

1. Name of the medicinal product

Ophtatrov plus 40 micrograms/mL + 5 mg/mL eye drops, solution.

2. Qualitative and quantitative composition

Each mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate).

Excipient(s) with known effect:

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Ophthalmic solution

Clear, colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

Ophtatrov plus is indicated in adults for the decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (see section 5.1).

4.2 Posology and method of administration

Posology

Use in adults, including the older population

The dose is one drop of Ophtatrov plus in the conjunctival sac of the affected eye(s) once daily, in the morning or evening. It should be administered at the same time each day.

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.

Special Populations

Hepatic and renal impairment

No studies have been conducted with Ophtatrov plus eye drops in patients with hepatic or 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 dose adjustment was necessary in these patients.

Patients with hepatic or renal impairment are unlikely to require dose adjustment with Ophtatrov plus (see section 5.2).

Paediatric population

The safety and efficacy of Ophtatrov plus in children and adolescents below the age of 18 years have not been established. No data are available.

Method of administration

For ocular use.

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.

When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity (see section 4.4).

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).

When substituting another ophthalmic antiglaucoma medicinal product with Ophtatrov plus, the other medicinal product should be discontinued and Ophtatrov plus should be started the following day.

Patients must be instructed to remove soft contact lenses prior to application of Ophtatrov plus and wait 15 minutes after instillation of the dose before reinsertion (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substances, or to any of the excipients listed in section 6.1.

Hypersensitivity to other beta-blockers.

Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease.

Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second or third degree atrioventricular block not controlled with pace-maker. Overt cardiac failure, cardiogenic shock. Severe allergic rhinitis and corneal dystrophies.

4.4 Special warnings and precautions for use

Systemic effects

Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking medicinal products may occur. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

Ophthalmic beta-blockers should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD) and only if the potential benefit outweighs the potential risk.

Hypoglycaemia/diabetes

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Muscle weakness

Beta-adrenergic blocking medicinal products have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (eg, diplopia, ptosis and generalised weakness).

Corneal diseases

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol, acetazolamide) after filtration procedures.

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol is given to the patients already receiving a systemic beta-blocking medicinal product. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 4.5).

Surgical anaesthesia

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline. The anaesthesiologist should be informed when the patient is receiving timolol.

Hyperthyroidism

Beta-blockers may mask the signs of hyperthyroidism.

Skin contact

Prostaglandins and prostaglandin analogues are biologically active substances 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.

Anaphylactic reactions

While taking beta-blockers, patients with history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

Concomitant therapy

Timolol may interact with other medicinal products (see section 4.5).

The use of two local prostaglandins is not recommended.

Ocular effects

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 become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

In controlled clinical trials, periorbital and/or eyelid skin darkening in association with the use of travoprost has been reported.

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.

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 plus 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.

Macular oedema has been reported during treatment with prostaglandin F_{2α} analogues. Caution is recommended when using Ophtatrov plus 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.

In patients with known predisposing risk factors for iritis/uveitis, and in patients with active intraocular inflammation, Ophtatrov plus can be used with caution.

Excipients

Patients must be instructed to remove contact lenses prior to application of Ophtatrov plus and wait 15 minutes after instillation of the dose before reinsertion (see section 4.2).

Ophtatrov plus contains Benzalkonium chloride :

- May contains 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 specific drug interaction studies have been performed with travoprost or timolol.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic medicinal products. Beta-blockers can mask the signs and symptoms of hypoglycaemia (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

Ophtatrov plus must not be used in women who may become pregnant 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. There are no or limited amount of data from the use of Ophtatrov plus or the individual components in pregnant women. Timolol should not be used during pregnancy unless clearly necessary.

Epidemiological studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If Ophtatrov plus is administered until delivery, the neonate should be carefully monitored during the first days of life.

Ophtatrov plus should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Breastfeeding

It is unknown whether travoprost from eye drops is excreted in human breast milk. studies have shown excretion of travoprost and metabolites in breast milk. Timolol is excreted in breast milk having the potential to cause serious adverse reactions in the breastfeeding infant. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

The use of Ophtatrov plus by breast-feeding women is not recommended.

Fertility

There are no data on the effects of Ophtatrov plus on human fertility. Animal studies showed no effect of travoprost or timolol 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 plus has no or negligible influence on the ability to drive and use machines. As with any eye drop, temporary blurred vision or other visual disturbances may occur. 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 studies involving 2170 patients treated with Ophtatrov plus the most frequently reported treatment-related adverse reaction was ocular hyperaemia (12.0%).

Tabulated summary of adverse reactions

The following adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$), very rare ($< 1/10,000$), or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

| System Organ Class | Frequency | Adverse Reactions |
|--------------------------|-----------------|--|
| Immune system disorders | <u>Uncommon</u> | hypersensitivity. |
| Psychiatric disorders | Rare | nervousness. |
| | Not known | depression. |
| Nervous system disorders | Uncommon | dizziness, headache. |
| | Not known | cerebrovascular accident, syncope, paraesthesia. |
| Eye disorders | Very common | ocular hyperaemia |
| | Common | punctate keratitis, , eye pain, visual disturbance, vision blurred, dry eye, eye pruritus, ocular discomfort, eye irritation. |
| | Uncommon | keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes eye allergy, conjunctival oedema, eyelid oedema. |
| | Rare | corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis. |
| | Not known | macular oedema, eyelid ptosis, corneal disorder. |
| Cardiac disorders | Uncommon | bradycardia.. |
| | Rare | arrhythmia, heart rate irregular |
| | Not known | cardiac failure, tachycardia, chest pain palpitations. |

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|--|-----------------------|---|
| Vascular disorders | Uncommon Not known | hypertension, hypotension. oedema peripheral |
| Respiratory, thoracic and mediastinal disorders | Uncommon | dyspnoea, postnasal drip. |
| | Rare | dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort |
| | Not known | asthma. |
| Gastrointestinal disorders | Not known | dysgeusia |
| Hepatobiliary disorders | Rare | alanine aminotransferase increased, aspartate aminotransferase increased. |
| Skin and subcutaneous tissue disorders | Uncommon | dermatitis contact, hypertrichosis |
| | Rare | urticaria, skin discolouration, alopecia, skin hyperpigmentation (periocular). |
| | Not known | rash. |
| Musculoskeletal and connective tissue disorders | Rare | pain in extremity. |
| Renal and urinary disorders | Rare | chromaturia. |
| General disorders and administration site conditions | Rare | thirst, fatigue. |

Additional adverse reactions that have been seen with one of the active substances and may potentially occur with Ophtatrov plus:

Travoprost

| <u>System Organ Class</u> | <u>MedDRA preferred Term</u> |
|--|---|
| Eye disorders | uveitis, conjunctival disorder, conjunctival follicles, iris hyperpigmentation. |
| Skin and subcutaneous tissue disorders | skin exfoliation. |

Timolol

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Additional listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers. The incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see 4.2.

| <u>System Organ Class</u> | <u>MedDRA preferred Term</u> |
|------------------------------------|--|
| Immune system disorders | Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis. |
| Metabolism and nutrition disorders | Hypoglycaemia. |
| Psychiatric disorders | Insomnia, nightmares, memory loss. |
| Nervous system disorders | Cerebral ischaemia, increases in signs and symptoms of myasthenia gravis. |
| Eye disorders | signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), choroidal detachment following filtration surgery (see 4.4 Special warnings and |

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| | special precautions for use), decreased corneal sensitivity, diplopia. |
| Cardiac disorders | Chest pain, palpitations, oedema, congestive heart failure, atrioventricular block, cardiac arrest. |
| Vascular disorders | Raynaud's phenomenon, cold hands and feet. |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm (predominantly in patients with pre-existing bronchospastic disease). |
| Gastrointestinal disorders | Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting. |
| Skin and subcutaneous tissue disorders | Psoriasiform rash or exacerbation of psoriasis. |
| Musculoskeletal and connective tissue disorders | Myalgia. |
| Reproductive system and breast disorders | Sexual dysfunction, decreased libido. |
| General disorders and administration site conditions | Asthenia. |

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

A topical overdose with Ophtatrov plus is not likely to occur or to be associated with toxicity. In case of accidental ingestion, symptoms of overdose from systemic beta blockade may include bradycardia, hypotension, bronchospasm and heart failure. If overdose with Ophtatrov plus occurs, treatment should be symptomatic and supportive. Timolol does not dialyse readily.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; Antiglaucoma preparations and miotics, ATC code: S01ED51.

Mechanism of action

Ophtatrov plus contains two active substances: travoprost and timolol maleate. These two components lower intraocular pressure by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone. Travoprost, a prostaglandin F_{2α} analogue, is a full agonist which is highly selective and 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 IOP in man starts within approximately 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.

Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Secondary pharmacology

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

Pharmacodynamic effects

Clinical effects

In a twelve-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 25 to 27 mmHg, the mean IOP-lowering effect of travoprost & timolol dosed once-daily in the morning was 8 to 10 mmHg. The non-inferiority of travoprost & timolol as compared to latanoprost 50 micrograms/ml + timolol 5 mg/ml in the mean IOP reduction was demonstrated across all time-points at all visits.

In a three-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 27 to 30 mmHg, the mean IOP-lowering effect of travoprost & timolol dosed once-daily in the morning was 9 to 12 mmHg, and was up to 2 mmHg greater than that of travoprost 40 micrograms/ml dosed once-daily in the evening and 2 to 3 mmHg greater than that of timolol 5 mg/ml dosed twice daily. A statistically superior reduction in morning mean IOP (8AM-24 hours after the last dose of travoprost & timolol) was observed compared to travoprost at all visits throughout the study.

In two three-month, controlled clinical studies in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 23 to 26 mmHg, the mean IOP-lowering effect of Ophtatrov plus dosed once-daily in the morning was 7 to 9 mmHg. Mean IOP reductions were non-inferior, although numerically lower, to those achieved by concomitant therapy with travoprost 40 micrograms/ml dosed once-daily in the evening and timolol 5 mg/ml dosed once-daily in the morning.

In a 6-week, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and baseline mean IOP of 24 to 26 mmHg, the mean IOP-lowering effect of travoprost & timolol (polyquaternium-1-preserved) dosed once-daily in the morning was 8 mmHg and equivalent to that of Ophtatrov plus (benzalkonium chloride-preserved).

Inclusion criteria were common across the studies, with the exception of the IOP entry criteria and response to previous IOP therapy. The clinical development of Ophtatrov plus included both patients naive and on therapy. Insufficient responsiveness to monotherapy was not an inclusion criterion.

Existing data suggest that evening dosing might have some advantages in the mean IOP reduction. Consideration should be given to patient convenience and their likely compliance when recommending morning vs. evening dosing.

5.2 Pharmacokinetic properties

Absorption

Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes rapid ester hydrolysis in the cornea to the active free acid. Following once-daily administration of Ophtatrov plus PQ in healthy subjects (N=22) for 5 days, travoprost free acid was not quantifiable in plasma samples from the majority of subjects (94.4%) and generally was not detectable one hour after dosing. When measurable (≥ 0.01 ng/ml, the assay limit of quantitation), concentrations ranged from 0.01 to 0.03 ng/ml. The mean timolol steady-state C_{max} was 1.34 ng/ml and T_{max} was approximately 0.69 hours after once-daily administration of Ophtatrov plus.

Distribution

Travoprost free acid can be measured in the aqueous humour during the first few hours in animals and in human plasma only during the first hour after ocular administration of travoprost & timolol. Timolol can be measured in human aqueous humour after ocular administration of timolol and in plasma for up to 12 hours after ocular administration of travoprost & timolol.

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.

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a

second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma $t_{1/2}$ of timolol is 4 hours after ocular administration of travoprost & timolol .

Elimination

Travoprost free acid and its metabolites are mainly excreted by the kidneys. Less than 2% of an ocular dose of travoprost was recovered in urine as free acid. Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20% of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites.

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 dehydrate , Sodium hydroxide/Hydrochloric acid , Purified water .

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in a temperature not exceeding 30 °C

After opening : used within 30 days at a temperature not exceeding 30 °C

6.5 Nature and contents of container

Carton box contains round sterile white plastic bottle (LDPE) containing 2.5 ml solution, with white dropper plug (LDPE) and sterile white screw cap (HDPE) and an insert leaflet.

Manufactured by Minapharm for pharmaceutical & chemical industries