NOVARTIS

TRAVOPROST / TIMOLOL

DUOTRAV®

40 mcg/5 mg per mL (0.004%/ 0.5% w/v) Sterile Ophthalmic Solution

Anti-Glaucoma

DESCRIPTION AND COMPOSITION

Pharmaceutical form
Eye drops, solution.

Active substances
One mL of solution contains 40 micrograms of travoprost and 5 mg of timolol (6.8 mg timolol maleate).

Excipients
Boric acid, mannitol, polyoxyethylene hydrogenated castor oil 40 (HCO-40), polyquaternium-1 (POLYQUAD), propylene glycol, sodium chloride, sodium hydroxide and/ or hydrochloric acid (for pH adjustment), and purified water.

INDICATIONS

Travoprost/Timolol (DUOTRAV®) Sterile Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers, prostaglandins, or other IOP-lowering agents, and when the use of Travoprost/Timolol (DUOTRAV®) Sterile Ophthalmic Solution (the fixed combination drug) is considered appropriate.

Travoprost/Timolol (DUOTRAV®) Sterile Ophthalmic Solution should not be used to initiate therapy.

The use of Travoprost/Timolol (DUOTRAV®) Sterile Ophthalmic Solution is not recommended for pediatric patients.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

General target population

Adults
The recommended dosage of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution is one drop 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. The dosage of Travoprost/Timolol (DUOTRAV®) Sterile Ophthalmic Solution should not exceed one drop in the affected eye(s) once daily since it has been shown that more frequent administration of prostaglandin analogues may decrease the intraocular pressure lowering effect.

If a dose is missed, treatment should continue with the next dose as planned. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

When substituting another ophthalmic antiglaucoma medicinal product with TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution, the other medicinal product should be discontinued and TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution should be started the following day.

Special Populations

Hepatic and renal impairment
No studies have been conducted with TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution or with timolol 5 mg/mL eye drops in patients with hepatic or renal impairment.

Travoprost alone 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 TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution.

Pediatric population (below 18 years)
The use of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution in pediatric patients is currently not recommended. The safety and efficacy of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution in children and adolescents below the age of 18 years have not been established. No data are available.

Geriatric patients (65 years of age and above)
No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

Method of administration

For ocular use only.

To avoid contamination, the dropper tip should not touch any surface. The dropper tip should also not come into contact with the eye as this may cause injury to the eye. When using nasolacrimal occlusion or closing the eyelids for 2 minutes, the systemic absorption is reduced. This may result in a decrease in systemic side effects and an increase in local activity.

If more than one topical ophthalmic medicinal product is being used, the medicinal products must be administered at least 5 minutes apart. Eye ointments should be administered last.
Patients must be instructed to remove soft contact lenses prior to application of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution and wait 15 minutes after instillation of the dose before reinsertion.

CONTRAINDICATIONS

- Hypersensitivity to the active substances, or to any of the excipients.
- Reactive airway disease including bronchial asthma, or a history of bronchial asthma, severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome (including sino-arterial block), second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.

WARNINGS AND PRECAUTIONS

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

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

Vascular disorders
Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders
Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

Hypoglycemia/diabetes
Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycemia.

Hyperthyroidism
Beta-blockers may also mask the signs of hyperthyroidism

Muscle weakness
Beta-adrenergic blocking agents have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalized weakness)

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 doses of adrenaline (epinephrine) used to treat anaphylactic reactions.

Ocular effects
Travoprost may gradually change the eye color 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 color. The change in iris color occurs slowly and may not be noticeable for months to years.

Periorbital and/or eyelid skin darkening has been reported in association with the use of travoprost. 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 include increased length, thickness, pigmentation, and/or number of lashes.

Macular edema has been reported during treatment with prostaglandin F_{2a} analogues. Travoprost should be used with caution in aphakic patients, pseudophakic patients with torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular edema.

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

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

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

Contact lenses
Patients must be instructed to remove contact lenses prior to application of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution and wait at least 15 minutes before reinsertion.

ADVERSE DRUG REACTIONS

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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).

Table 1 Percentage of patients with adverse drug reactions in clinical trials

System organ classification	Adverse drug reaction	Frequency category
Immune system disorders	Hypersensitivity	*Uncommon*
Nervous system disorders	Dizziness, headache	*Uncommon*
Eye disorders	Ocular hyperemia	*Very common*
	Punctate keratitis, vision blurred, dry eye, eye pain, eye pruritus, ocular discomfort, eye irritation	*Common*
	Keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes	*Uncommon*
	Corneal erosion, meibomianitis, trichiasis, distichiasis, conjunctival hemorrhage, eyelid margin crusting	*Rare*
Cardiac disorders	Bradycardia	*Uncommon*
Vascular disorders	Hypertension, hypotension	*Uncommon*
	Dyspnea	*Uncommon*

System organ classification	Adverse drug reaction	Frequency category
Respiratory, thoracic and mediastinal disorders	Bronchospasm, dysphonia, cough, throat irritation	*Rare*
Skin and subcutaneous tissue disorders	Dermatitis contact, hypertrichosis, skin hyperpigmentation (periorbital or eyelid pigmentation)	*Uncommon*
	Urticaria, skin discoloration	*Rare*

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ classification	Adverse drug reaction
Psychiatric disorders	Hallucination, depression
Eye disorders	Macular edema, eyelid ptosis, lid sulcus deepened, iris hyperpigmentation
Cardiac disorders	Chest pain, palpitations
Vascular disorders	Edema peripheral
Respiratory, thoracic and mediastinal disorders	Asthma
Gastrointestinal disorders	Dysgeusia
Skin and subcutaneous tissue disorders	Rash, alopecia

Additional adverse reactions previously reported with the individual components of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution

Travoprost

System organ classification	Adverse reactions
Psychiatric disorders	Anxiety
Eye disorders	Iris hyperpigmentation, cataract, uveitis, conjunctival follicles, hypoaesthesia eye, eye inflammation, eye discharge, eyelid irritation, eyelash discoloration, sunken eyes, eczema eyelids, eyelash thickening, iridocyclitis, anterior chamber pigmentation, dark circle around the eyes
Ear and labyrinth disorders	Tinnitus
Respiratory, thoracic and mediastinal disorders	Nasal dryness
Gastrointestinal disorders	Dry mouth, diarrhea, constipation, abdominal pain, nausea
Skin and subcutaneous tissue disorders	Hair color changes, erythema, pruritus, madarosis
Musculoskeletal and connective tissue disorders	arthralgia, musculoskeletal pain
Renal and urinary disorders	Dysuria, urinary incontinence
Investigations	Prostatic specific antigen increased
General disorders and administration site conditions	Asthenia

Timolol

Like other topically applied ophthalmic drugs, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Additional listed adverse reactions include reactions seen within the class of ophthalmic beta-blockers.

Incidence of systemic adverse reactions after topical ophthalmic administration is lower than for systemic administration.

System organ classification	**Adverse reactions**
Immune system disorders	Systemic allergic reactions including angioedema, localized and generalized rash, pruritus, anaphylaxis
Metabolism and nutrition disorders	Hypoglycemia
Psychiatric disorders	Insomnia, nightmares, memory loss
Nervous system disorders	Cerebral ischemia, increases in signs and symptoms of myasthenia gravis
Eye disorders	Choroidal detachment following filtration surgery (see section WARNING AND PRECAUTIONS), decreased corneal sensitivity, diplopia
Cardiac disorders	Edema, congestive heart failure, atrioventricular block, cardiac arrest
Vascular disorders	Raynaud's phenomenon, cold hands and feet.
Gastrointestinal disorders	Nausea, dyspepsia, diarrhea, 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

INTERACTIONS

The following interactions are expected with TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution due to potential drug interactions with the mono-components:

- Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine) and timolol.
- There is a potential for additive effects resulting in hypotension and/or marked bradycardia when an ophthalmic beta-blocker solution is administered concomitantly with oral calcium channel blockers, beta-adrenergic blocking agents, antiarrhythmics (including amiodarone), digitalis glycosides or parasympathomimetics.
- Beta-blockers can decrease the response to adrenaline used to treat anaphylactic reactions. Special caution should be exercised in patients with a history of atopy of anaphylaxis (see section WARNINGS AND PRECAUTIONS).
- Mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

There is limited amount of data from the use of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution or the individual components in pregnant women.

Studies in rats and mice with subcutaneous (s.c.) administration of travoprost during organogenesis have shown reproductive toxicity at the dose of 34 times and 1.7 times, respectively, the maximum recommended ocular human dose (MROHD) based on body surface area (BSA). Reproduction studies in mice, rats and rabbits with orally administered timolol showed no malformations at doses up to 675 times the MROHD based on BSA (see Animal data).

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 hypoglycemia) have been observed in the neonate when systemic beta-blockers have been administered to the mother until delivery.

TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution should not be used during pregnancy unless clearly necessary. However, if TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution is administered during pregnancy up to the time of delivery, the neonate should be carefully monitored during the first days of life.

Animal data

Travoprost
An embryo-fetal study was conducted in pregnant mice administered travoprost once daily by subcutaneous injection during the period of organogenesis. At 1 microgram /kg/day (1.7 times the MROHD, based on BSA), travoprost caused post-implantation loss and decreased fetal weight. The no-observed-effect-level (NOEL) for embryofetal toxicity was 0.3 micrograms/kg/day (0.5 times the MROHD, based on BSA). The maternal NOEL was 1 micrograms/kg/day.

An embryo-fetal study was conducted in pregnant rats administered travoprost once daily by s.c. injection during the period of organogenesis. At 10 micrograms/kg/day (34 times the MROHD, based on BSA), travoprost was teratogenic in rats, as evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, including fused sternebrae, domed head and hydrocephaly. Travoprost caused post-implantation loss at 10 micrograms/kg/day. The NOEL for post-implantation loss was 3 micrograms/kg/day (10 times the MROHD based on BSA).

Pre and postnatal development studies were conducted in rats administered with travoprost once daily by s.c. injection during organogenesis and lactation. At doses of ≥0.12 micrograms/kg/day (0.4 times the MROHD, based on BSA), adverse pregnancy outcomes (embryofetal lethality, abortion, early delivery), low birth weight and developmental delays were observed for F1 offspring. The NOEL for adverse pregnancy outcomes, low birth weight and developmental delay was 0.1 micrograms/kg/day (0.3 times the MROHD, based on BSA). The NOEL for F2 offspring development was 0.36 micrograms/kg/day (1.2 times the MROHD, based on BSA).

Timolol
Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (675 times the MROHD based on BSA) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1,000 mg/kg/day (13,500 times the MROHD based on BSA) were maternal toxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at 100 mg/kg/day or 5,400 times the MROHD based on BSA, and without apparent maternal toxicity.

Lactation

Risk summary

There is a limited amount of data from the use of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution in breast-feeding women.

Timolol is transferred into human breast milk following ocular topical administration. Oral beta-blockers have the potential to cause serious adverse reactions in the breast-fed infant. However, in the case of ocular administration at therapeutic doses, the amounts of timolol present in breast milk are not likely to produce clinical symptoms of beta-blockade in the infant.

It is unknown whether travoprost is transferred into human breast milk after ocular administration. An animal study has shown transfer of travoprost and/or metabolites into milk following subcutaneous administration (see Animal data).

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution and any potential adverse effects on the breast-fed child from TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution.

Animal data

A study in lactating rats demonstrated that radiolabeled travoprost and/or its metabolites were excreted in milk following subcutaneous administration with highest concentrations of travoprost and/or metabolites observed 6 hours post dose with a milk to plasma ratio of 11.

Females and males of reproductive potential

Infertility

There are no data on the effects of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution on human fertility. Fertility studies in rats showed no effect of travoprost or timolol at doses up to 34 times and 4,050 times the MROHD, respectively, based on BSA (see section NON-CLINICAL SAFETY DATA).

OVERDOSAGE

An ocular overdose of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution may be flushed from the eye(s) with lukewarm water.

No specific reactions are to be expected with an ocular overdose of the product.

In case of accidental ingestion, symptoms of overdose from systemic beta blockade may include bradycardia, hypotension, cardiac failure and bronchospasms.

Treatment of an accidental ingestion should be symptomatic and supportive.

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution contains two active ingredients: travoprost and timolol maleate. These two agents reduce intraocular pressure by complementary mechanisms of action with a combined effect greater than that of either compound administered alone (synergistic effect).

Travoprost, a prostaglandin F_{2alpha} 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 humor via trabecular meshwork and uveoscleral pathways. Reduction of IOP in human starts within approximately 2 hours after administration and maximum effect is achieved after 12 hours. Significant intraocular pressure reduction can be maintained for periods exceeding 24 hours following a single dose.

Timolol is a non-selective adrenergic blocking agent that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilizing activity. Its predominant ocular mechanism of action is to reduce aqueous humor formation and a slight increase in outflow facility.

Pharmacodynamics (PD)

In addition to reducing IOP, travoprost has been shown to increase optic nerve head blood flow based on data in rabbits following 7 days of topical ocular administration (1.4 micrograms, once daily (QD).

Pharmacokinetics (PK)

Absorption
Travoprost and timolol are absorbed through the cornea. Travoprost is an isopropyl ester prodrug which undergoes rapid hydrolysis in the cornea to produce the active free acid. Following once-daily administration of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution (polyquaternium-1-preserved) to healthy subjects for 5 days, travoprost free acid plasma concentrations were below the 0.010 ng/mL assay quantitation limit in the majority of samples. Quantifiable free acid concentrations were observable in some cases within 1 hour post-dose, ranging from 0.010 to 0.030 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 Travoprost/Timolol (DUOTRAV®) Sterile Ophthalmic Solution. Timolol has a plasma elimination half-life of about 4 hours.

Distribution
Travoprost free acid can be measured in aqueous humor for several hours in animals and in human plasma up to 1 hour post-dose. Timolol can be measured in human aqueous humor after topical ocular administration of timolol and in plasma for up to 12 hours following topical ocular administration of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution.

Biotransformation/metabolism
Metabolism is the primary clearance mechanism for both travoprost and its free acid. The systemic metabolic pathways for travoprost free acid parallel those of endogenous prostaglandin F_{2alpha}, which are characterized by reduction of the 13 to 14 double bond, oxidation of the 15-hydroxyl to form a ketone, and beta-oxidative cleavages of the carboxylic acid side chain.

Timolol is metabolized by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other generates an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. No timolol metabolism occurs within the eye.

Elimination
Both travoprost free acid and timolol, along with their respective metabolites, are primarily excreted in urine. Less than 2% of an ocular dose of travoprost was recovered in urine as travoprost free acid. Approximately 20% of a timolol dose was found in urine as parent drug with the remainder excreted as metabolites.

Due to the very low concentrations and rapid disappearance of travoprost free acid from plasma, elimination half-life could not be determined. Timolol has a plasma elimination half-life of about 4 hours.

Linearity/non-linearity
Both travoprost and timolol exhibit linear pharmacokinetics following topical administration, either alone or in combination.

Pediatric patients (below 18 years)
The pharmacokinetics of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution in pediatric patients has not been studied.

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

CLINICAL STUDIES

In a 12-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 25 to 27 mmHg, the mean IOP-lowering of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution dosed once-daily in the morning was 8 to 10 mmHg. The non-inferiority of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution as compared with latanoprost 0.005% plus timolol 0.5% in mean IOP reduction was demonstrated across all time points at all visits.

In a 3-month, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 27 to 30 mmHg, the mean IOP-lowering effect of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution dosed once-daily in the morning was up to 2 mmHg greater than that of travoprost 0.004% dosed once-daily in the evening and 2 to 3 mmHg greater than that of timolol 0.5% dosed b.i.d. A statistically significant superior reduction in mean morning IOP (8 AM - 24 hours after the previous dose of Travoprost/Timolol (DUOTRAV®) Sterile Ophthalmic Solution) was observed compared with travoprost 0.004% at all visits throughout the study.

In two 3-month, controlled clinical studies in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 23 to 26 mmHg, the mean IOP-lowering effect of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution dosed once-daily in the morning was 7 to 9 mmHg. Mean IOP reductions were non-inferior, although numerically lower, compared with those achieved by concomitant therapy with travoprost 0.004% dosed once-daily in the evening and timolol 0.5% dosed once-daily in the morning.

In a 6-week, controlled clinical study in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP range of 24 to 26 mmHg, the mean IOP-lowering effect of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution (polyquaternium 1-preserved) dosed once-daily in the morning was 8 mmHg and equivalent to that of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution (benzalkonium chloride-preserved).

Inclusion criteria were similar across the above clinical studies, with the exception of the IOP entry criteria and response to previous IOP-lowering therapy. The clinical development of TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution included both treatment-naive patients and patients on therapy. Insufficient responsiveness to monotherapy was not an inclusion criterion. TRAVOPROST/TIMOLOL (DUOTRAV®) Sterile Ophthalmic Solution was well tolerated with no serious adverse events observed.

Additional randomized, double- or observer-masked, active-controlled studies have been performed in which over 500 subjects with open-angle glaucoma or ocular hypertension were treated with Travoprost 0.004%/Timolol 0.5%.

Many of these studies measured the IOP-lowering effects Travoprost 0.004%/Timolol 0.5% after a wash-out period and these demonstrated an IOP-lowering effect from baseline that is consistent with that shown in the pivotal studies described above.

NON-CLINICAL SAFETY DATA

Non-clinical data for travoprost and timolol reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, and topical ocular irritation studies. Ocular irritation studies were also conducted with travoprost plus timolol, and no adverse effects were observed with the exception of widened palpebral fissure and increased iris pigmentation in monkeys, which is consistent with the topical ocular administration of prostaglandins in humans. For details

on reproductive studies, see Section PREGNANCY, LACTATION, FEMALE AND MALE OF REPRODUCTIVE POTENTIAL.

Fertility studies in rats dosed with travoprost subcutaneously resulted in significant reductions in the number of corpora lutea, viable fetuses, and an increased early post-implantation loss as well as resorption rate at 10 micrograms/kg/day (34 times the MROHD based on BSA). The no effect level was set at 3 micrograms/kg/day (10 times the MROHD based on BSA). In contrast, fertility studies with timolol in rats showed no effects at oral doses up to 150 mg/kg/day (4,050 times the MROHD based on BSA).

INCOMPATIBILITIES

Not applicable.

STORAGE

Store at temperatures not exceeding 30ºC. Do not use this medicine after the expiry date which is stated on the packaging. Discard 4 weeks after first opening. Keep this medicine out of the reach and sight of children.

AVAILABILITY

White syndiotactic polypropylene (SPP) oval droptainer with a polypropylene (PP) natural dispensing plug and a white polypropylene (PP) closure with foil overwrap x 2.5 mL (Box of 1's)

CAUTION: Food, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: **www.fda.gov.ph**

The patient is advised to seek IMMEDIATE medical attention at the first sign of adverse drug reaction.

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