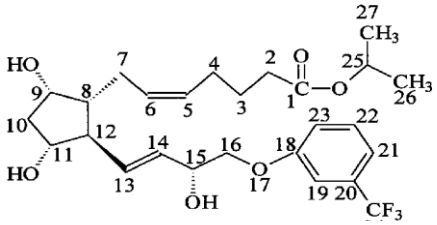
PRODUCT INFORMATION

DuoTrav* (travoprost 0.004% and timolol 0.5%) Eye Drops

NAME OF THE MEDICINE

DuoTrav Eye Drops is a combination eye drop containing a topical prostaglandin analogue, travoprost 0.004% and a topical beta-adrenergic receptor blocking agent, timolol maleate 0.68% (equivalent to timolol 0.5%). This product is benzalkonium chloride (BAK) free and uses polyquaternium-1(POLYQUAD) as a preservative.

The chemical structure of travoprost is:



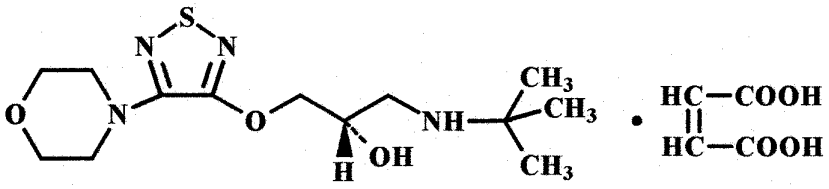
Molecular weight: 500.56

Empirical formula: $C_{26}H_{35}F_3O_6$

Chemical name: (5Z,13E)-(9S,11R,15R)-9,11,15-Trihydroxy-16-(*m* trifluoromethylphenoxy) 17,18,19,20-tetranor-5,13-prostadienoic acid, isopropyl ester.

CAS Number: 157283-68-6

The chemical structure of timolol maleate is:



Molecular weight: 432.50

Empirical formula: $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$

Chemical name: (S)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl) oxy]-2 propanol maleate (1:1) (salt).

CAS Number: 26921-17-5.

DESCRIPTION

*Travoprost i*s a clear to slightly opalescent, colourless to yellow oil. Travoprost is practically insoluble in water (approximately 44 ppm).

Timolol maleate is a white to off-white, crystalline powder which is soluble in water, alcohol and practically insoluble in ether.

DuoTrav Eye Drops is a sterile, isotonic aqueous solution of travoprost and timolol maleate with a buffered pH of approximately 6.8 and an osmolality of approximately 290 mOsmol/kg for topical application to the eye**.**

Each mL of DuoTrav Eye Drops contains 40 micrograms travoprost and 6.83 mg timolol maleate (equivalent to 5 mg timolol) together with Castor oil – ethoxylated hydrogenated, propylene glycol, boric acid, mannitol, sodium chloride, sodium hydroxide and/or hydrochloric acid (for pH adjustment) and purified water. The solution is preserved with polyquaternium-1 (POLYQUAD*)

Note: For further information about the active components contained in DuoTrav Eye Drops, refer to travopost and timolol individual product information documents.

PHARMACOLOGY

Pharmacodynamics

DuoTrav Eye Drops contains two active components, travoprost and timolol, which lower intraocular pressure (IOP) by complementary mechanisms of action. Following the administration of DuoTrav Eye Drops, the reduction in IOP starts within 30 minutes and the maximum effect is reached after 12 hours. Significant IOP reduction is maintained for at least 24 hours after multiple treatments.

Glaucoma is defined as an optic neuropathy resulting in optic nerve head damage and visual field loss. The pathogenesis of glaucoma is multi-factorial; the primary risk factors, however, are considered to be sustained elevated IOP and poor ocular perfusion. Clinical studies have shown that DuoTrav Eye Drops results in additional IOP reduction compared to either component administered alone and that the IOP-lowering effect is comparable to Travatan* Eye Drops (travoprost 0.004%) and timolol 0.5% administered concomitantly once daily.

Travoprost: Travoprost is an ester prodrug of a $PGF_{2\alpha}$ analogue and is hydrolysed to the active acid. The free acid is a prostaglandin FP receptor agonist. $PGF_{2\alpha}$ analogues are believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. Reduction of IOP in man starts about 2 hours after administration and maximum effect is reached after twelve hours. Pressure reduction is maintained for at least twenty-four hours. Pivotal clinical studies have demonstrated that Travatan Eye Drops is effective as monotherapy at reducing IOP. Repeated observations over a period of one year indicate that the IOP-lowering effect of travoprost is well maintained. In addition, travoprost slightly, but significantly, increased optic nerve head blood flow in a single study in rabbits.

Timolol: Timolol maleate is a non-selective β1- and β2-adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane stabilising) activity. Timolol lowers IOP by decreasing the formation of aqueous humour in the ciliary epithelium. The precise mechanism of action is not clearly established.

Pharmacokinetics

Absorption: Travoprost and timolol are absorbed through the cornea. Travoprost undergoes rapid ester hydrolysis in the cornea to the active free acid. Following topical ocular administration of DuoTrav Eye Drops (POLYQUAD preserved)once-daily in healthy subjects (n=22) for 5 days, the travoprost free acid was not quantifiable in plasma samples from the majority of subjects (94.4%) and generally was not detectable in samples one hour after dosing. In those subjects in whom travoprost free acid was measurable (≥0.01 ng/mL, the assay limit of quantitation), plasma concentration ranged from 0.01 to 0.03 ng/mL. The mean peak timolol steady-state concentration was 1.34 ng/mL after once-daily administration of DuoTrav Eye Drops (POLYQUAD preserved). Timolol T_{max} was approximately 0.69 hours after dosing.

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 topical ocular administration of DuoTrav Eye Drops. Timolol can be measured in human aqueous humour after topical ocular administration of timolol and in plasma for up to 12 hours after topical ocular administration of DuoTrav Eye Drops.

Metabolism: The metabolic pathways of the travoprost free acid parallel those of endogenous $PGF_{2\alpha}$ and are characterised by reduction of the 13-14 double bond, oxidation of the 15-hydroxyl group and β-oxidation of the carboxylic acid chain. The plasma elimination of the free acid was rapid with a mean apparent $t_{1/2}$ of approximately 45 minutes. There was no difference in plasma concentrations between Days 1 and 3, indicating lack of drug accumulation following repeated administration of DuoTrav Eye Drops. Timolol is extensively metabolised in the liver. The apparent terminal elimination $t_{1/2}$ of timolol in plasma was approximately 4 hours after topical ocular administration of DuoTrav Eye Drops.

Excretion: Travoprost free acid and its metabolites are mainly excreted by the kidneys. In humans, less than 2% of a topical 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.

CLINICAL TRIALS

Clinical Studies with DuoTrav Eye Drops (POLYQUAD preserved, BAK free)

Pharmacokinetics

A double blind, two way crossover pharmacokinetic study (n=24) was conducted comparing DuoTrav Eye Drops preserved with POLYQUAD (BAK-free) or preserved with benzalkonium chloride (BAK). Patients were dosed in the morning for 5 days to evaluate the steady state plasma pharmacokinetics of travoprost (travoprost free acid (AL-5848)) and timolol. Plasma concentrations were below the limit of quantitation (LOQ =0.0100 µg /mL) in 94% of samples. T_{max} and $T_{1/2}$ were similar for timolol.

Efficacy Studies

A randomised double blind clinical equivalence study (n=388) was conducted to compare DuoTrav (BAK-free) against DuoTrav (BAK). Patients with open angle glaucoma or ocular hypertension were dosed once daily in the morning for 6 weeks. The primary efficacy parameter was mean IOP at the 9 AM, 11 AM and 4 PM time points at Week 6. The percentage of patients with IOP < 18 mmHg or IOP percent reduction of ≥ 30% was a secondary variable.

DuoTrav Eye Drops (BAK-free) and DuoTrav Eye Drops (BAK) produced statistically equivalent IOP lowering efficacy. Mean IOP reductions from baseline for both formulations were clinically relevant and stastically significant at all measurement times. Mean IOP reductions ranged from 7.5 to 8.3 mmHg for DuoTrav Eye Drops (BAK-free) and from 8.1 to 8.5 mmHg for DuoTrav Eye Drops (BAK). Differences in mean IOP between DuoTrav Eye Drops (BAK-free) and DuoTrav Eye Drops (BAK) ranged from 0.1 to 0.7 mmHg when evaluated across all on therapy visits and times (i.e. 3 diurnal times at 2 visits).

The percentage of patients with IOP <18 mmHg or percent reduction ≥30% at each study visit ranged from 60% to 73% in the DuoTrav Eye Drops (BAK-free) group and from 67% to 73% in the DuoTrav Eye Drops (BAK) group. The estimates of pooled IOP response in the two treatment groups were similar and not statistically significantly different (67% vs 70%, p=0.3710). No clinically relevant safety differences were identified.

Clinical Studies with DuoTrav Eye Drops (BAK)

Adult patients with diagnoses of predominately primary open angle glaucoma, ocular hypertension or pigmentary glaucoma participated in three randomised, double-masked, parallel group multicenter studies (n=982) to demonstrate the safety and efficacy of DuoTrav Eye Drops. These studies evaluated the IOP-lowering effect of DuoTrav Eye Drops dosed once daily (morning) over three-months compared to:

- monotherapy with its individual components (mean baseline intraocular pressures of 27 to 30 mmHg), travoprost 0.004% dosed once daily (evening) and timolol 0.5% dosed twice daily (contribution-of-elements; Study 1)

- concomitant administration of travoprost 0.004% and timolol 0.5% (mean baseline intraocular pressures of 23 to 26 mmHg), both dosed once daily (evening and morning, respectively; Study 2). One study also used timolol 0.5% dosed twice daily (Study 3).

The primary efficacy parameter for all studies was mean IOP at 8 AM, 10 AM and 4 PM. The proportion of patients with IOP < 18 mmHg was measured as a secondary efficacy parameter.

Approximately 22% to 37% of the patients included in the studies were treatment-naïve patients. All other patients were receiving monotherapy (49% to 57%) with either timolol, a prostaglandin or other medication; two medications (11% to 17%) or three plus medications (2% to 4%).

In the contribution-of-elements study (Study 1), the mean IOP-lowering effect of DuoTrav Eye Drops dosed once-daily in the morning was 8.7 to 11.5 mmHg, and was 0.4 to 1.8 mmHg greater than Travatan 0.004% dosed once daily in the evening and 1.5 to 2.7 mmHg greater than that of timolol 0.5% dosed twice-daily. However there are no data to show the optimal dose of these agents in combination. In the two concomitant administration studies, the mean IOP reductions of DuoTrav Eye Drops were similar to those achieved by concomitant therapy with Travatan dosed once daily in the evening and timolol dosed once daily in the morning (see Table 1). Differences in mean IOP change from baseline at 10 AM and 4 PM were approximately 1 mmHg, favouring concomitant therapy. No differences were observed at 8 AM. When DuoTrav Eye Drops was compared to concomitant therapy (Study 2 and Study 3), non-inferiority was not demonstrated at all time points. However pooled analyses revealed non-inferiority. Six month extension data were consistent with previous findings in the individual studies.

DuoTrav Eye Drops yielded IOP < 18 mmHg at one or more time-points at all visits throughout the entire 3-month period for 50% of patients in the contribution-of-elements study, and for 74% of patients in a pooled analysis of the concomitant administration studies.

Table 1 Mean IOP (mmHg) for Study 2 and Study 3

Visit	Time point	Mean IOP (mmHg)			
		Study 2		Study 3	
		DuoTrav Eye Drops (n=151)	TRAVATAN Eye Drops + Timolol qd (n=142)	DuoTrav Eye Drops (n=155)	TRAVATANEye Drops + Timolol bid (n=151)
Baseline	8AM	25.2	25.1	25.6	25.0
	10AM	24.0	23.9	24.0	23.9
	4PM	23.0	23.1	23.1	22.9
Week 2	8AM	16.2	16.0	17.5	16.8
	10AM	15.5	15.2	16.8	15.7
	4PM	15.2	14.8	16.2	15.4
Week 6	8AM	15.9	15.7	17.0	16.6
	10AM	15.8	14.8	16.6	15.6
	4PM	15.6	14.7	16.2	15.5
Month 3	8AM	16.6	16.0	17.1	16.7
	10AM	16.1	15.1	16.5	15.8

	4PM	15.6	14.7	16.3	15.5

Double-masked extensions of the three studies mentioned above were conducted for up to an additional three months. The IOP-lowering effect of DuoTrav Eye Drops was maintained during this period.

A separate dosing study (morning or evening) confirmed that the IOP-lowering efficacy of once-daily DuoTrav Eye drops is independent of the time of dosing.

A similar safety profile was observed comparing therapy with DuoTrav Eye Drops to concomitant therapy with the individual components (travoprost 0.004% + timolol 0.5%) or to monotherapy with each component (travoprost 0.004%; timolol 0.5%).

INDICATIONS

Reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension for whom single agent therapy provides insufficient intraocular pressure reduction.

CONTRAINDICATIONS

DuoTrav Eye Drops are contraindicated in patients with a known hypersensitivity to travoprost, timolol or any of the excipients in DuoTrav (see DESCRIPTION).

DuoTrav Eye Drops are also contraindicated in pregnant women or women attempting to become pregnant (see Use in Pregnancy).

Reactive airway disease including bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease.

Sinus bradycardia, sick sinus syndrome, including sino-atrial block, second or third degree atrioventricular block, overt cardiac failure or cardiogenic shock.

PRECAUTIONS

Not for injection or oral ingestion.

Cardiovascular/respiratory reaction: Like other topically applied ophthalmic agents, DuoTrav may be absorbed systemically. Due to the beta-adrenergic component timolol, the same types of adverse reactions seen with systemic beta-blockers may occur including aggravation of Prinzmetal angina, aggravation of severe peripheral and central circulatory disorders, bradycardia and hypotension.

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 monitored for signs of deterioration of these diseases and for adverse reactions.

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 and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death associated with cardiac failure have been reported following administration of timolol. Cardiac failure should be adequately controlled before treatment.

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, whether accidental, diagnostic or therapeutic. In addition, such patients may be unresponsive to the usual doses of adrenaline used to treat anaphylactic reactions.

Concomitant therapy: Timolol may react with other drugs (see Interactions with Other Medicines). The effect on IOP or the known effects of systemic beta-blockade may be exaggerated when DuoTrav Eye Drops is given to patients already receiving an oral beta-blocking agent. The response of these patients should be closely monitored. The use of two topical beta-blockers or topical prostaglandins is not recommended.

The use of DuoTrav Eye Drops may be considered in patients who require both timolol and travoprost, but it is unknown whether patients who are adequately controlled with timolol given twice daily plus travoprost given once daily will be as well controlled with DuoTrav Eye Drops given once daily. DuoTrav Eye Drops should not be used to initiate therapy.

Additional effects of beta-blockade: Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycaemic agents. Beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Therapy with beta-blockers may mask certain symptoms of hyperthyroidism and abrupt withdrawal of therapy may precipitate a worsening of symptoms.

Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

Surgical anaesthesia

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

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 these changes. 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. It may be permanent. 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.

Periorbital and/or eyelid skin darkening and deepening of the eyelid sulcus have been reported in association with the use of Travoprost.

Eyelash changes occurred in over a third of patients treated with DuoTrav Eye Drops. These changes include: increased length, thickness, pigmentation, and/or number of lashes.

There is no experience of DuoTrav Eye Drops in inflammatory ocular conditions, inflammatory, neovascular, angle-closure or congenital glaucoma and only limited experience in open-angle glaucoma of pseudophakic patients and in pigmentary glaucoma.

Although not reported during pivotal clinical trials with DuoTrav Eye Drops, macular oedema, including cystoid macular oedema, has been reported during treatment with prostaglandin $F_{2\alpha}$ analogues. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule or anterior chamber lenses, or in patients with known risk factors for macular oedema. DuoTrav Eye Drops should be used with caution in these patients.

DuoTrav Eye Drops should be used with caution in patients with active intraocular inflammation, as well as patients with predisposing risk factors for uveitis.

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

Use of contact lens(es)

If patients continue to wear contact lenses while under treatment with DuoTrav Eye Drops they should remove their lens(es) prior to instilling DuoTrav Eye Drops in the affected eye(s) and should not insert their lens(es) until 15 minutes after instillation of the eye drops.

Actions the health care professional should take

Systemic absorption can be minimised if patients are instructed to gently occlude the nasolacrimal ducts for two minutes immediately after instillation of the eye drop.

Effects on fertility

There are no human data on the effects of DuoTrav Eye Drops on male or female fertility.

Travoprost. Travoprost had no effects on mating behaviour or fertility in male and female rats at subcutaneous doses up to 10 μg/kg/day (equivalent to 54 times the human exposure at the MRHOD), although embryo-foetal resorption was increased at 10 μg/kg/day (further information on effects on pregnancy is included under Use in Pregnancy).

Timolol. Timolol maleate alone had no effects on male or female fertility when administered at 300 μg/kg/day, PO.

Use in Pregnancy - Category C

No adequate and well-controlled studies have been performed in pregnant women. DuoTrav Eye Drops may interfere with the maintenance of pregnancy. It should not be used by women during pregnancy or by women attempting to become pregnant.

Travoprost. The human dose of travoprost with the recommended dosage of DuoTrav Eye Drops is 2.2 μg/day or 0.044 μg/kg/day, with plasma concentrations of up to 0.020 ng/mL. Travoprost and/or its metabolites crossed the placenta in rats. Travoprost was teratogenic in rats at intravenous doses of 10 μg/kg/day, equivalent to 98 times the human exposure; it increased the incidence of hydrocephaly and bone abnormalities (e.g. vertebral malformations). Travoprost was not teratogenic in rats at intravenous doses of up to 3 μg/kg/day (29 times the human exposure). When administered to rats during organogenesis (gestation days 6 to 17), travoprost produced increases in post-implantation loss and early delivery at intravenous doses of 10 μg/kg/day (98 times the human exposure). Post-implantation loss increased in rats at subcutaneous doses of 10 μg/kg/day (54 times human exposure) administered from 2 weeks prior to mating to gestation day 7. Travoprost was not teratogenic in mice at subcutaneous doses of up to 0.3 μg/kg/day; post-implantation loss and early delivery were increased in mice at subcutaneous doses of 1 μg/kg/day (5.8 times the human exposure), but not at 0.3 μg/kg/day (1.7 times the human exposure).

Travoprost Eye Drops, 0.003% administered to rabbits during organogenesis, appeared to increase incidence of foetal loss.

In rats administered travoprost from gestation day 7 to lactation day 21 by subcutaneous injection, abortions occurred at 0.72 μg/kg/day (4 times human exposure), and decreased gestation length and increased still births (see also Use in Lactation) occurred at ≥ 0.12 μg/kg/day (0.65 times human exposure).

Timolol: Timolol maleate was not teratogenic in mice, rats and rabbits. Embryo-foetal development studies with timolol maleate in mice and rabbits showed no evidence of embryo-foetal toxicity at doses up to 50 mg/kg/day. At higher doses, increases in resorptions and foetal variations (14 ribs and hypoplastic sternebrae) were noted in mice (1,000 mg/kg/day) and increased resorption in rabbits (≥ 90 mg/kg/day). In rats, delayed ossification was seen at ≥ 50 mg/kg/day and a decreased number of caudal vertebral bodies and arches and an increase in hypoplastic sternebrae were noted at 500 mg/kg/day.

Epidemiological studies show a risk for intra-uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when systemic beta-blockers have been administered to the mother until delivery.

Use in Lactation

Nursing women who use DuoTrav Eye Drops should use caution because of the potential for serious adverse reactions from DuoTrav Eye Drops in breastfeeding infants.

Travoprost: There are no data on the excretion of travoprost into human milk or on the safety of travoprost exposure in infants. Because many drugs are excreted in human milk and adverse effects in rat pups were observed at low doses of travoprost (see below), nursing women who use DuoTrav Eye Drops should stop breastfeeding. A study in rats showed that travoprost and/or its metabolites were excreted in milk. Increased pup mortality and depressed pup growth and development occurred in rats where the dams were subcutaneously administered travoprost from gestation day 7 to lactation day 21 at greater than or equal to 0.12 μg/kg/day, corresponding to 2.7 the expected human dose.

Timolol: Timolol maleate has been detected in human milk following oral and ocular administration.

Paediatric use

DuoTrav Eye Drops is not recommended for use in children. The safety and effectiveness in paediatric patients have not been established.

Use in the Elderly

No overall differences in safety and effectiveness have been reported between elderly and other adult patients.

Hepatic/Renal Impairment

No dosage alteration of DuoTrav Eye Drops is necessary in these patients.

Carcinogenicity

Carcinogenicity studies with DuoTrav Eye Drops have not been conducted.

Travoprost: Long term studies in mice and rats at subcutaneous doses up to 100 μg/kg/day did not provide any evidence of carcinogenic potential. These doses correspond to exposure levels over 200 times human exposure at the maximum recommended human ophthalmic dose (MRHOD), based on plasma active drug levels.

Timolol: No evidence of carcinogenicity was observed with timolol maleate at oral doses up to 100 mg/kg/day in rats and 50 mg/kg/day in mice. However, there was a statistically significant increase in the incidence of adrenal phaeochromocytomas in male rats administered 300 mg/kg/day. In female mice, statistically significant increases in the incidence of benign and malignant pulmonary tumours, benign uterine polyps and mammary carcinomas were found at 500 mg/kg/day. The increased incidence of mammary tumours was considered to be attributed to a species elevation in serum prolactin.

Genotoxicity

Mutagenicity studies with DuoTrav Eye Drops have not been conducted.

Travoprost: Travoprost did not cause gene mutation in bacteria or chromosomal aberrations in bone marrow cells of mice and rats. A slight increase in mutation frequency was observed in one of two mouse lymphoma L5178Y assays. Weight of evidence indicates that travoprost is unlikely to pose a genotoxic risk from clinical use.

Timolol: In vitro and *in vivo* studies with timolol maleate did not reveal a mutagenic potential.

INTERACTIONS WITH OTHER MEDICINES

No pharmacokinetic interactions were observed between travoprost and timolol following topical ocular administration of DuoTrav Eye Drops. No specific interaction studies were performed with DuoTrav Eye Drops and other drugs.

Travoprost

The plasma protein binding of the active free acid form of travoprost is moderate (approximately 80%) and, therefore, drug-drug interactions involving protein binding are unlikely.

Timolol

The potential exists for additive effects resulting in hypotension, and/or marked bradycardia when timolol ophthalmic drops are administered with oral calcium channel blockers, catecholamine depleting drugs or β-adrenergic blocking agents, antiarrhythmics (including amiodarone and quinidine), digitalis glycosides, parasympathomimetics, narcotics and monoamine oxidase inhibitors (MAOIs).

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.

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 or anaphylaxis. (See PRECAUTIONS).

Although DuoTrav Eye Drops used alone has little or no effect on pupil size, mydriasis has occasionally been reported when timolol is given with adrenaline.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic agents.

Effects on ability to drive and use machines

As with other ophthalmic medications, patients should be advised to exercise caution if they experience transient blurred vision following instillation of eye drops. Patients should wait until their vision clears before driving or using machinery.

ADVERSE EFFECTS

Adverse events arising from clinical trials of 6 week to 12 month duration involving DuoTrav (POLYQUAD*-preserved) were consistent with the known safety profile for DuoTrav (BAK-preserved).

DuoTrav (POLYQUAD-preserved)

In 3 clinical trials involved in the development of DuoTrav (POLYQUAD-preserved), 372 patients/subjects were exposed for up to 12 months. The most frequently reported treatment-related undesirable effect with DuoTrav (POLYQUAD-preserved) was hyperaemia of the eye (11.8%), which included ocular or conjunctival hyperaemia. The majority of patients (91%) who experienced hyperaemia of the eye did not discontinue therapy as a result of this reaction.

The following adverse reactions listed 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.

The following adverse reactions listed below were observed in the clinical studies.

Immune system disorders

Uncommon: hypersensitivity

Nervous system disorders

Uncommon: Headache

Eye disorders

Common: eye pain, ocular discomfort, dry eye, eye pruritus, ocular hyperaemia

Uncommon: punctate keratitis, iritis, photophobia, vision blurred, conjunctivitis, meibomianitis, eyelid margin crusting, asthenopia, lacrimation increased, growth of eye lashes

Cardiac disorders

Uncommon: Bradycardia

Vascular disorders

Uncommon: hypotension

Skin and subcutaneous tissue disorders

Uncommon: skin discolouration, hair growth abnormal

General disorders and administration site conditions

Uncommon: fatigue

Investigations

Uncommon: heart rate decreased

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

Travoprost

Eye disorders: uveitis, conjunctival disorder, conjunctival follicles, iris hyperpigmentation

Skin and subcutaneous tissue disorders: skin exfoliation.

Timolol

Metabolism and nutrition disorders: hypoglycaemia

Nervous system disorders: cerebral ischaemia, myasthenia gravis

Eye disorders: diplopia

Cardiac disorders: cardiac arrest, atrioventricular block, palpitations

Respiratory, thoracic and mediastinal disorders: respiratory failure, nasal congestion

Gastrointestinal disorders: diarrhoea, nausea

General disorders and administration site conditions: asthenia.

Post Marketing Experience

The following adverse reactions have been reported during clinical studies with DuoTrav (POLYQUAD*-preserved) and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

Immune system disorders

Uncommon: hypersensitivity

Nervous system disorders

Uncommon: headache

Eye disorders

Common: eye pain, dry eye, eye pruritus, ocular discomfort, ocular hyperaemia

Uncommon: punctate keratitis, iritis, conjunctivitis, vision blurred, photophobia, eyelids pruritus, asthenopia, meibominitis, eyelid margin crusting, growth of eyelashes

Cardiac disorders

Uncommon: Bradycardia

Vascular disorders

Uncommon: hypotension

Skin and subcutaneous tissue disorders

Uncommon: skin discolouration

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

Nervous system disorders

Dizziness

Eye disorders

Macular oedema, keratitis, blepharitis, conjunctivitis, erythema of eyelid, eye swelling, lacrimation increased, eyelid oedema, eyelid ptosis, eye irritation

Cardiac disorders

Chest pain, palpitations

Vascular disorders

Hypertension

Respiratory, thoracic and mediastinal disorders

Dyspnoea, cough, asthma

Skin and subcutaneous tissue disorders

Alopecia

DuoTrav (BAK-preserved)

In clinical studies involving 938 patients, DuoTrav (BAK-preserved) was administered once-daily. No serious ophthalmic or systemic adverse reactions related to DuoTrav were reported. The most frequently reported treatment-related adverse reaction was ocular hyperaemia (15.0%). Almost all patients (96%) who experienced ocular hyperaemia did not discontinue therapy as a result of this reaction.

The following adverse reactions listed 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.

Psychiatric disorders

Common: nervousness

Not known: depression

Nervous system disorders

Common: dizziness, headache

Not known: cerebrovascular accident, syncope, paraesthesia

Eye disorders

Very common: ocular discomfort, ocular hyperaemia

Common: punctate keratitis, anterior chamber inflammation, eye pain, photophobia, eye

swelling, conjunctival haemorrhage, visual acuity reduced, visual disturbance, vision blurred, dry eye, eye pruritus, conjunctivitis, lacrimation increased, erythema of eyelid, blepharitis, asthenopia, growth of eyelashes

Uncommon: corneal erosion, keratitis, eye allergy, conjunctival oedema, eyelid oedema

Rare: iritis

Not known; macular oedema, eyelid ptosis, corneal disorder

Cardiac disorders

Common: heart rate irregular, heart rate decreased

Uncommon: arrhythmia

Not known: cardiac failure, tachycardia

Vascular disorders

Common: blood pressure increased, blood pressure decreased

Respiratory, thoracic and mediastinal disorders

Common: bronchospasm

Uncommon: dyspnoea, cough, oropharyngeal pain, throat irritation, nasal discomfort, postnasal drip

Not known: asthma

Hepatobiliary disorders

Uncommon: alanine aminotransferase increased, aspartate aminotransferase increased

Skin and subcutaneous tissue disorders

Common: urticaria, skin hyperpigmentation (periocular)

Uncommon: dermatitis contact

Rare: alopecia

Not known: rash

Musculoskeletal and connective tissue disorders

Common: pain in extremity

Renal and urinary disorders

Uncommon: chromaturia

General disorders and administration site conditions

Uncommon: thirst

Not known: chest pain.

Post Marketing Experience

The following adverse reactions have been reported during clinical studies with DuoTrav (BAK-preserved) and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

Immune system disorders

Uncommon: hypersensitivity

Nervous system disorders

Uncommon: dizziness, headache

Eye disorders

Very common: ocular hyperaemia

Common: punctate keratitis, vision blurred, dry eye, eye pain, eye pruritus, ocular discomfort, eye irritation

Uncommon: keratitis, iritis, conjunctivitis, anterior chamber inflammation, blepharitis, photophobia, visual acuity reduced, asthenopia, conjunctival haemorrhage, eye swelling, lacrimation increased, erythema of eyelid, growth of eyelashes

Rare: corneal erosion, trichiasis, distichiasis

Cardiac disorders

Uncommon: bradycardia

Vascular disorders

Uncommon: hypertension, hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: dyspnoea, bronchospasm, cough

Rare: dysphonia, throat irritation

Skin and subcutaneous tissue disorders

Uncommon: dermatitis contact, hypertrichosis, skin hyperpigmentation

Rare: urticaria

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

Psychiatric disorders

Depression

Eye disorders

Macular oedema

Cardiac disorders

Chest pain, palpitations

Vascular disorders

Oedema peripheral

Respiratory, thoracic and mediastinal disorders

Asthma

Skin and subcutaneous tissue disorders

Alopecia

Gastrointestinal disorders

Dysgeusia.

DOSAGE AND ADMINISTRATION

Recommended dosage for adults (including the elderly)

Instil one drop of DuoTrav Eye Drops once daily at about the same time each day in the conjunctival sac of the affected eye(s).

DuoTrav Eye Drops should not be given more than once daily because travoprost is most effective at this dosage. If there is inadequate response to DuoTrav Eye Drops consideration should be given to using the individual agents with timolol dosed twice daily.

If more than one topical ophthalmic product is being used, the eye drop products should be administered at least five minutes apart.

Switching to therapy with DuoTrav Eye Drops

When substituting another ophthalmic antiglaucoma agent with DuoTrav Eye Drops, discontinue the other agent and start the following day with DuoTrav Eye Drops.

OVERDOSAGE

There are no human data available on overdosage with DuoTrav Eye Drops, although overdosage data are available on timolol, one of its individual active constituents.

If DuoTrav Eye Drops is accidentally ingested the following information should be useful. One 2.5 mL bottle contains travoprost 0.1 mg and timolol 12.5 mg. Both timolol and travoprost are extensively metabolised in the liver.

Travoprost

A single-dose intravenous study in rats was conducted to elucidate maximal acute hazard. The dose employed was 250,000 times the proposed daily clinical exposure and over 5,000 times the possible exposure from the entire contents of one product container. No treatment related pharmacotoxic signs were present in the animals receiving travoprost.

Timolol

Symptoms of systemic timolol overdosage are bradycardia, hypotension, bronchospasm and cardiac arrest. If such symptoms occur, treatment should be symptomatic and supportive. Studies have shown that timolol is not readily dialysable.

If overdosage with DuoTrav Eye Drops occurs, treatment should be symptomatic.

A topical overdose of DuoTrav Eye Drops may be flushed from the eyes with warm tap water.

POISON SCHEDULE OF THE DRUG

Prescription Only Medicine, S4.

PRESENTATION AND STORAGE

DuoTrav Eye Drops: 2.5 mL oval DROP-TAINER* dispenser with or without pouch.

Store below 25 ^{o}C.

Discard four weeks after opening.

Contains: travoprost 0.004% and timolol maleate 0.68% (equivalent to timolol 0.5%).

Consumer Medicine Information is supplied with this product.

NAME AND ADDRESS OF SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

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DATE OF FIRST INCLUSION IN THE ARTG

15 March 2012

DATE OF MOST RECENT AMENDMENT

5 July 2017

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