1. NAME OF THE MEDICINAL PRODUCT

DUOTRAV* 40 micrograms/ml + 5 mg/ml eye drops, solution (travoprost and timolol)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate).
Preservative: 1 ml of solution contains 10 microgram polyquaternium-1 (POLYQUAD* preservative).
Excipients with known effect: 1 ml of solution contains 7.5 mg propylene glycol and 1 mg polyoxyethylene hydrogenated castor oil 40 (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution
Clear, colourless to light yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 section 5.1).

4.2 Posology and method of administration

Posology

Use in adults, including the elderly population
The dose is 1 drop of DUOTRAV eye drops 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 normal. The dose should not exceed 1 drop in the affected eye(s) once daily since it has been shown that more frequent administration of prostaglandin analogues may decrease the intraocular pressure lowering effect.

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.

Special populations

Use in children
The use of DUOTRAV eye drops in paediatric 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.

Use in patients with hepatic or renal impairment
No studies have been conducted with DUOTRAV eye drops or with timolol 5 mg/ml 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 DUOTRAV eye drops (see section 5.2).

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. Keep the bottle tightly closed when not in use.

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.

If more than one topical ophthalmic medicinal product is being used, the medicinal products should be administered at least 5 minutes apart. Eye ointments should be administered last.

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

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, overt cardiac failure or cardiogenic shock.
- Severe allergic rhinitis.
- Corneal dystrophies.

4.4 Special warnings and precautions for use

General

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

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 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, 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-blockers 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.

Other beta-blocking agents

- The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when DUOTRAV eye drops are given to patients already receiving a systemic beta-blocker. The response of these patients should be closely observed. The use of two topical beta-blockers is not recommended (see section 4.5).

Other prostaglandins

- The use of two topical prostaglandins is not recommended.

Anaphylactic reactions

- While taking beta-blockers, patients with a 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. 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 has been reported in association with the use of travoprost.
- 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 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.
  DUOTRAV eye drops should therefore be used with caution in patients with active intraocular inflammation, as well as in patients with predisposing risk factors for iritis/uveitis.
- Macular oedema has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. Use DUOTRAV eye drops 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. Periorbital and lid changes including deepening of the eyelid sulcus have been observed with prostaglandin analogues.
- 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 patient is receiving DUOTRAV eye drops.

Contact lenses

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

Excipients

- DUOTRAV eye drops contains propylene glycol which may cause skin irritation.
- DUOTRAV eye drops contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.

4.5 Interaction with other medicinal products and other forms of interaction

- No specific drug interaction studies have been performed with timolol and travoprost.
- 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-blockers, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or guanethidine.
- The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.
- 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).
- 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 of anaphylaxis (see section 4.4).
- Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception
DUOTRAV eye drops 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. Studies in animals with travoprost have shown reproductive toxicity.
There are no or limited amount of data from the use of DUOTRAV eye drops or the individual components in pregnant women.
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.

Breast-feeding
It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and its metabolites in breast milk. Beta-blockers are excreted in human breast milk having the potential to cause serious undesirable effects in the breast-feeding infant.

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

Fertility
There are no data on the effects of DUOTRAV eye drops 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

DUOTRAV eye drops has no or negligible influence on the ability to drive and use machines.

However, 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 machinery.

4.8 Undesirable effects

Summary of the safety profile
In clinical trials, the most common adverse drug reaction was hyperaemia of the eye (conjunctival, ocular), which occurred in up to 13% of subjects.

Tabulated summary of adverse reactions
The following adverse reactions have been identified during clinical studies or post-marketing experience. They are classified according to the following 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) or not known (cannot be estimated from the available data, data from post-marketing surveillance). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reactions
Immune system disorders	Uncommon	hypersensitivity
Psychiatric disorders	Rare Not known	nervousness depression
Nervous system disorders	Uncommon Not known	dizziness, headache cerebrovascular accident, syncope, paraesthesia
Eye disorders	Very common Common Uncommon Rare Not known	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, eye allergy corneal erosion, visual impairment, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis macular oedema, eyelid ptosis, corneal disorder
Cardiac disorders	Uncommon Rare Not known	bradycardia arrhythmia, heart rate irregular cardiac failure, tachycardia, chest pain, palpitations
Vascular disorders	Uncommon Not known	hypertension, hypotension oedema peripheral
Respiratory, thoracic and mediastinal disorders	Uncommon Rare Not known	dyspnoea dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort, upper-airway cough syndrome asthma
Gastrointestinal disorders	Not known	dysgeusia
Hepatobiliary disorders	Rare	alanine aminotransferase increased, aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Uncommon Rare Not known	dermatitis contact, hypertrichosis, skin hyperpigmentation (periocular) urticaria, skin discolouration, alopecia 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

Description of selected adverse reactions
Additional adverse reactions that have been seen with one of the active substances and may potentially occur with DUOTRAV* eye drops:

Travoprost

System organ class	Adverse reactions
Psychiatric disorders	anxiety
Eye disorders	iris hyperpigmentation, cataract, uveitis, conjunctival follicles, hypoaesthesia eye, eye inflammation, eye discharge, eyelid irritation, eyelash discolouration, sunken eyes, eczema eyelids, eyelash thickening, iridocyclitis, anterior chamber pigmentation, dark circle around the eyes
Ear and labyrinth disorders	tinnitus
Respiratory, thoracic and mediastinal disorders	nasal dryness
Gastrointestinal disorders	dry mouth, diarrhoea, constipation, abdominal pain, nausea
Skin and subcutaneous tissue disorders	hair colour changes, erythema, pruritus, madarosis
Musculoskeletal and connective tissue disorders	arthralgia, musculoskeletal pain
Renal and urinary disorders	dysuria, urinary incontinence
Investigations	prostatic specific antigen increased
General disorders and administration site conditions	asthenia

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.

Incidence of systemic adverse reaction after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

System organ class	Adverse reactions
Immune system disorders	systemic allergic reactions including angioedema, 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	choroidal detachment following filtration surgery (see section 4.4), decreased corneal sensitivity, diplopia
Cardiac disorders	oedema, congestive heart failure, atrioventricular block, cardiac arrest
Vascular disorders	Raynaud's phenomenon, cold hands and feet.
Gastrointestinal disorders	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

4.9 Overdose
An ocular overdose of DUOTRAV eye drops may be flushed from the eye(s) with lukewarm water.

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. Timolol does not dialyse readily.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antiglaucoma preparations and miotics, beta-blocking agents. ATC code: S01ED51.

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

Travoprost, a prostaglandin $F_{2\alpha}$ analogue, 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. Tonography and fluorophotometry studies in humans suggest that its predominant ocular mechanism of action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Pharmacodynamic effects
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).

Clinical efficacy and safety
In a twelve-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 25 to 27 mmHg, the mean IOP-lowering effect of DUOTRAV eye drops dosed once-daily in the morning was 8 to 10 mmHg. The non-inferiority of DUOTRAV eye drops as compared to latanoprost 50 micrograms/ml plus timolol 5 mg/ml in 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 a mean baseline IOP range of 27 to 30 mmHg, the mean IOP-lowering effect of DUOTRAV eye drops 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 mean morning IOP (8 AM - 24 hours after the previous dose of DUOTRAV eye drops) was observed compared to travoprost 40 micrograms/ml at all visits throughout the study.

In two three-month, controlled clinical studies in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 23 to 26 mmHg, the mean IOP-lowering effect of DUOTRAV eye drops dosed once-daily in the morning was 7 to 9 mmHg. Mean IOP reductions were non-inferior, although numerically lower, compared 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 a mean baseline IOP range of 24 to 26 mmHg, the mean IOP-lowering effect of DUOTRAV eye drops (polyquaternium-1-preserved) dosed once-daily in the morning was 8 mmHg and similar to that of DUOTRAV eye drops (benzalkonium chloride preserved).

Inclusion criteria were common 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 patients naive and on therapy. Insufficient responsiveness to monotherapy was not an inclusion criterion. DUOTRAV eye drops was well tolerated with no serious adverse events observed.

5.2 Pharmacokinetic properties
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 (N=22) for 5 days, travoprost free acid plasma concentrations were below the 0.010 ng/ml assay quantitation limit in the majority of samples (94.4%) and generally was not detectable one hour after dosing. Quantifiable free acid concentrations were observable in some cases within one hour post-dose, ranging from 0.010 to 0.030 ng/ml. Due to the very low concentrations and rapid disappearance of travoprost free acid from plasma, elimination half-life could not be determined. 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. Following repeated administration of DUOTRAV eye drops, the mean steady state elimination half-life of timolol was 0.58 hours.

Distribution
Following administration of DUOTRAV eye drops (polyquaternium-1-preserved) to rabbits, mean maximum aqueous humor concentrations of 23.3 and 1610 ng/mL for travoprost free acid and timolol, respectively, were achieved within 1 hour.

Biotransformation
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 metabolised by 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.

Elimination
Following administration of radiolabelled travoprost to rats, approximately 95% of the dose was eliminated within 24 hours. Approximately 75% of the dose was eliminated in the faeces and the remainder excreted in urine. Following oral administration of radiolabelled timolol to human volunteers, approximately 72% of the dose was excreted within 84 hours, with 66% excreted in urine and 6% in faeces. Approximately 20% of the dose was excreted as unchanged drug in the urine.

Linearity/non-linearity
Both travoprost and timolol exhibit linear pharmacokinetics.

Paediatric population
The pharmacokinetics of DUOTRAV eye drops in paediatric patients has not been reported.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, and carcinogenic potential. Adverse reproductive and developmental toxicity was observed in animals at exposure levels of travoprost similar to clinical exposure levels and is possibly relevant to clinical use.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Polyquaternium-1, mannitol (E421), propylene glycol (E1520), polyoxyethylene hydrogenated castor oil 40 (HCO-40), boric acid, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH), purified water.

6.2 Incompatibilities
Not applicable.

6.3 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.

6.4 Nature and contents of container
Oval bottle containing 2.5 ml with dispensing plug and screw cap, all plastic, presented in an overwrap.
Carton containing 1 bottle.

6.5 Special precautions for disposal
No special requirements.

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