

Regulatory Affairs

**DUOTRAV®**  
(travoprost 40 micrograms/mL / timolol 5 mg/mL)  
Eye drops, solution

**Leaflet**

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## **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 ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  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

| <b>System organ class</b>                       | <b>MedDRA preferred term</b>                                                                                                                                                                                                                                                                                                                   |
|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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.

| <b>System organ class</b>                            | <b>MedDRA preferred term</b>                                                                                                                                                                              |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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.

## **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 ( $\geq 0.01$  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  $\beta$ -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 <sup>3</sup>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**

1.5mL (medical sample) and 2.5 mL oval polypropylene (PP) bottle and PP dispensing plug with PP screw cap, presented in an overwrap.

Pack size of 1 bottle.

## **6.6 Special precautions for disposal**

No special requirements.

Manufactured by: S.A. Alcon-Couvreur N.V., Puurs, Belgium.

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