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 5 mg, polyoxyethylene hydrogenated castor oil 40 1 mg (see section 4.4).

For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Eye drop, solution (eye drop).

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 older population*

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

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

When substituting another ophthalmic antiglaucoma medicinal product with 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 pace-maker. Overt cardiac failure, cardiogenic shock. Severe allergic rhinitis and corneal dystrophies.

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

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

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

Vascular disorders
Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud’s disease or Raynaud’s syndrome) should be treated with caution.
Respiratory disorders
Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

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 to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

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

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

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

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

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

Hyperthyroidism
Beta-blockers may mask the signs of hyperthyroidism.

Skin contact
Prostaglandins and prostaglandin analogues are biologically active substances that may be absorbed through the skin. Women who are pregnant or attempting to become pregnant should exercise appropriate precautions to avoid direct exposure to the contents of the bottle. In the unlikely event of coming in contact with a substantial portion of the contents of the bottle, thoroughly cleanse the exposed area immediately.

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

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

The use of two local prostaglandins is not recommended.

Ocular effects
Travoprost may gradually change the eye colour by increasing the number of melanosomes (pigment granules) in melanocytes. Before treatment is instituted, patients must be informed of the possibility of
a permanent change in eye colour. Unilateral treatment can result in permanent heterochromia. The long-term effects on the melanocytes and any consequences thereof are currently unknown. The change in iris colour occurs slowly and may not be noticeable for months to years. The change in eye colour has predominantly been seen in patients with mixed coloured irides, i.e., blue-brown, grey-brown, yellow-brown and green-brown; however, it has also been observed in patients with brown eyes. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may become more brownish. After discontinuation of therapy, no further increase in brown iris pigment has been observed.

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

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

Travoprost may gradually change eyelashes in the treated eye(s); these changes were observed in about half of the patients in clinical trials and include: increased length, thickness, pigmentation, and/or number of lashes. The mechanism of eyelash changes and their long term consequences are currently unknown.

Travoprost has been shown to cause slight enlargement of the palpebral fissure in studies in the monkey. However, this effect was not observed during the clinical trials and is considered to be species specific.

There is no experience of 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 blockers solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-blockers.
Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.

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

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception
DuoTrav must not be used in women who may become pregnant unless adequate contraceptive measures are in place (see section 5.3).

Pregnancy
Travoprost has harmful pharmacological effects on pregnancy and/or the foetus/new-born child.

There are no or limited amount of data from the use of 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 intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If 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. To reduce the systemic absorption, see section 4.2.

Breastfeeding
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 having the potential to cause serious adverse reactions in the breastfeeding infant. However, at therapeutic doses of timolol in eye drops it is not likely that sufficient amounts would be present in breast milk to produce clinical symptoms of beta-blockade in the infant. To reduce the systemic absorption, see section 4.2.

The use of 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 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 has no or negligible influence on the ability to drive and use machines.

As with any eye drop, temporary blurred vision or other visual disturbances may occur. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machines.
### 4.8 Undesirable effects

**Summary of the safety profile**

In clinical studies involving 2170 patients treated with DuoTrav the most frequently reported treatment-related adverse reaction was ocular hyperaemia (12.0%).

**Tabulated summary of adverse reactions**

The following adverse reactions listed in the table below were observed in clinical studies or with post-marketing experience. They are ranked according to system organ class and classified according to the following convention: very common (≥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). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Uncommon</td>
<td>hypersensitivity.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Rare</td>
<td>nervousness.</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>depression.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon</td>
<td>dizziness, headache.</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>cerebrovascular accident, syncope, paraesthesia.</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Very common</td>
<td>ocular hyperaemia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>punctate keratitis, eye pain, visual disturbance, vision blurred, dry eye, eye pruritus, ocular discomfort, eye irritation.</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>corneal erosion, meibomianitis, conjunctival haemorrhage, eyelid margin crusting, trichiasis, distichiasis.</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>macular oedema, eyelid ptosis, corneal disorder.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon</td>
<td>bradycardia,..</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>arrhythmia, heart rate irregular</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>cardiac failure, tachycardia, chest pain palpitations.</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon</td>
<td>hypertension, hypotension.</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>oedema peripheral</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Uncommon</td>
<td>dyspnoea, postnasal drip.</td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td>dysphonia, bronchospasm, cough, throat irritation, oropharyngeal pain, nasal discomfort.</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>asthma.</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Not known</td>
<td>dysgeusia</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Rare</td>
<td>alanine aminotransferase increased, aspartate aminotransferase increased.</td>
</tr>
</tbody>
</table>
Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>dermatitis contact, hypertrichosis</td>
</tr>
<tr>
<td>Rare</td>
<td>urticaria, skin discoloration, alopecia, skin hyperpigmentation (periocular).</td>
</tr>
<tr>
<td>Not known</td>
<td>rash</td>
</tr>
</tbody>
</table>

Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>pain in extremity.</td>
</tr>
</tbody>
</table>

Renal and urinary disorders

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>chromaturia.</td>
</tr>
</tbody>
</table>

General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>thirst, fatigue.</td>
</tr>
</tbody>
</table>

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

**Travoprost**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>MedDRA preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye disorders</td>
<td>uveitis, conjunctival disorder, conjunctival follicles, iris hyperpigmentation.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>skin exfoliation.</td>
</tr>
</tbody>
</table>

**Timolol**

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>MedDRA preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Systemic allergic reactions including angioedema, urticaria, localized and generalized rash, pruritus, anaphylaxis.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Hypoglycaemia.</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia, nightmares, memory loss.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Cerebral ischaemia, increases in signs and symptoms of myasthenia gravis.</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>signs and symptoms of ocular irritation (e.g. burning, stinging, itching, tearing, redness), choroidal detachment following filtration surgery (see 4.4 Special warnings and special precautions for use), decreased corneal sensitivity, diplopia.</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Chest pain, palpitations, oedema, congestive heart failure, atrioventricular block, cardiac arrest.</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Raynaud's phenomenon, cold hands and feet.</td>
</tr>
<tr>
<td>Category</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Bronchospasm (predominantly in patients with pre-existing bronchospastic disease).</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Dysgeusia, nausea, dyspepsia, diarrhoea, dry mouth, abdominal pain, vomiting.</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Psoriasisiform rash or exacerbation of psoriasis.</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Myalgia.</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>Sexual dysfunction, decreased libido.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Asthenia.</td>
</tr>
</tbody>
</table>

**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 (8AM-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 twice daily. A statistically superior reduction in morning mean IOP (8AM-24 hours after the last dose of DuoTrav) was observed compared to travoprost at all visits throughout the study.

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\text{max} was 1.34 ng/ml and T\text{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 giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. The plasma $t_{1/2}$ of timolol is 4 hours after ocular administration of 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 rat, mice and rabbit by systemic route. Findings are related to FP receptor agonist activity in uterus with early embryolethality, post-implantation loss, foetotoxicity. In pregnant rat, systemic administration of travoprost at doses more than 200 times the clinical dose 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, repeat 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 AUTHORITY ORGANISATION HOLDER
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom.

8. MARKETING AUTHORITY ORGANISATION NUMBER(S)
EU/1/06/338/001-6

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorisation: 24/04/06
Date of last renewal: 07/10/10

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 AUTHORIZATION

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

S.A. Alcon Couvreur N.V.,
Rijksweg 14,
B-2870,
Puurs,
Belgium

or

Alcon Cusí, S.A.,
Camil Fabra 58,
08320 El Masnou,
Barcelona,
Spain

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 AUTHORIZATION

- Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
### 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.
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
Frimley Business Park
Camberley GU16 7SR
United Kingdom.

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16 INFORMATION IN BRAILLE

duotrav
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
Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your 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 any of the side effects gets serious, 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 drops solution is a combination of two active substances (travoprost and timolol). Travoprost is a prostaglandin analogue which works by increasing the outflow of liquid of 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 eye drops solution

- if you are allergic to travoprost, prostaglandins, timolol, beta-blockers or any of the other ingredients.
- 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 heart beat, heart failure or disorders of heart rhythm (irregular heart beats).
- If the surface of your eye is cloudy.

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

Warning and Precautions

Before you use this medicine, tell your doctor 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 heart beat.
- 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
- Tell your doctor before you have an operation that you are using DuoTrav as timolol may change effects of some medicines used during anaesthesia.
- If you have myasthenia gravis (chronic neuromuscular weakness).
- 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. So when receiving any other treatment please tell the doctor that you are using DuoTrav.
- If you have had cataract surgery talk to your doctor before you use DuoTrav.
- If you have current or previous history of an eye inflammation talk to your doctor before you use DuoTrav.
- 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

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 medicine including quinidine (used to treat heart conditions and some types of malaria), medicines to treat diabetes or antidepressants known as fluoxetine and paroxetine.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding and fertility

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.

Ask your doctor for advice before taking any medicine during breast feeding.

Driving and using machines

You may find that your vision is blurred for a time just after you use DuoTrav. Do not drive or use machines until this 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. Use it for as long as your doctor told you to.

Only use DuoTrav for dropping in your eyes.

- Immediately before using a bottle for the first time, tear-off the overwrap pouch take it out (picture 1) and write the date of opening on the label in the space provided.
- Get the DuoTrav bottle and a mirror.
- Wash your hands.
- Twist off the cap.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid 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 tip close to the eye. Use the mirror if it helps.
- Do not touch your eye or eyelid, 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).
- After using DuoTrav, press a finger into the corner of your eye, by the nose for 2 minutes (picture 4). This helps to stop DuoTrav getting into the rest of the body.
- If you use drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use.
- Only use one bottle at a time. Do not open the pouch until you need to use the bottle.

Turn the page for more advice.

How much to use
<see side 1
If a drop misses your eye, try again.

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

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, leave at least 5 minutes between putting in 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 other questions about your medicine, ask a 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 taking the drops, unless the effects are serious. If you're 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.

**General side effects**
- drug allergy, 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 1000 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 discoloration, skin darkening, 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).
**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 2 active substances. Like other medicines applied into eyes, travoprost and timolol (a beta-blocker) are absorbed into the blood. This may cause similar side effects as seen with intravenous and/or oral beta-blocking medicines. The incidence of side effects after topical ophthalmic administration is lower than when medicines are, for example, taken by mouth or injected. Listed side effects which include reactions seen within the class of beta-blockers when used for treating eye conditions are as follows:

**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, changes in the colour of the iris.

**General side effects**

**Heart and circulation:** slow heart rate, palpitations, oedema (fluid build up), changes in the rhythm or speed of the heartbeat, 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), difficulty breathing, stuffy nose.

**Nervous system and general disorders:** difficulty sleeping (insomnia), nightmares, memory loss, loss of strength and energy.

**Gastric:** taste disturbances, nausea, indigestion, diarrhoea, dry mouth, abdominal pain, vomiting.

**Allergy:** generalized 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, localized and generalized rash, itchiness, severe sudden life-threatening allergic reaction.

**Skin:** skin rash with white silvery coloured appearance (psoriasiform rash) or worsening of psoriasis, peeling skin.

**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.

**Reproduction:** sexual dysfunction, decreased libido.

**Metabolism:** Low blood sugar levels

**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 out of the sight and reach of children.
Do not use DuoTrav eye drops solution after the expiry date which is stated on the bottle and outer carton after “EXP”. The expiry date refers to the last day of the month.

Do not store above 30°C.

You must throw away the bottle 4 weeks after you first opened it to prevent infections and use a new bottle. Write down the date you open it in the space on each bottle label and box.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. 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 placed in a pouch. Packs of 1, 3 or 6 bottles.

Not all pack sizes may be marketed.

<table>
<thead>
<tr>
<th>Marketing Authorisation Holder</th>
<th>Manufacturer</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis Europharm Limited</td>
<td>S.A. Alcon-Couvreur N.V</td>
<td>Alcon Cusí, S.A.,</td>
</tr>
<tr>
<td>Frimley Business Park</td>
<td>Rijksweg 14</td>
<td>Camil Fabra 58,</td>
</tr>
<tr>
<td>Camberley GU16 7SR</td>
<td>B-2870 Puurs</td>
<td>08320 El Masnou,</td>
</tr>
<tr>
<td>United Kingdom.</td>
<td>Belgium</td>
<td>Spain.</td>
</tr>
</tbody>
</table>
For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in.

Detailed information on this medicine is available on the European Medicines Agency website: [http://www.ema.europa.eu](http://www.ema.europa.eu)