Macular edema has been reported in treatments with prostaglandin F_{2a} analogs. Caution is recommended when using DRASOTER 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.

Periorbital and eyelid changes, including deepening of the eyelid sulcus have been reported with prostaglandin analogues.

Since transdermal absorption of travoprost has been shown in rabbits, skin contact with DRASOTER must be avoided.

DRASOTER should be used with caution in patients with intraocular inflammation, like those with known risk factors for iritis/uveitis.

Prostaglandins and prostaglandin analogs are biologically active materials that can be absorbed through the skin. Pregnant women or women attempting to conceive should take 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.

Patients must be instructed to remove their contact lenses before applying DRASOTER and to wait for 15 minutes after instillation of the dose before reinsertion.

Data on the efficacy and safety in infants aged 2 months and children under 3 years old (9 patients) are limited. No data are available for infants under 2 months of age.

In children under 3 years of age with primary congenital glaucoma (PCG) who have undergone surgery (e.g., trabeculotomy/goniotomy), it is first-line treatment.

Long-term safety data in the pediatric population are not available.

The propylene glycol in DRASOTER may cause skin irritation.

The PEG-40 hydrogenated castor oil in DRASOTER may cause skin reactions.

The benzalkonium chloride in DRASOTER may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses before administration and wait at least 15 minutes before reinserting them. It is known to cause discoloration of soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

The interaction of DRASOTER with other medicines has not yet been clearly evaluated.

4.6 Fertility, pregnancy and lactation

General recommendation

Pregnancy category: C

Women of childbearing potential / Birth control (Contraception)
DRASOTER should not be used in women of childbearing potential who do not use adequate contraception (see section 5.3).

Pregnancy
There is insufficient data regarding the use of DRASOTER in pregnant women.

Travoprost has harmful pharmacological effects during pregnancy and/or on the fetus/newborn. Studies in animals have shown that travoprost causes reproductive toxicity.

DRASOTER should not be used during pregnancy unless necessary.

Lactation
It is not known whether travoprost is excreted in human milk. Studies in animals have shown that travoprost and its metabolites are excreted in milk. When deciding whether breastfeeding should be stopped or whether DRASOTER treatment should be stopped or avoided, the benefits of breastfeeding for the child and the benefits of DRASOTER treatment for the breastfeeding mother should be considered. DRASOTER is not recommended for use in breastfeeding mothers.

Reproductive ability/Fertility
No studies have been conducted on the effect of DRASOTER on fertility.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to humans is not known.

4.7 Effects on ability to drive and use machines
As with any eye drop, blurred vision may affect the ability to drive or use machinery. If blurring of vision occurs during instillation, patients should wait for their vision to clear before driving or operating machinery.

4.8 Undesirable effects
In clinical trials of travoprost, the most common adverse reactions were ocular hyperemia and iris hyperpigmentation, occurring in approximately 20% and 6% of patients, respectively.

The undesirable effects listed below have been evaluated as treatment-related (monotherapy with Travoprost eye drops) and are classified as follows:
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); not known (cannot be estimated from the available data).

Within each frequency group, undesirable effects are presented in decreasing order of seriousness.

Infections and infestations
Rare: Herpes simplex, herpetic keratitis

Immune system disorders
Uncommon: Hypersensitivity, seasonal allergy

Psychiatric disorders
Not known: Depression, anxiety

Nervous system disorders
Uncommon: Headache, dizziness, visual field disturbances
Rare: Dysgeusia, dizziness

Eye disorders
Very common: Ocular hyperemia
Common: Iris hyperpigmentation, eye pain, eye irritation, dry eyes, eye itching, ocular discomfort
Uncommon: Corneal erosion, uveitis, iritis, anterior chamber inflammation, keratitis, punctate keratitis, photophobia, eye discharge, blepharitis, erythema of the eyelid, periorbital edema, eyelid itching, decreased visual acuity, blurred vision, increased lacrimation, conjunctivitis, ectropion cataract, crusting at the edge of the eyelid, eyelash lengthening, eyelash discoloration, asthenopia
Rare: Iridocyclitis, eye inflammation, photopsia, eyelid eczema, conjunctival edema, halo vision, conjunctival follicles, reduced eye sensitivity, inflammation of the meibomian glands, anterior chamber pigmentation, mydriasis, eyelash thickening
Not known: Macular edema, deepened eye

Ear and inner ear disorders
Not known: Vertigo, tinnitus

Cardiac disorders
Uncommon: Palpitations
Rare: Irregular heart rhythm, decreased heart rate
Not known: Chest pain, bradycardia, tachycardia

Vascular disorders
Rare: Decreased diastolic blood pressure, increased systolic blood pressure, hypotension, hypertension

Respiratory, thoracic, and mediastinal disorders
Uncommon: Dyspnea, asthma, nasal congestion, throat irritation
Rare: Respiratory disorders, pharyngeal and laryngeal pain, cough, dysphonia
Not known: Worsened asthma

Gastrointestinal disorders
Rare: Peptic ulcer reactivation, gastrointestinal disturbances, constipation, dry mouth
Not known: Diarrhea, abdominal pain, nausea

Skin and subcutaneous tissue disorders
Uncommon: Skin hyperpigmentation (periocular), skin discoloration, hair follicle abnormalities, hypertrichosis
Rare: Allergic dermatitis, contact dermatitis, erythema, body hair color changes, madarosis
Not known: Itching, abnormal body hair growth.

Musculoskeletal, connective tissue, and bone disorders
Rare: Musculoskeletal pain
Not known: Arthralgia

Kidney and urinary tract disorders
Not known: Dysuria (painful urination), urinary incontinence

General disorders and administration site conditions
Uncommon: Asthenia

Investigations
Not known: PSA increase

Undesirable effects identified in post-marketing experience were not previously reported in clinical trials with monotherapy using travoprost.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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.

4.9 Overdose
No overdose cases have been reported. A topical overdose is not expected to occur or to be associated with toxicity. In case of a topical overdose of DRASOTER, the eyes should be rinsed with lukewarm water. The treatment of 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: S01EE04

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.

As a primary treatment, a single daily dose of 0.004% Travoprost ophthalmic solution has reduced intraocular pressure by 7 to 9 mmHg. In three well-controlled studies, stable diurnal reductions in intraocular pressure were achieved just 2 weeks after treatment initiation and were maintained over 6 to 12 months of treatment.

Pharmacodynamic effects

In addition to reducing intraocular pressure, Travoprost has been shown to increase optic nerve head blood flow and reduce tear film instability and tear secretion. Travoprost does not affect respiratory rate/volume or systolic blood pressure during exercise and recovery. Prostaglandin $F_{2\alpha}$ analogs can induce the anagen phase in hair follicles and stimulate melanogenesis in the skin.

Clinical efficacy and safety
In a clinical study, patients with open-angle glaucoma or ocular hypertension treated with a single evening dose of Travoprost ophthalmic solution showed reductions of 8 to 9 mmHg (approximately 33%) in intraocular pressure from baseline levels of 24 to 26 mmHg.

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 has increased optic nerve head blood flow in rabbits for up to 7 days following topical ocular application (1.4 micrograms, once daily).

Pediatric 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 4 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 the mean IOP changes from baseline at the 12th week

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)

SE = Standard Error, CI = Confidence Interval
[a] The mean difference is Travoprost – Timolol. Estimates based on least square means are derived from a statistical model that includes the primary diagnosis and baseline IOP strata corresponding to the IOP measurements in the patient population.

5.2 Pharmacokinetic properties

General characteristics

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 showed that Travoprost reached peak free acid concentrations of 20 nanograms/milliliter in the aqueous humor within one to two hours after topical application. Aqueous humor concentrations decrease with a half-life of approximately 1.5 hours. Additionally, low doses of free Travoprost acid were found in the plasma after topical dosing.

Distribution:

Following topical ocular administration of Travoprost to healthy volunteers, low systemic exposure to active free acids was observed. Plasma concentrations of active free acid were observed to be 25 pg/ml or less within 10 to 30 minutes post-dosing. Subsequently, plasma levels quickly decreased below the 10 pg/ml measurement limit within one hour after administration. Due to the low plasma concentrations and rapid elimination following topical dosing, the elimination half-life of active free acids in humans cannot be determined.

Biotransformation:

The major clearance route for travoprost and its free acids in non-clinical species is metabolism. The primary route of elimination for travoprost and the active free acid is metabolism. 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:

The free acid of travoprost and its metabolites are primarily eliminated through the kidneys. Travoprost has been studied in patients with mild to severe hepatic insufficiency and renal insufficiency (with creatinine clearance as low as 14 ml/min). Dose adjustment is not required in these patients.

Linearity/Non-linearity:

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

Pharmacokinetic/pharmacodynamic relationship(s):

No pharmacokinetic/pharmacodynamic relationship was identified for travoprost following topical ocular administration.

Characteristics in patients

Pharmacokinetics in special populations:

The systemic pharmacokinetics of 0.004% Travoprost eye drops have been studied in patients with mild to moderate hepatic insufficiency, as well as in those with mild to moderate renal insufficiency (with a creatinine clearance of 14 ml/min). There is no need for dose adjustment in these populations.

Pediatric pharmacokinetics:

The systemic pharmacokinetics of travoprost after topical ocular administration in patients aged 2 months to under 18 years revealed concentrations similar to those in adults, with the highest plasma samples being below the 10 pg/ml quantification limit.

5.3 Preclinical safety data

Ocular toxicity studies in monkeys showed that administering travoprost at a dose of 0.45 micrograms twice a day could lead to an increase in palpebral fissure. Travoprost has been applied topically to the right eye of monkeys at doses up to 0.012% twice daily for one year without causing any 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

Benzalkonium chloride
Propylene glycol
PEG-40 hydrogenated castor oil
Boric acid
Sodium chloride
Mannitol
Sodium hydroxide
Hydrochloric acid
Water for injection

6.2 Incompatibilities

None reported.
Specific *in vitro* interaction studies with thiomersal-containing medical products have been conducted with Travoprost. No precipitation was observed.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25°C. Ensure the bottle cap is tightly closed when not in use.

Once opened, should be used within 4 weeks if stored at room temperature below 25°C.

6.5 Nature and contents of container

The primary packaging material is a dropper, transparent, low density polyethylene bottle and a twist-off white polypropylene cap. The box contains one 2.5 ml bottle of solution with a peelable sachet and instructions for use.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

2019/14

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10.01.2019
Date of latest renewal:

10. DATE OF REVISION OF THE SPC