ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DuoTrav 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

Each mL of solution contains polyquaternium-1 (POLYQUAD) 10 microgram, propylene glycol 7.5 mg and polyoxyethylene hydrogenated castor oil 40 1 mg (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution (eye drops).

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DuoTrav 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 elderly
The dose is one drop of DuoTrav 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 DuoTrav 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 (see section 5.2).

Paediatric population
The safety and efficacy of DuoTrav 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 nasolacrimal occlusion is used or the eyelids are closed for 2 minutes, 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 DuoTrav, the other medicinal product should be discontinued and DuoTrav should be started the following day.

Patients must be instructed to remove soft contact lenses prior to application of DuoTrav 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 pacemaker. 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. For information on how to reduce 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 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 their 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.

DuoTrav 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 in 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 (e.g. 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 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 anaesthetist 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 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.

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 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.

Macular oedema has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. 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, and in patients with active intraocular inflammation, DuoTrav can be used with caution.

Excipients

DuoTrav contains propylene glycol which may cause skin irritation.

DuoTrav contains polyoxyethylene hydrogenated castor oil 40 which may cause skin reactions.

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

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-blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics or 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

DuoTrav must not be used in women of child-bearing age/potential unless adequate contraceptive measures are in place (see section 5.3).

Pregnancy

Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/newborn child.

There are no or limited amount of data from the use of DuoTrav 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 intrauterine 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 DuoTrav is administered until delivery, the neonate should be carefully monitored during the first days of life.

DuoTrav should not be used during pregnancy unless clearly necessary. For information on how to reduce systemic absorption, see section 4.2.

Breast-feeding

It is unknown whether travoprost from eye drops is excreted in human breast milk. Animal studies have shown excretion of travoprost and metabolites in breast milk. Timolol is excreted in breast milk and has the potential to cause serious adverse reactions in the breast-fed 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. For information on how to reduce systemic absorption, see section 4.2.

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

Fertility

There are no data on the effects of DuoTrav on human fertility. Animal studies showed no effect of travoprost on fertility at doses up to 75 times the maximum recommended human ocular dose, whereas no relevant effect of timolol was noted at this dose level.

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

Summary of the safety profile

In clinical studies involving 2,170 patients treated with DuoTrav the most frequently reported treatment-related adverse reaction was ocular hyperaemia (12.0%).

Tabulated summary of adverse reactions

The 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (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	Uncommon	Hypersensitivity
Psychiatric disorders	Rare	Nervousness
	Not known	Hallucinations*, 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, lid sulcus deepened, iris hyperpigmentation, corneal disorder
Cardiac disorders	Uncommon	Bradycardia
	Rare	Arrhythmia, heart rate irregular
	Not known	Cardiac failure, tachycardia, chest pain, palpitations
Vascular disorders	Uncommon	Hypertension, hypotension
	Not known	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, skin hyperpigmentation (periocular)
	Rare	Urticaria, skin discolouration, alopecia
	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

* adverse reactions observed with timolol.

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

occur with DuoTrav:

Travoprost

System organ class	MedDRA preferred term
Immune system disorders	Seasonal allergy
Psychiatric disorders	Anxiety, insomnia
Eye disorders	Uveitis, conjunctival follicles, eye discharge, periorbital oedema, eyelids pruritus, ectropion, cataract, iridocyclitis, ophthalmic herpes simplex, eye inflammation, photopsia, eczema eyelids, halo vision, hypoaesthesia eye, anterior chamber pigmentation, mydriasis, eyelash hyperpigmentation, eyelash thickening, visual field defect
Ear and labyrinth disorders	Vertigo, tinnitus
Vascular disorders	Blood pressure diastolic decreased, blood pressure systolic increased
Respiratory, thoracic and mediastinal disorders	Asthma aggravated, rhinitis allergic, epistaxis, respiratory disorder, nasal congestion, nasal dryness
Gastrointestinal disorders	Peptic ulcer reactivated, gastrointestinal disorder, diarrhoea, constipation, dry mouth, abdominal pain, nausea, vomiting
Skin and subcutaneous tissue disorders	Skin exfoliation, hair texture abnormal, dermatitis allergic, hair colour changes, madarosis, pruritus, hair growth abnormal, erythema
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, arthralgia
Renal and urinary disorders	Dysuria, urinary incontinence
General disorders and administration site conditions	Asthenia
Investigations	Prostatic specific antigen increased

Timolol

Like other topically applied ophthalmic medicinal products, timolol is absorbed into the systemic circulation. This may cause undesirable effects similar to those 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. For information on how to reduce systemic absorption, see section 4.2.

System organ class	MedDRA preferred term
Immune system disorders	Systemic allergic reactions including angioedema, urticaria, localised and generalised rash, pruritus, anaphylaxis
Metabolism and nutrition disorders	Hypoglycaemia
Psychiatric disorders	Hallucinations, 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 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
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 listed in Appendix V.

4.9 Overdose

A topical overdose with DuoTrav 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 DuoTrav 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

DuoTrav 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 $F_{2\alpha}$ 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 DuoTrav dosed once daily in the morning was 8 to 10 mmHg. The non-inferiority of DuoTrav 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 DuoTrav 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 (08:00, 24 hours after the last dose of DuoTrav) 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 DuoTrav 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 DuoTrav (polyquaternium-1-preserved) dosed once daily in the morning was 8 mmHg and equivalent to that of DuoTrav (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 DuoTrav 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 as regards 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 DuoTrav 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 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.

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 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.

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.

5.3 Preclinical safety data

In monkeys, administration of DuoTrav twice daily was shown to induce increased palpebral fissure and to increase iris pigmentation similar to that observed with ocular administration of prostanoids.

DuoTrav preserved with polyquaternium-1 induced minimal ocular surface toxicity, compared to eye drops preserved with benzalkonium chloride, on cultured human corneal cells and following topical ocular administration in rabbits.

Travoprost

Topical ocular administration of travoprost to monkeys at concentrations of up to 0.012% to the right eye, twice daily for one year resulted in no systemic toxicity.

Reproduction toxicity studies with travoprost have been undertaken in rats, mice and rabbits using the systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss and foetotoxicity. In pregnant rats, systemic administration of travoprost at doses more than 200 times the clinical dose during the period of organogenesis resulted in an increased incidence of malformations. Low levels of radioactivity were measured in amniotic

fluid and foetal tissues of pregnant rats administered ^{3}H-travoprost. Reproduction and development studies have demonstrated a potent effect on foetal loss with a high rate observed in rats and mice (180 pg/mL and 30 pg/mL plasma, respectively) at exposures 1.2 to 6 times the clinical exposure (up to 25 pg/mL).

Timolol

Non-clinical data revealed no special hazard for humans with timolol based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Reproduction toxicity studies with timolol showed delayed foetal ossification in rats with no adverse effects on postnatal development (7000 times the clinical dose) and increased foetal resorptions in rabbits (14000 times the clinical dose).

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 (for pH adjustment)
Purified water

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 30°C.

6.5 Nature and contents of container

2.5 mL oval polypropylene (PP) or low-density polyethylene (LDPE) bottle and PP or LDPE dispensing plug with PP screw cap, presented in an overwrap.

Pack sizes of 1, 3 or 6 bottles.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/338/001-6

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 April 2006
Date of last renewal: 07 October 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Novartis Manufacturing NV
Rijksweg 14
2870 Puurs-Sint-Amands
Belgium

Novartis Farmacéutica, S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR SINGLE BOTTLE 2.5 mL + CARTON FOR 3 x 2.5 mL BOTTLES + CARTON FOR 6 x 2.5 mL BOTTLES

1. NAME OF THE MEDICINAL PRODUCT

DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution
travoprost/timolol

2. STATEMENT OF ACTIVE SUBSTANCE

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

3. LIST OF EXCIPIENTS

Contains: 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.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution.

1 x 2.5 mL
3 x 2.5 mL
6 x 2.5 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Ocular use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Discard 4 weeks after first opening.
Opened:
Opened (1):
Opened (2):
Opened (3):

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBERS

EU/1/06/338/001	1 x 2.5 ml – PP bottle
EU/1/06/338/002	3 x 2.5 ml – PP bottle
EU/1/06/338/003	6 x 2.5 ml – PP bottle
EU/1/06/338/004	1 x 2.5 ml – LDPE bottle
EU/1/06/338/005	3 x 2.5 ml – LDPE bottle
EU/1/06/338/006	6 x 2.5 ml – LDPE bottle

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16 INFORMATION IN BRAILLE

duotrav

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

DuoTrav 40 micrograms/mL + 5 mg/mL eye drops
travoprost/timolol
Ocular use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Open here

3. EXPIRY DATE

EXP
Discard 4 weeks after first opening.
Opened:

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mL

6 OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

OVERWRAP

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

DuoTrav 40 micrograms/mL + 5 mg/mL eye drops
travoprost/timolol

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP
Discard 4 weeks after first opening.

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 mL

6 OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

DuoTrav 40 micrograms/mL + 5 mg/mL eye drops, solution
travoprost/timolol

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DuoTrav is and what it is used for
2. What you need to know before you use DuoTrav
3. How to use DuoTrav
4. Possible side effects
5. How to store DuoTrav
6. Contents of the pack and other information

1. What DuoTrav is and what it is used for

DuoTrav eye drop solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of aqueous fluid from the eye, which lowers its pressure. Timolol is a beta blocker which works by reducing the production of fluid within the eye. The two substances work together to reduce pressure within the eye.

DuoTrav eye drops are used to treat high pressure in the eye in adults, including the elderly**.** This pressure can lead to an illness called glaucoma.

2. What you need to know before you use DuoTrav

Do not use DuoTrav
- if you are allergic to travoprost, prostaglandins, timolol, beta blockers or any of the other ingredients of this medicine (listed in section 6).
- if you have now or have had in the past respiratory problems such as asthma, severe chronic obstructive bronchitis (severe lung disease which may cause wheeziness, difficulty in breathing and/or long-standing cough), or other types of breathing problems.
- if you have severe hay fever.
- if you have a slow heartbeat, heart failure or a disorder of heart rhythm (irregular heartbeat).
- if the surface of your eye is cloudy.

Ask your doctor for advice if any of these applies to you.

Warning and precautions
Talk to your doctor before using DuoTrav if you have now or have had in the past

- coronary heart disease (symptoms can include chest pain or tightness, breathlessness or choking), heart failure, low blood pressure.
- disturbances of heart rate such as slow heartbeat.
- breathing problems, asthma or chronic obstructive pulmonary disease.
- poor blood circulation disease (such as Raynaud's disease or Raynaud's syndrome).
- diabetes (as timolol may mask signs and symptoms of low blood sugar).
- overactivity of the thyroid gland (as timolol may mask signs and symptoms of thyroid disease).
- myasthenia gravis (chronic neuromuscular weakness).
- cataract surgery.
- eye inflammation.

If you need to have any type of surgery, tell your doctor that you are using DuoTrav as timolol may change the effects of some medicines used during anaesthesia.

If you get any severe allergic reaction (skin rash, redness and itching of the eye) while using DuoTrav**,** whatever the cause, adrenaline treatment may not be as effective. It is therefore important to tell the doctor that you are using DuoTrav when you are to receive any other treatment.

DuoTrav may change the colour of your iris (the coloured part of your eye). This change may be permanent.

DuoTrav may increase the length, thickness, colour and/or number of your eyelashes and may cause unusual hair growth on your eyelids.

Travoprost may be absorbed through the skin and therefore should not be used by women who are pregnant or are attempting to become pregnant. If any of the medicine comes into contact with the skin then it should be washed off straight away.

Children
DuoTrav is not to be used by children and adolescents under 18 years of age.

Other medicines and DuoTrav
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

DuoTrav can affect or be affected by other medicines you are using, including other eye drops for the treatment of glaucoma. Tell your doctor if you are using or intend to use medicines to lower blood pressure, heart medicines including quinidine (used to treat heart conditions and some types of malaria), medicines to treat diabetes or the antidepressants fluoxetine or paroxetine.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not use DuoTrav if you are pregnant unless your doctor considers it necessary. If you could get pregnant you must use adequate contraception whilst you use the medicine.

Do not use DuoTrav if you are breast-feeding. DuoTrav may get into your milk**.**

Driving and using machines
You may find that your vision is blurred for a time just after you use DuoTrav. DuoTrav may also cause hallucinations, dizziness, nervousness or fatigue in some patients.

Do not drive or use machines until any such symptoms has worn off.

DuoTrav contains hydrogenated castor oil and propylene glycol which may cause skin reactions and irritation**.**

3. How to use DuoTrav

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one drop in the affected eye or eyes once a day in the morning or in the evening. Use at the same time each day.

Only use DuoTrav in both eyes if your doctor told you to do so.

Only use DuoTrav as eye drops.


1


2


3


4

- Immediately before using a bottle for the first time, tear open the overwrap (picture 1), remove the bottle and write the date of opening on the label in the space provided.
- Make sure you have a mirror available.
- Wash your hands.
- Twist off the bottle cap.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull your lower eyelid down with a clean finger until there is a “pocket” between the eyelid and your eye. The drop will go in here (picture 2)**.**
- Bring the bottle dropper close to the eye. Use the mirror if it helps.
- Do not touch your eye or eyelid, the surrounding areas or other surfaces with the dropper. It could infect the drops.
- Gently squeeze the bottle to release one drop of DuoTrav at a time (picture 3). If a drop misses your eye, try again.
- After using DuoTrav, press your finger into the corner of your eye by your nose for 2 minutes (picture 4). This helps to stop DuoTrav getting into the rest of the body.
- If you have to use DuoTrav in both eyes, repeat the above steps for your other eye.
- Close the bottle cap firmly immediately after use.
- Only use one bottle at a time. Do not open the overwrap until you need to use the bottle.

Use DuoTrav for as long as your doctor has told you to.

If you use more DuoTrav than you should
If you use more DuoTrav than you should, rinse it all out with warm water. Do not put in any more drops until it is time for your next regular dose.

If you forget to use DuoTrav
If you forget to use DuoTrav, continue with the next dose as planned. Do not use a double dose to make up for the forgotten dose. The dose should not exceed one drop daily in the affected eye(s).

If you stop using DuoTrav
If you stop using DuoTrav without speaking to your doctor the pressure in your eye will not be controlled, which could lead to loss of sight.

If you are using other eye drops in addition to DuoTrav, leave at least 5 minutes between applying DuoTrav and the other drops.

If you wear soft contact lenses do not use the drops with your lenses in. After using the drops wait 15 minutes before putting your lenses back in.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects although not everybody gets them.

You can usually carry on using the drops, unless the effects are serious. If you are worried, talk to a doctor or pharmacist. Do not stop using DuoTrav without speaking to your doctor.

Very common side effects (may affect more than 1 in 10 people)
Effects in the eye
Eye redness.

Common side effects (may affect up to 1 in 10 people)
Effects in the eye
Eye surface inflammation with surface damage, eye pain, blurred vision, abnormal vision, dry eye, itchy eye, eye discomfort, signs and symptoms of eye irritation (e.g. burning, stinging).

Uncommon side effects (may affect up to 1 in 100 people)
Effects in the eye
Inflammation of the eye surface, inflammation of the eyelid, swollen conjunctiva, increased growth of eyelashes, iris inflammation, eye inflammation, sensitivity to light, reduced vision, tired eyes, eye allergy, eye swelling, increased tear production, eyelid redness, eyelid colour change, skin darkening (around the eye).

General side effects
Allergic reaction to active substance, dizziness, headache, increased or decreased blood pressure, shortness of breath, excessive hair growth, drip at back of throat, skin inflammation and itching, decreased heart rate.

Rare side effects (may affect up to 1 in 1,000 people)
Effects in the eye
Thinning of the eye surface, inflammation of the eyelid glands, broken blood vessel in the eye, eyelid crusting, abnormally positioned eyelashes, abnormal growth of lashes.

General side effects
Nervousness, irregular heart rate, loss of hair, voice disorders, difficulty breathing, cough, throat irritation, hives, abnormal liver blood tests, skin discolouration, thirst, tiredness, discomfort inside of nose, coloured urine, pain in hands and feet.

Not known (frequency cannot be estimated from the available data)
Effects in the eye
Droopy eyelid (making the eye stay half closed), sunken eyes (eyes appear more inset), changes in the colour of the iris (coloured part of the eye).

General side effects
Rash, heart failure, chest pain, stroke, fainting, depression, asthma, increased heart rate, numbness or tingling sensation, palpitations, swelling in the lower limbs, bad taste.

Additionally:
DuoTrav is a combination of two active substances, travoprost and timolol. Like other medicines administered to the eyes, travoprost and timolol (a beta blocker) are absorbed into the blood. This may cause side effects similar to those seen when beta-blocking medicines that are administered by mouth or by injection. The incidence of side effects after administration to the eyes is lower than after administration by mouth or by injection.

The side effects listed below include reactions seen with the class of beta blockers used for treating eye conditions or reactions seen with travoprost alone:

Effects in the eye
Inflammation of the eyelid, inflammation in the cornea, detachment of the layer below the retina that contains blood vessels following filtration surgery which may cause visual disturbances, decreased corneal sensitivity, corneal erosion (damage to the front layer of the eyeball), double vision, eye discharge, swelling around the eye, eyelid itching, outward turning of eyelid with redness, irritation and excessive tears, blurred vision (sign of clouding of the eye lens), swelling of a section of the eye (uvea), eczema of the eyelids, halo vision, decreased eye sensation, pigmentation inside the eye, dilatated pupils, change in eyelash colour, change in the texture of the eyelashes, abnormal field of vision.

General side effects
Ear and labyrinth disorders: dizziness with spinning sensation, ringing in the ears.

Heart and circulation: slow heart rate, palpitations, oedema (fluid build-up), changes in heartbeat rhythm or speed, congestive heart failure (heart disease with shortness of breath and swelling of the feet and legs due to fluid build-up), a type of heart rhythm disorder, heart attack, low blood pressure, Raynaud's phenomenon, cold hands and feet, reduced blood supply to the brain.

Respiratory: constriction of the airways in the lungs (predominantly in patients with pre-existing disease), runny or stuffy nose, sneezing (due to allergy), difficulty breathing, nose bleed, nasal dryness.

Nervous system and general disorders: difficulty sleeping (insomnia), nightmares, memory loss, hallucinations, loss of strength and energy, anxiety (excessive emotional distress).

Gastrointestinal: taste disturbances, nausea, indigestion, diarrhoea, dry mouth, abdominal pain, vomiting and constipation.

Allergy: increased allergic symptoms, generalised allergic reactions including swelling beneath the skin that can occur in areas such as the face and limbs and can obstruct the airway. which may cause difficulty swallowing or breathing, localised and generalised rash, itchiness, severe sudden life-threatening allergic reaction.

Skin: skin rash with white silvery coloured appearance (psoriasiform rash) or worsening of psoriasis, peeling skin, abnormal hair texture, inflammation of the skin with itchy rash and redness, hair colour change, loss of eyelashes, itching, abnormal hair growth, skin redness.

Muscular: increases in signs and symptoms of myasthenia gravis (muscle disorder), unusual sensations like pins and needles, muscle weakness/tiredness, muscle pain not caused by exercise, joint pain.

Renal and urinary disorders: difficulty and pain when passing urine, involuntary leakage of urine,

Reproduction: sexual dysfunction, decreased libido.

Metabolism: low blood sugar levels, increase in prostate cancer marker.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DuoTrav

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.

You must throw away the bottle 4 weeks after you first opened it to prevent the risk of infections. Each time you start a new bottle write down the date you open it in the spaces on the bottle label and carton.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What DuoTrav contains

- The active substances are travoprost and timolol. Each mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate).
- The other ingredients are Polyquaternium-1, mannitol (E421), propylene glycol (E1520), polyoxyethylene hydrogenated castor oil 40, boric acid, sodium chloride, sodium hydroxide or hydrochloric acid (to adjust pH), purified water.
  Tiny amounts of sodium hydroxide or hydrochloric acid are added to keep acidity levels (pH levels) normal.

What DuoTrav looks like and contents of the pack
DuoTrav is a liquid (a clear, colourless solution) supplied in a 2.5 mL plastic bottle with a screw cap. Each bottle is packed in an overwrap.

Packs of 1, 3 or 6 bottles.

Not all pack sizes may be marketed.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu