1. Tradename(s)

DUOTRAV® Travoprost 40 µg/mL/Timolol Maleate 5 mg/mL Eye drops, Solution.

2. Description and composition

Pharmaceutical form(s)

Eye drops, solution.

Active substance(s)

Polyquad-preserved formulation: One mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate).

Excipients

Polyquad-preserved formulation: Boric acid, mannitol, polyoxyethylene hydrogenated castor oil 40 (HCO-40), polyquaternium-1 (POLYQUAD), propylene glycol, sodium chloride, sodium hydroxide and/ or hydrochloric acid (for pH adjustment), and purified water.

3. Indications

DUOTRAV® eye drops contains travoprost, a prostaglandin analogue, and timolol, a non-selective beta-adrenergic receptor blocking agent (beta-blocker).

DUOTRAV eye drops is indicated for the decrease of intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta blockers or prostaglandin analogues (see sections11 and 12).

4. Dosage regimen and administration

Dosage regimen

Adults (including the elderly (65 years and above))

The recommended dosage is one drop 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.

The dosage of DUOTRAV eye drops should not exceed once daily since it has been shown that more frequent administration of prostaglandin analogues may decrease the IOP lowering effect.

General target population

Special populations

Pediatric patients (below 18 years)

The use of DUOTRAV eye drops in pediatric patients is currently not recommended. The safety and efficacy of the use of DUOTRAV eye drops in children and adolescents below the age of 18 years have not been established. No data are available.

Geriatric patients (65 years and above)

No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

Hepatic and renal impairment

No studies have been conducted with DUOTRAV eye drops or with timolol 5 mg/ml eye drops in patients with renal and hepatic impairment.

Travoprost alone 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 a dose adjustment with DUOTRAV eye drops.

Method of administration

For ocular use only.

If a dose is missed, treatment should be continued with the next dose as normal. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

When substituting another ophthalmic antiglaucoma medicinal product with DUOTRAV eye drops, the other medicinal product should be discontinued and DUOTRAV eye drops should be started the following day.

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.

Patients must be instructed to remove contact lenses prior to application of DUOTRAV eye drops and wait at least 15 minutes before reinsertion.

5. Contraindications

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- 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, overt cardiac failure or cardiogenic shock.

6. Warnings and precautions

General

- Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. Due to the beta-adrenergic blocking component in ophthalmic timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking agents may occur.
- 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.

Cardiac disorders

- Rarely deaths in association with cardiac failure have been reported following systemic or ophthalmic administration of timolol maleate.

- 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 for adverse reactions.

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.

Hypoglycaemia/diabetes

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

Hyperthyroidism

- Beta-blockers may also mask the signs of hyperthyroidism.

Muscle weakness

- Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalized weakness).

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.

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. The change in iris colour occurs slowly and may not be noticeable for months to years.

• Periorbital and/or eyelid skin darkening has been reported in association with the use of travoprost.

• Travoprost may gradually change eyelashes in the treated eye(s); these changes include increased length, thickness, pigmentation, and/or number of lashes.

• There is no experience of DUOTRAV eye drops 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 edema has been reported during treatment with prostaglandin F2a analogues. Use travoprost with caution in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema.

• DUOTRAV eye drops should be used with caution in patients with active intraocular inflammation, as well as patients with predisposing risk factors for uveitis.

• Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues.

Choroidal detachment

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

Surgical anaesthesia

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

Adverse drug reactions (or constellations of reactions)

Interactions

Other beta-blocking agents

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be exaggerated when timolol is given to the patients already receiving a systemic beta-blocking agent. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking agents is not recommended (see section 8).

7. Adverse drug reactions

Tabulated summary of adverse drug reactions from clinical trials

The following adverse reactions have been reported during clinical studies with DUOTRAV® eye drops and are classified according to the subsequent convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000).

System organ classification	**Frequency**	**Adverse reactions** *MedDRA Preferred Term (v. 19.1)*
Immune system disorders	*Uncommon:*	hypersensitivity
Nervous system disorders	*Uncommon:*	dizziness, headache
Eye disorders	*Very common:* *Common*: *Uncommon*: *Rare*:	ocular hyperaemia punctate keratitis, vision blurred, dry eye, eye pain, eye pruritus, ocular discomfort, eye irritation keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis
Cardiac disorders	*Uncommon:*	bradycardia
Vascular disorders	*Uncommon:*	hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	*Uncommon*: *Rare*:	Dyspnoea dysphonia, bronchospasm, cough, throat irritation
Skin and subcutaneous tissue disorders	*Uncommon:* *Rare*:	dermatitis contact, hypertrichosis, skin hyperpigmentation (periorbital or eyelid pigmentation) urticaria, skin discolouration

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with DUOTRAV® eye drops via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA.

System organ classification	Adverse reactions *MedDRA Preferred Term (v.19.1)*
Psychiatric disorders	Depression
Eye disorders	Macular oedema, eyelid ptosis, lid sulcus deepened, iris hyperpigmentation
Cardiac disorders	Chest pain, palpitations
Vascular disorders	Oedema peripheral
Gastrointestinal disorders	Dysgeusia
Respiratory, thoracic and mediastinal disorders	Asthma
Skin and subcutaneous tissue disorders	Rash, alopecia

Additional adverse reactions previously reported with the individual components of [Travoprost-Timolol Eye Drops, Solution], are listed in the product information for [Timolol 5 mg/mL Eye Drops, Solution] and [Travoprost 30 µg/mL and 40 µg/mL Eye Drops, Solution].

8. Interactions

Combination therapy

The following interactions are expected with DUOTRAV® eye drops due to potential drug interactions with the mono-components:

- 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.
- There is a potential for additive effects resulting in hypotension and/or marked bradycardia when an ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics.
- Beta-blockers can decrease the response to adrenaline used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy or anaphylaxis (See section 6).
- Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

9. Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

There are no or limited amount of data from the use of DUOTRAV eye drops or the individual components in pregnant women.

Studies in rats and mice with travoprost have shown reproductive toxicity. 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 systemic beta-blockers have been administered to the mother until delivery.

DUOTRAV eye drops should not be used during pregnancy unless clearly necessary. However, if DUOTRAV eye drops is administered during pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

9.2 Lactation

Risk summary

It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and/or metabolites in breast milk. Timolol is excreted in human breast milk following topical administration. Oral beta blockers have the potential to cause serious undesirable effects in the breast-feeding infant. However, in the case of ocular administration at therapeutic doses, the amounts of timolol present in breast milk are not likely to produce clinical symptoms of beta-blockade in the infant.

The use of DUOTRAV eye drops by breast-feeding mothers is not recommended.

9.3 Females and males of reproductive potential

There are no data on the effects of DUOTRAV eye drops on human fertility. Fertility studies in rats showed no effect of travoprost or timolol at doses up to 75 times and 21,000 times, respectively, the maximum recommended human ocular dose (see section 13 Non-clinical safety data).

10. Overdosage

No specific reactions are to be expected with an ocular overdose of the product.
In case of accidental ingestion, symptoms of overdose from systemic beta-blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.
Treatment of an accidental ingestion should be symptomatic and supportive.

11. Clinical pharmacology

Pharmacotherapeutic group, ATC

Ophthalmologicals antiglaucoma preparations and miotics. ATC code: S01ED51

Mechanism of action (MOA)

DUOTRAV eye drops contain two active substances: travoprost and timolol maleate. These two agents reduce IOP by complementary mechanisms of action with a combined effect greater than that of either compound administered alone (synergistic effect).

Travoprost, a prostaglandin $F_{2\alpha}$ analog, is a full agonist which is highly selective and has a high affinity for the prostaglandin FP receptor, and reduces IOP by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in humans starts within approximately 2 hours of administration and maximum effect is achieved within 12 hours. Significant IOP reduction can be maintained for periods exceeding 24 hours following a single dose.

Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Its predominant ocular mechanism of action is to reduce aqueous humor formation and a slight increase in outflow activity.

Pharmacodynamics (PD)

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).

Pharmacokinetics (PK)

Absorption

Travoprost and timolol are absorbed through the cornea. Travoprost is an isopropyl ester prodrug which undergoes rapid hydrolysis in the cornea to produce the active free acid. Following once-daily administration of DUOTRAV eye drops (polyquaternium-1-preserved) to healthy subjects for 5 days, travoprost free acid plasma concentrations were below the 0.010 ng/mL assay quantitation limit in the majority of samples. Quantifiable free acid concentrations were observable in some cases within 1 hour post-dose, ranging from 0.010 to 0.030 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 DUOTRAV eye drops. Timolol has a plasma elimination half-life of about 4 hours.

Distribution

Travoprost free acid can be measured in the aqueous humor for several hours in animals and in human plasma up to 1 hour post-dose. Timolol can be measured in human aqueous humor after topical ocular administration of timolol and in plasma for up to 12 hours following topical ocular administration of DUOTRAV eye drops.

Radioactivity was found in milk of rats following a single subcutaneous dose of radioactive travoprost. Maximal levels in milk were observed 6 hours after dosing, which then declined to <3% of those measured at C_{max} by 24 hours, and by this time, were essentially similar to those in maternal plasma.

Biotransformation/metabolism

Metabolism is the primary clearance mechanism for both travoprost and its free acid. The systemic metabolic pathways for travoprost free acid parallel those of endogenous prostaglandin $F_{2\alpha}$, which are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl to form a ketone and β-oxidative cleavages of the carboxylic acid side chain.

Timolol is primarily metabolised by CYP2D6 via two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other generates an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl function adjacent to the nitrogen. CYP2C19 was found to play a minor role in timolol metabolism.

Elimination

Both travoprost free acid and timolol, along with their respective metabolites, are primarily excreted in urine. Less than 2 % of an ocular dose of travoprost was recovered in urine as travoprost free acid. Approximately 20 % of a timolol dose was found in urine as parent drug with the remainder excreted as metabolites.

Due to the very low concentrations and rapid disappearance of travoprost free acid from plasma, elimination half-life could not be determined. Timolol has a plasma elimination half-life of about 4 hours.

Pediatric patients (below 18 years)
The pharmacokinetics of DUOTRAV eye drops in pediatric patients has not been reported.

Pharmacogenomics
Higher plasma concentrations were detected in CYP2D6 poor metabolisers compared with extensive metabolisers. Similar results have been obtained after the administration of ophthalmic timolol.

12. Clinical studies
In a 12-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 25-27 mmHg, the mean IOP-lowering of DUOTRAV eye drops dosed once-daily in the morning was 8-10 mmHg. The non-inferiority of DUOTRAV eye drops as compared to latanoprost 0.005% plus timolol 0.5% in mean IOP reduction was demonstrated across all time points at all visits.

In a 3-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 27-30 mmHg, the mean IOP-lowering effect of DUOTRAV eye drops dosed once-daily in the morning was up to 2 mmHg greater than that of travoprost 0.004% dosed once-daily in the evening and 2-3 mmHg greater than that of timolol 0.5% dosed twice daily. A statistically superior reduction in mean morning IOP (8 AM - 24 hours after the previous DUOTRAV eye drops dose) was observed compared to travoprost 0.004% at all visits throughout the study.

In two 3-month, controlled clinical studies in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 23-26 mmHg, the mean IOP-lowering effect of DUOTRAV eye drops dosed once-daily in the morning was 7-9 mmHg. Mean IOP reductions were non-inferior, although numerically lower, compared with those achieved by concomitant therapy with travoprost 0.004% dosed once-daily in the evening and timolol 0.5% dosed once-daily in the morning.

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

Inclusion criteria were similar across the above clinical studies, with the exception of the IOP entry criteria and response to previous IOP-lowering therapy. The clinical development of DUOTRAV eye drops included both treatment-naive patients and patients on therapy. Insufficient responsiveness to monotherapy was not an inclusion criterion.

Additional randomized, double- or observer-masked, active-controlled studies have been performed in which over 500 subjects with open-angle glaucoma or ocular hypertension were treated with Travoprost 0.004%/Timolol 0.5%.

Many of these studies measured the IOP lowering effects Travoprost 0.004%/Timolol 0.5% after a wash-out period and these demonstrated an IOP lowering effect from baseline that is consistent with that shown in the pivotal studies described above.

13. Non-clinical safety data

Non-clinical data for travoprost and timolol reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, and carcinogenic potential. Reproductive and developmental toxicity was observed in animals at dose levels of travoprost similar to clinical ocular dose level.

Studies in rats and mice with travoprost have shown reproductive toxicity. Embryo-fetal development toxicity studies in mice showed an increase in the mean number of early resorptions and a decrease in the total and mean number of viable fetuses per pregnant female at 1 µg/kg/day following subcutaneous administration. The no effect level for embryo-fetal toxicity was reported to be 0.3 µg/kg/day.

In peri-and postnatal development studies in rats, subcutaneous administration of travoprost increased postnatal mortality and reduced neonatal body weight gain at doses > 0.12 µg/kg/day. In a second study with reduced doses, no effects were observed on the fetus or on postnatal development at doses up to 0.1 µg/kg/day, or twice the recommended clinical ophthalmic dose.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternal toxicity.

Fertility studies in rats dosed with travoprost subcutaneously resulted in significant reductions in the number of corpora lutea, viable fetuses, and an increased early post-implantation loss as well as resorption rate at 10 µg/kg/day (250 times the maximum recommended human ocular dose of 0.04 µg/kg/day on a µg/kg basis). The no effect level was set at 3 µg/kg/day (75 times the maximum recommended human ocular dose). In contrast, studies with timolol in rats showed no effects at doses up to 21,000 times the systemic exposure following the maximum recommended human ocular dose.

14. Pharmaceutical information

Incompatibilities

Not applicable.

Shelf life

2.5ml, 24 months
1.5ml, 18 months

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 4 weeks after first opening.
Keep this medicine out of the sight and reach of children.

Nature and contents of container

Oval bottle containing 1.5 ml or 2.5 ml with dispensing plug and screw cap, all plastic, presented in an overwrap.
Cartons containing 1 bottle.

Not all preparations may be available commercially.

Special precautions for disposal

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

Manufacturers

See folding box.

(Information issued: May 2017.SINv1)

Novartis Pharma AG, Basel, Switzerland