NOVARTIS

DUOTRAV® (travoprost/timolol)

travoprost 40 µg/ml and timolol 5 mg/ml, solution

Professional Information

Document status:	Final
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SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

DUOTRAV® eye drops, solution

2 QUALITIVE AND QUANTITIVE COMPOSITION

1 ml of solution contains 40 µg travoprost and 6,83 mg timolol maleate equivalent to 5 mg timolol

Preservative: polyquaternium-1 (POLYQUAD®) 0,001 % (*m/v*)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Decrease of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma for whom treatment with either travoprost or timolol given alone provides insufficient IOP reduction.

4.2 Posology and method of administration

Posology

Use in adults, including the elderly:

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

If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart *(see section 4.5).*

If a dose is missed, treatment should continue with the next dose as planned.

The dose should not exceed one drop in the affected eye(s) daily.

When substituting another ophthalmic anti-glaucoma agent with DUOTRAV®, discontinue the other agent and start the following day with DUOTRAV®.

Special populations

Use in hepatic and renal impairment:

No studies have been conducted with DUOTRAV® 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 dosage adjustment was necessary in these patients.

Paediatric population

Use in children and adolescents:

The efficacy and safety of DUOTRAV® in patients below the age of 18 years have not been established and its use is not recommended in these patients until further data becomes 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.
- Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of DUOTRAV® administered via the ocular route and result in a decrease in systemic side effects.

4.3 Contraindications

- Hypersensitivity to travoprost, timolol, or to any of the excipients.
- Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure or cardiogenic shock.

4.4 Special warnings and precautions for use

Systemic effects

DUOTRAV® is absorbed systemically.

Cardiac disorders

Due to the beta-adrenergic component, timolol, the same types of cardiovascular and pulmonary adverse reactions as seen with systemic beta-adrenergic blocking agents may occur**.** Cardiac failure should be adequately controlled before beginning therapy with timolol. Patients with a history of severe

cardiac disease should be observed for signs of cardiac failure and have their pulse rates checked.

Respiratory disorders

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failures, have been reported following administration of timolol maleate.

Hypoglycaemia/diabetes

DUOTRAV® should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) as beta adrenergic blocking agents may mask the signs and symptoms of, and the response to hypoglycaemia.

Hyperthyroidism

It may also mask the signs of hyperthyroidism and cause worsening of Prinzmetal angina, peripheral and central circulatory disorders and hypotension.

Anaphylactic reactions

While using DUOTRAV®, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant therapy

Timolol may interact with other medicines. The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when DUOTRAV® is given to patients already receiving an oral beta-blocking agent. The use of two local beta-adrenergic blocking agents or two local

prostaglandins is not recommended *(see section 4.5).*

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 irises, 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 of 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 DUOTRAV® 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.

- Caution is recommended when using DUOTRAV® 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, DUOTRAV® can be used with caution.
- DUOTRAV® contains propylene glycol and polyoxyethylene hydrogenated castor oil 40 which may cause skin irritation.
- Patients must remove contact lenses prior to application of DUOTRAV® and wait 15 minutes after instillation of DUOTRAV® before reinsertion.

4.5 Interaction with other medicines and other forms of interaction

Interactions of DUOTRAV® with other medications have not been specifically evaluated.

- There is a potential for additive effects resulting in hypotension and/or marked bradycardia when eye drops with timolol are administered concomitantly with oral calcium channel blockers, or beta- blocking agents, antidysrhythmics, digoxin or parasympathomimetics.
- The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta- blockers.
- Beta-blockers such as timolol contained in DUOTRAV® may increase the hypoglycaemic effect of antidiabetic agents and may mask the signs and symptoms of hypoglycaemia *(see Section 4.4).*
- 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 as contained in DUOTRAV® and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ Contraception in males and females

DUOTRAV® must not be used in women who may become pregnant unless adequate contraceptive measures are in place.

Pregnancy

There are no adequate data from the use of DUOTRAV® in pregnant women. Animal studies with travoprost have shown reproductive toxicity. DUOTRAV® should not be used during pregnancy.

Breastfeeding

Animal studies have shown excretion of travoprost and/or metabolites in breast milk. Timolol is excreted in breast milk following topical administration. Oral beta blockers have the potential to cause serious undesirable effects in the breastfeeding 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.

Therefore mothers breastfeeding their babies should not be treated with DUOTRAV®.

Fertility

There are no data on the effects of DUOTRAV® on human fertility.

4.7 Effects on ability to drive and use machines

DUOTRAV® has minor influence on the ability to drive and use machines. As with any eye drops, 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. DUOTRAV® may also cause hallucinations, dizziness, nervousness and/or fatigue (see section 4.8) which may affect the ability to drive and use machines. Patients should be advised not to drive and use machines if these symptoms occur.

4.8 Undesirable effects

a. Summary of the safety profile

In 3 clinical trials involved in the development of DUOTRAV® (polyquaternium-1-preserved), 372 patients/subjects were exposed for up to 6 months. No serious ophthalmic or systemic side effects related to the product were reported in any of the clinical trials. The most frequently reported treatment-related side-effect with DUOTRAV® was hyperaemia of the eye (10,8 %), which included ocular or conjunctival hyperaemia. The majority of patients (90 %) who experienced hyperaemia of the eye did not discontinue therapy as a result of this reaction.

The following side effects were observed in clinical studies. They are ranked according to system organ class and classified according to the following convention: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare < 1/10 000).
Within each frequency grouping, side effects are presented in decreasing order of seriousness.

Tabulated list of adverse reactions

System Organ Class	Undesirable effect

	Very common	Common	Uncommon	Rare
Immune system disorders:			hypersensitivity	
Psychiatric disorders				Nervousness
Nervous system disorders:			headache dizziness	
Eye disorders:	ocular hyperaemia	eye pain, eye irritation, foreign body sensation in eyes, dry eye, eye pruritus, conjunctival hyperaemia, ocular hyperaemia punctate keratitis, blurred vision, ocular discomfort,	keratitis, photophobia, keratoconjunctivitis sicca, conjunctivitis, asthenopia, increased lacrimation, iris hyperpigmentation, growth of eye lashes, dark circles under eyes, anterior chamber inflammation, blepharitis, visual acuity reduced, eye swelling, erythema of eyelid	corneal erosion, trichiasis, distichiasis, conjunctival haemorrhage, meibomianitis, eyelid margin crusting
Cardiac disorders:			bradycardia	
Vascular disorders:			hypotension hypertension	
Respiratory, thoracic and mediastinal disorders:			dyspnoea	dysphonia, bronchospasm, cough, throat irritation
Skin and subcutaneous tissue disorders:			skin hyperpigmentation (periorbital or eyelid pigmentation), abnormal hair growth contact dermatitis	Skin discolouration, urticaria
General disorders and administration site conditions:			fatigue	
Investigations:			decreased heart rate	

Description of adverse reactions derived from post-marketing experience with DUOTRAV

System Organ Classification	Undesirable effect
Psychiatric disorders:	Hallucination, depression
Cardiac disorders:	chest pain, palpitations
Vascular disorders:	oedema peripheral
Respiratory, thoracic and mediastinal disorders:	asthma
Gastrointestinal disorders:	dysgeusia
Eye disorders:	macular oedema, eyelid ptosis, lid sulcus deepened, iris hyperpigmentation
Skin and subcutaneous tissue disorders:	rash, alopecia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

If overdosage with DUOTRAV® occurs, treatment should be symptomatic.

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8*).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.15.4 Ophthalmic preparations, other.

Pharmacotherapeutic group and ATC code:

Ophthalmologicals; Antiglaucoma preparations and miotics.

ATC code: S01ED51.

Mechanism of action:

DUOTRAV® contains two active components: travoprost and timolol maleate. These two components lower intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound alone.

Travoprost is a prostaglandin selective F2*α* analogue agonist with an affinity for the prostaglandin FP receptor. It 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. Low 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.

5.2 Pharmacokinetic properties

Absorption

Travoprost and timolol are absorbed through the cornea. Travoprost is a prodrug that undergoes ester hydrolysis in the cornea to the active free acid.

Following once-daily administration of DUOTRAV® 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 DUOTRAV.

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 DUOTRAV®.

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 DUOTRAV®.

Metabolism

Metabolism is the major route of elimination of both travoprost and the active free acid. The systemic metabolic pathways parallel those of endogenous prostaglandin F2*α* 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 gives 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 DUOTRAV®.

Excretion

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.

Pharmacogenomics

Timolol

Higher plasma concentrations were detected in CYP2D6 poor metabolizers (PMs) compared with extensive metabolizers (EMs). Similar results have been obtained after the administration of ophthalmic timolol.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Boric acid

Polyquaternium-1

Mannitol (E421)

Propylene glycol (E1520)

Polyoxyethylene hydrogenated castor oil 40 (HCO-40)

Purified water

Sodium chloride

Sodium hydroxide and/ or hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Discard 4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 25 °C.

Discard four weeks after first opening.

KEEP OUT OF REACH AND SIGHT OF CHILDREN.

Store in the original package/container.

6.5 Nature and contents of container

White 4 ml bottle, containing a 2,5 ml fill with colourless dispensing plug and white screw cap, all polypropylene.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

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