Name of the medicinal product

Ophtatrov 40 micrograms/mL eye drops, solution

2. Qualitative and quantitative composition

Each mL of solution contains 40 micrograms of travoprost .

Excipient(s) with known effect:

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Ophthalmic solution

Clear, colourless solution free from visible particles.

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 Ophtatrov 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 Optatrov , the other medicinal product should be discontinued and Ophtatrov should be started the following day.

Hepatic and renal impairment

Ophtatrov 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

Ophtatrov 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 Ophtatrov 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.

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.

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

Ophtatrov 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.

Ophtatrov 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.

Ophtatrov 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 Ophtatrov 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. Ophtatrov should therefore be used with caution in patients with active intraocular inflammation.

Aphakic patients

Macular oedema has been reported during treatment with prostaglandin F2a analogues. Caution is recommended when using Ophtatrov 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, Ophtatrov should be used with caution.

Contact with the skin

Skin contact with Ophtatrov must be avoided as transdermal absorption of Ophtatrov 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 Ophtatrov and wait 15 minutes after instillation of the dose before reinsertion.

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.

Ophtatrov contains Benzalkonium chloride:

- May cause eye irritation
- Avoid contact with soft contact lenses
- Remove contact lenses prior to application and wait at least 15 minutes before reinsertion
- Known to discolour soft contact lenses

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
OPHTATROV must not be used in women of child bearing age/potential unless adequate contraceptive measures are in place (see section 5.3).
Pregnancy
Ophtatrov has harmful pharmacological effects on pregnancy and/or the fetus/new-born child. OPHTATROV should not be used during pregnancy unless clearly necessary.
Breastfeeding
It is unknown whether Ophtatrov from the eye drops is excreted in human breast milk. Animal studies have shown excretion of Ophtatrov and metabolites in breast milk. The use of OPHTATROV by breast-feeding mothers is not recommended.
Fertility
There are no data on the effects of Ophtatrov on human fertility. Animal studies showed no effect of Ophtatrov on fertility at doses more than 250 times the maximum recommended human ocular dose.
4.7 Effects on ability to drive and use machines
Ophtatrov 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 , the most common adverse reactions were ocular hypearemia 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<1/1,000), 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 .

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Uncommon	hypersensitivity, seasonal allergy
Psychiatric 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 disorders	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 administration site conditions	Rare	asthenia
Investigations	Not known	prostatic specific antigen increased

Paediatric Population

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 and growth of eyelashes, keratitis, lacrimation increase and photophobia.

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: PV.center @eda.mohealth.gov.eg

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 Ophtatrov 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.

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 OPHTATROV. Aqueous humour concentrations declined with a half-life of approximately 1.5 hours.

Distribution

Following topical ocular administration of OPHTATROV 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 Ophtatrov 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

Ophtatrov free acid and its metabolites are mainly excreted by the kidneys. Ophtatrov 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.

6. Pharmaceutical particulars

6.1 List of excipients

Each 1 ml contains: Benzalkonium chloride, Macrogolglycerol hydroxystearate, Sorbitol powder, Disodium Edetate , Disodium hydrogen phosphate dihydrate , Sodium dihydrogen phosphate dihydrate , Sodium hydroxide/Hydrochloric acid , Purified water

6.2 Incompatibilities

None known.

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

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Before opening: Store in a temperature not exceeding 30 °C.

After opening: used within 30 days when stored at temperature not exceeding 30 °C.

6.5 Nature and contents of container

Carton box containing 2.5 ml ophthalmic solution in round sterile white plastic LDPE bottle with white LDPE plastic dropper plug and sterile white HDPE screw cap with insert leaflet.

6.6 Special precautions for disposal and other handling

No special requirements.

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