

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrDUOTRAV® PQ

travoprost and timolol ophthalmic solution

0.004% w/v and 0.5% w/v (as timolol maleate)
with POLYQUAD® (polyquaternium-1 0.001%) as preservative

Elevated Intraocular Pressure Therapy

Prostaglandin F_{2α} analogue and beta-adrenergic receptor blocker

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DUOTRAV® PQ (travoprost and timolol) is indicated for the reduction of elevated IOP in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers, prostaglandins, or other IOP lowering agents AND when the use of DUOTRAV PQ (the fixed combination drug) is considered appropriate.

DUOTRAV PQ should not be used to initiate therapy.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

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

2 CONTRAINDICATIONS

DUOTRAV PQ is a combination of travoprost 0.004% and timolol 0.5% (as timolol maleate). When DUOTRAV PQ is prescribed, the relevant Product Monographs for travoprost and/or timolol maleate should be consulted.

DUOTRAV PQ is contraindicated in patients who:

- Are hypersensitive to this drug or to any ingredient in the formulation, including any non-medical ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION and PACKAGING.
- Have reactive airway diseases, including bronchial asthma.
- Have a history of bronchial asthma.
- Have severe chronic obstructive pulmonary disease (see WARNINGS AND PRECAUTIONS).
- Have sinus bradycardia.
- Have sick sinus syndrome or sino-atrial block.
- Have second or third degree atrioventricular block.
- Have overt cardiac failure (see WARNINGS AND PRECAUTIONS).
- Have cardiogenic shock.

DUOTRAV PQ may interfere with the maintenance of pregnancy and should not be used by women during pregnancy or by women attempting to become pregnant.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage is one drop in the affected eye(s) once daily either morning or evening. The dosage of DUOTRAV PQ should not exceed once daily since it has been shown that more frequent administration of prostaglandin analogues may decrease the intraocular pressure lowering effect.

Special populations

Renal Impairment

DUOTRAV PQ has not been studied in patients with renal impairment; caution should be exercised in treating such patients.

Use in Pediatric patients (below 18 years)

The use of DUOTRAV PQ in pediatric patients <18 years of age is currently not recommended. The safety and effectiveness of DUOTRAV PQ in these patients have not been established.

Geriatrics (65 years or above)

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

4.3 Administration

Apply DUOTRAV PQ to the conjunctival sac of the affected eye(s). Nasolacrimal occlusion or gently closing the eyelid for 2 minutes after application is recommended.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

4.5 Missed Dose

If one dose is missed, treatment should continue with the next dose as normal.

5 OVERDOSAGE

There are no human data available on overdosage with DUOTRAV PQ or other travoprost-containing products.

Symptoms of systemic timolol overdosage are bradycardia, hypotension, bronchospasm, and cardiac arrest. If such symptoms occur, treatment should be symptomatic and supportive.

Specific therapeutic measures for the treatment of overdosage with timolol maleate are reproduced below for ease of reference.

Gastric Lavage: If ingested.

Symptomatic bradycardia: Use atropine sulfate intravenously in a dosage of 0.25 to 2 mg to induce vagal blockade. If bradycardia persists, intravenous isoproterenol hydrochloride should be administered cautiously. In refractory cases the use of transvenous cardiac pacemaker may be considered.

Hypotension: Use sympathomimetic pressor drug therapy, such as dopamine, dobutamine or levarterenol. In refractory cases the use of glucagons hydrochloride has been reported to be useful.

Bronchospasm: Use isoproterenol hydrochloride. Additional therapy with aminophylline may be considered.

Acute cardiac failure: Conventional therapy with digitalis, diuretics and oxygen should be instituted immediately. In refractory cases the use of intravenous aminophylline is suggested. This may be followed if necessary by glucagon hydrochloride which has been reported to be useful.

Heart block (second or third degree): Use isoproterenol hydrochloride or a transvenous cardiac pacemaker.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ocular	Each mL contains: Solution 0.04 mg travoprost and 6.8 mg timolol maleate (equivalent to 5 mg timolol base)	Each mL contains: boric acid, mannitol (E421), polyoxyethylene hydrogenated castor oil 40 (HCO-40) (1 mg), polyquaternium-1 (POLYQUAD) (10 µg) as preservative, propylene glycol (E1520) (5 mg), purified water, sodium chloride, sodium hydroxide and /or hydrochloric acid.

DUOTRAV PQ is a sterile, isotonic, buffered, preserved, aqueous solution.

DUOTRAV PQ is supplied in the DROP-TAINER® dispenser bottle. This package system comprises a white, opaque, polypropylene dispenser bottle with a natural polypropylene dropper tip and a white polypropylene closure. Tamper evidence is provided with a neck-band which shrinks to conform around the closure and neck area of the package.

DUOTRAV PQ is supplied as 2.5 mL solution in a 4 mL bottle or 5 mL solution in a 7.5 mL bottle.

A 2.5 mL bottle of DUOTRAV PQ solution contains at least 94 drops of solution.

7 WARNINGS AND PRECAUTIONS

General

DUOTRAV PQ is a combination of travoprost 0.004% and timolol 0.5% (as timolol maleate). When DUOTRAV PQ is prescribed, the relevant Product Monographs for travoprost and/or timolol maleate should be consulted.

DUOTRAV PQ may result in higher ocular and systemic exposure to travoprost, especially timolol, as compared to DUOTRAV after topical ocular administration (see ACTION AND CLINICAL PHARMACOLOGY).¹

FOR TOPICAL OPHTHALMIC USE ONLY.

Systemic Effects

Like other topically applied ophthalmic agents, travoprost and timolol are absorbed systemically. The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration of DUOTRAV PQ due to the beta-adrenergic component, timolol. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

DUOTRAV PQ may result in higher systemic exposure to travoprost, especially timolol, as compared to DUOTRAV after topical ocular administration (see ACTION AND CLINICAL PHARMACOLOGY).²

Cardiovascular

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 for adverse reactions.

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning treatment with DUOTRAV PQ. Patients with a history of severe cardiac disease should be watched for signs of cardiac failure and have their pulse rates checked. Caution should be exercised in treating patients with severe cardiovascular disease or with severe peripheral circulatory disturbances/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome).

Concomitant Therapy: Timolol may interact with other drugs (see DRUG INTERACTIONS). The effect on IOP or the known effects of systemic beta-blockers may be exaggerated when DUOTRAV PQ is given to patients already receiving an oral beta-blocking agent. The response of these patients should be closely observed. The use of two local beta-blockers or two local prostaglandins is not recommended.

Driving and Operating Machinery

¹ DUOTRAV PQ is preserved with polyquaternium-1 (POLYQUAD). DUOTRAV is preserved with benzalkonium chloride (BAK). These two products contain the same active ingredients at the same concentrations.

² DUOTRAV PQ is preserved with polyquaternium-1 (POLYQUAD®). DUOTRAV is preserved with benzalkonium chloride (BAK). These two products contain the same active ingredients at the same concentrations.

DUOTRAV PQ, as with other similar medications, can potentially cause fatigue and/or drowsiness in some patients. Patients who engage in hazardous activities should be cautioned regarding the potential for a decrease in mental alertness.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery.

Endocrine and Metabolism

Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs of hyperthyroidism (e.g., tachycardia). Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

Neurologic

Cerebrovascular Insufficiency

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with DUOTRAV PQ, alternative therapy should be considered.

Muscle Weakness

Beta-adrenergic blockade has been reported to increase muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis and generalized weakness). Timolol maleate has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Ophthalmologic

Travoprost and other prostaglandin analogues have been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

DUOTRAV PQ may gradually change eye color, increasing the amount of brown pigmentation in the iris. The color change is due to increased melanin content in stromal melanocytes on the iris rather than to an increase in the number of melanocytes, although the exact mechanism of action is unknown at this time. 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 browner. Iris pigmentation changes may be more noticeable in patients with mixed colored irides, i.e., blue-brown, grey-brown, yellow-brown, and green-brown; however, it has also been observed in patients with brown eyes. The change in iris color occurs slowly and may

not be noticeable for several months to years. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. Patients should be informed of the possibility of iris color change since the increased pigmentation is permanent. Patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues.

Eyelid skin darkening has been reported in association with the use of DUOTRAV PQ. DUOTRAV PQ may gradually change eyelashes in the treated eye; these changes include increased length, thickness, pigmentation, and/or number of lashes. Periorbital and lid changes, including deepening of the eyelid sulcus, have also been observed with prostaglandin analogues.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital and/or eyelid tissue, and eyelashes in the treated eye and thus heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes.

Patients prescribed IOP-lowering medication should be routinely monitored for IOP status. DUOTRAV PQ should be used with caution in patients with active intraocular inflammation (iritis/uveitis) as well as patients with predisposing risk factors for uveitis.

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin F_{2α} analogues such as travoprost. These reports have mainly occurred in aphakic patients, pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. DUOTRAV PQ should be used with caution in these patients.

Angle-closure Glaucoma

DUOTRAV PQ should not be used alone in the treatment of acute angle-closure glaucoma

Contact Lenses

DUOTRAV PQ should not be administered while wearing contact lenses. The contact lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

Choroidal Detachment

Choroidal detachment after filtration procedures has been reported with administration of aqueous suppressant therapy (e.g., timolol maleate, acetazolamide). Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

Peri-Operative Considerations

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine or levarterenol.

Beta-blocking ophthalmic preparations may block systemic beta-agonist effects e.g. of

adrenaline. The anesthesiologist should be informed when the patient is receiving timolol.

Respiratory

Chronic Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which DUOTRAV PQ is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers or products containing them, including DUOTRAV PQ.

Sensitivity/Resistance

If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

Anaphylaxis

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Skin

DUOTRAV PQ contains propylene glycol, which may cause skin irritation, and polyoxyethylene hydrogenated castor oil 40, which may cause skin reactions.

7.1 Special Populations

7.1.1 Pregnant Women

No adequate and well controlled studies have been performed in pregnant women with DUOTRAV PQ. Studies in animals with travoprost have shown reproductive toxicity (see NON-CLINICAL TOXICOLOGY, Reproduction and Teratology). Because travoprost has harmful effects on pregnancy and/or the fetus/newborn child, DUOTRAV PQ is contraindicated during pregnancy and in women planning to become pregnant (see CONTRAINDICATIONS).

Since prostaglandins are biologically active and 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 case of accidental contact with the contents of the bottle, thoroughly cleanse the exposed area with soap and water immediately.

7.1.2 Breast-feeding

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Travoprost has been shown to be excreted in milk in animal studies; however, it is not known whether travoprost and/or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions from timolol maleate or travoprost in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7.1.3 Pediatrics

Pediatrics (<18 years of age)

The use of DUOTRAV PQ in pediatric patients <18 years of age is currently not recommended. The safety and effectiveness of DUOTRAV PQ in these patients have not been established.

7.1.4 Geriatrics

Geriatrics (>65 years of age)

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

8 ADVERSE REACTIONS

The clinical development of DUOTRAV PQ was based on the body of work that had been compiled for the approval of DUOTRAV³. These consisted of four Phase 3 clinical trials, one posology study, and one clinical pharmacokinetic study.

The clinical development for DUOTRAV PQ included three additional studies: one 5-day Phase 1 pharmacokinetic study in healthy subjects (Study C-09-009), one 6-week two-arm pivotal Phase 3 safety/efficacy study (Study C-07-64/C-08-08) and one 12-month Phase 3 single-arm safety study (Study C-09-032) conducted in patients with open-angle glaucoma or ocular hypertension. The 6-week safety /efficacy study was designed to demonstrate the non-inferiority of DUOTRAV PQ compared to DUOTRAV.

8.1 Adverse Reaction Overview

In the clinical trials involved in the development of DUOTRAV PQ, 23 healthy subjects and 349 patients diagnosed with open-angle glaucoma or ocular hypertension were exposed to DUOTRAV PQ. The most frequently reported adverse drug reaction was hyperemia of the eye (11.8%), which included ocular or conjunctival hyperemia. The majority of patients (91%) who experienced hyperemia of the eye did not discontinue therapy as a result of this reaction. This means that the discontinuation rate for patients experiencing hyperemia while receiving DUOTRAV PQ was 1.08%.

Seven and four patients discontinued DUOTRAV PQ due to ocular adverse reactions in the 12-month safety study and the pivotal 6-week study, respectively. In the long-term safety study, two cases of mild heart rate decrease and one case of mild hypotension were reported as related to treatment with DUOTRAV PQ.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The causal relationship of each adverse event to the study medication was assessed and

³ DUOTRAV PQ is preserved with polyquaternium-1 (POLYQUAD). DUOTRAV is preserved with benzalkonium chloride (BAK). These two products contain the same active ingredients at the same concentrations.

assigned by the individual study investigator. The adverse drug reactions in following sections have been assessed to be either definitely related or possibly related to the use of DUOTRAV PQ or DUOTRAV.

Adverse Drug Reactions in Clinical Trials Providing Medium (6 weeks) or Long-Term (12 Months) Exposure to DUOTRAV PQ in Patients with Primary Open-Angle Glaucoma or Ocular Hypertension.

In 2 clinical trials (C-07-64/C-08-08, and C-09-032), 349 patients with open-angle glaucoma or ocular hypertension had medium (6-week; C-07-64/C-08-08) or long-term (12 months; C-09-032) exposure to DUOTRAV PQ. Clinical trial C-07-64/C-08-08 also included 193 patients exposed to DUOTRAV. The adverse drug reactions reported in the clinical trials are presented in Table 2 and Table 3.

Table 2 - Adverse Drug Reactions Reported in Patients Exposed to DUOTRAV PQ or DUOTRAV – 6-Week Exposure (Study C-07-64/C-08-08)

	DUOTRAV PQ N = 195 %	DUOTRAV N = 193 %
Eye disorders		
Ocular hyperemia	11.8	13.0
Eye irritation	4.6	5.7
Eye pruritus	3.1	2.6
Eye pain	2.1	3.1
Foreign body sensation in eyes	2.1	2.6
Dry eye	1.0	2.6
Photophobia	1.0	1.0
Iritis	0.5	1.0
Punctate keratitis ^a	1.0	0.5
Ocular discomfort	0.5	0.5
Eyelids pruritus	0.5	-
Meibomianitis	0.5	-
Blurred vision	0.5	-
Lacrimation increased	-	1.6
Anterior chamber cell	-	0.5
Anterior chamber flare	-	0.5
Visual acuity reduced	-	0.5
Cardiac disorders		
Bradycardia	0.5	-
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	-	0.5

Adverse drug reactions coded using MedDRA version 12.0

Adverse drug reactions coding to conjunctival or ocular hyperaemia are presented together in the table as ocular hyperaemia.

^aTwo adverse drug reactions and 1 adverse drug reaction for punctate keratitis were reported in the DUOTRAV PQ and DUOTRAV treatment groups, respectively. An additional single report of punctate keratitis assessed as unrelated to the use of either DUOTRAV PQ or DUOTRAV was reported in each treatment group. All reports of punctate keratitis were reported in female patients.

DUOTRAV PQ = DUOTRAV (polyquaternium-1-preserved)

DUOTRAV = DUOTRAV (benzalkonium chloride–preserved)

In clinical trial C-07-64/C-08-08, treatment emergent adverse events for mild corneal erosion were reported in 2 female patients treated with DUOTRAV PQ and a treatment emergent adverse event for mild ulcerative keratitis was reported in 1 female patient treated with DUOTRAV. All reports of corneal erosion and ulcerative keratitis were assessed as unrelated to the use of either DUOTRAV PQ or DUOTRAV, where a more plausible explanation may exist.

Table 3 - Adverse Drug Reactions Reported in Patients Exposed to DUOTRAV PQ – Long-Term (12 month) Exposure (Study C-09-032)

	DUOTRAV PQ N = 154 %
Eye disorders	
Ocular hyperemia	7.1
Eye pruritus	4.5
Eye irritation	3.2
Eye pain	1.9
Dry eye	1.9
Growth of eyelashes	0.6
Abnormal sensation in eye	0.6
Conjunctivitis	0.6
Allergic conjunctivitis	0.6
Eyelid margin crusting	0.6
Eyelids pruritus	0.6
Keratoconjunctivitis sicca	0.6
Photophobia	0.6
Blurred vision	0.6
General disorders and administration site conditions	
Fatigue	0.6
Immune system disorders	
Hypersensitivity	1.3
Investigations	
Heart rate decreased	1.3
Musculoskeletal and connective tissue disorders	
Muscle tightness	0.6
Skin and subcutaneous tissue disorders	
Skin discoloration	0.6
Vascular disorders	
Hypotension	0.6

Adverse drug reactions coded using MedDRA version 12.0

Adverse drug reactions coding to conjunctival or ocular hyperaemia are presented together in the table as ocular hyperaemia.

Adverse Events in a Clinical Trial Providing Short-Term Exposure (5 Days) to DUOTRAV PQ in Normal Healthy Volunteer Subjects

In one pharmacokinetic trial of crossover design (C-09-009), 23 normal healthy volunteer subjects had short-term exposure (5 days) to DUOTRAV PQ and 24 normal healthy volunteer subjects had short-term exposure (5 days) to DUOTRAV. The most frequently reported adverse drug reaction was ocular hyperemia.

Table 4: All Adverse Drug Reactions Occurring in Subjects with Exposure to DUOTRAV PQ or DUOTRAV - Short-Term (Five-day) Study In Healthy Subjects (Study C-09-009)

	DUOTRAV PQ	DUOTRAV
	N=23	N=24
	%	%
Eye disorders		
Ocular hyperemia	43.5	50.0
Eye pain	21.7	16.7
Eye pruritus	4.3	-
Blurred vision	-	4.2
Dry eye	4.3	8.3
Asthenopia	4.3	4.2
Foreign body sensation in eyes	-	4.2
Keratitis	-	4.2
Nervous system disorders		
Headache	8.7	8.3
Respiratory, thoracic and mediastinal disorder		
Nasal discomfort	-	4.2

Adverse drug reactions coded using MedDRA version 12.0

This table includes all reported ocular and non-ocular adverse drug reactions.

DUOTRAV PQ = DUOTRAV (polyquaternium-1-preserved)

DUOTRAV = DUOTRAV (benzalkonium chloride-preserved)

Adverse Drug Reactions in Clinical Trials Providing Medium and Long-Term Exposure to DuoTrav

In 5 clinical trials (C-01-69, C-01-70, C-02-03, C-02-28, and C-02-41) completed during the development of DUOTRAV, 706 patients diagnosed with open-angle glaucoma or ocular hypertension had medium (6 weeks) or long-term (6 months to 12 months) of exposure to DUOTRAV. An additional 193 patients had medium exposure (6 weeks) to DUOTRAV during the development of DUOTRAV PQ.

Adverse drug reactions that occurred at an incidence of $\geq 1.0\%$ in patients with long-term exposure to DUOTRAV are described in Table 5.

Table 5 - Adverse Drug Reactions Occurring at an Incidence of $\geq 1\%$ in Patients with Exposure to DUOTRAV – Medium and Long-Term Studies (C-01-69, C-01-70, C-02-03, C-02-28, C-02-41, C-07-64/C-08-08)

	DUOTRAV BAC	Latanoprost 0.005%/ Timolol 0.5%	TRAVATAN® + Timolol 0.5%	TRAVATAN®	Timolol 0.5%
	N=899	N=200	N=313	N=86	N=176
	%	%	%	%	%
Eye Disorders					
Ocular hyperaemia	14.0	2.5	18.8	11.6	1.7
Eye irritation	4.4	2.0	6.7	2.3	2.8
Eye pruritis	4.3	2.0	4.8	2.3	0.6
Eye pain	3.3	1.5	4.2	3.5	2.8
Dry eye	2.0	0.5	2.9	2.3	1.7
Foreign body sensation in eyes	2.4	3.5	2.9	2.3	1.7
Photophobia	1.2	-	1.6	1.2	-
Growth of eyelashes	1.1	-	2.2	1.2	-

Adverse drug reactions coded using MedDRA version 12.0

Adverse drug reactions coding to conjunctival or ocular hyperaemia are presented together in the table as ocular hyperaemia.

No non-ocular adverse drug reactions occurred at an incidence $\geq 1\%$.

DUOTRAV (BAC) = DUOTRAV (benzalkonium chloride–preserved)

In a twelve-month study with DUOTRAV, ocular photographs were taken of the iris using a standardized procedure and evaluated by a centralized reading center masked to study treatment in order to assess effects on iris pigmentation. Following an initial latent period, the incidence of iris pigmentation changes increased in both treatment groups from Month 6 to Month 12 as shown in Table 6.

Table 6 - Patients with Iris Pigmentation Changes^a (C-02-28)

DUOTRAV			Latanoprost 0.005%/ Timolol 0.5%		
	N ^c	%		N ^c	%
Month 6 (N=169) ^b	1	0.6	Month 6 (N=161) ^b	1	0.6
Month 12 (N=166) ^b	4	2.4	Month 12 (N=163) ^b	2	1.2

^aChanges based upon review of ocular photographs by a centralized reading center

^bN values represent number of patients with ocular photographs

^cN values represent number of patients with iris pigmentation changes
(See CLINICAL TRIALS)

8.3 Less Common Clinical Trial Adverse Reactions

Adverse drug reactions that occurred at an incidence of <1.0% in patients with long-term exposure to DUOTRAV are included in Table 7.

Table 7 - Adverse Drug Reactions Occurring at an Incidence of < 1% in Patients with Exposure to DUOTRAV – Medium and Long-Term Studies (C-01-69, C-01-70, C-02-03, C-02-28, C-02-41, C-07-64/C-08-08)

MedDRA SOC ^a	MedDRA PT ^b
Immune system disorders	seasonal allergy
Psychiatric disorders	nervousness
Nervous system disorders	headache, dizziness
Eye disorders	blurred vision, punctate keratitis, anterior chamber cell, anterior chamber flare, corneal staining, lacrimation increased, ocular discomfort, abnormal sensation in eye, erythema of eyelid, eye swelling, visual acuity reduced, asthenopia, blepharitis, iritis, anterior chamber inflammation, conjunctival hemorrhage, conjunctivitis, conjunctivitis allergic, eyelid disorder, eyelid edema, eyelid pain, eyelids pruritus, keratitis, visual impairment, xerophthalmia
Vascular disorders	hypertension
Respiratory, thoracic and mediastinal disorders	bronchospasm, cough, dyspnea, oropharyngeal pain, throat irritation
Skin and subcutaneous tissue disorders	skin hyperpigmentation (periorbital or eyelid pigmentation), dermatitis allergic, dermatitis contact, hypertrichosis, urticaria
Musculoskeletal and connective tissue disorders	pain in extremity
Renal and urinary disorders	chromaturia
Congenital, familial and genetic disorders	distichiasis
Investigations	alanine aminotransferase increased ^c , aspartate aminotransferase increased ^c , blood pressure diastolic decreased, blood pressure diastolic increased, blood pressure increased, heart rate

MedDRA SOC ^a	MedDRA PT ^b
	decreased, heart rate irregular

Adverse drug reactions are presented in order of decreasing incidence; when reactions occurred at the same incidence they are presented alphabetically.

Adverse drug reactions coded using MedDRA version 12.

^aSOC = System Organ Class

^bPT = Preferred term

^cNo clinical laboratory evaluations were performed. These adverse drug reactions were based upon patient reports.

Additional Adverse Drug Reactions Observed with the Individual Components of DUOTRAV PQ

The following additional adverse drug reactions (Table 8) have been seen with one of the individual components of DUOTRAV PQ, have not been presented in the preceding tables or text, and may potentially occur with DUOTRAV PQ. For further detailed information, please consult the individual Product Monographs for travoprost or timolol maleate containing products.

Table 8 - Additional Adverse Drug Reactions^a Previously Observed in One of the Individual Components and That May Potentially Occur with DUOTRAV PQ

	TRAVATAN [®]	Timolol
MedDRA SOC ^b	MedDRA PT ^c	MedDRA PT
Metabolism and nutrition disorders	-	hypoglycemia
Psychiatric disorders	-	depression
Nervous system disorders	-	cerebrovascular accident, cerebral ischemia, myasthenia gravis, syncope, paresthesia
Eye disorders	conjunctival follicles, conjunctival disorder, macular edema, uveitis	corneal disorder, diplopia, eyelid ptosis
Cardiac disorders	-	arrhythmia, atrioventricular block, cardiac arrest, cardiac failure, palpitations
Respiratory, thoracic and mediastinal disorders	asthma	nasal congestion, respiratory failure
Gastrointestinal disorders	-	diarrhea, nausea
Skin and subcutaneous tissue disorders		alopecia, rash
General disorders and administration site conditions	-	asthenia, chest pain

^aAdverse drug reactions coded using MedDRA version 8.0

^bSOC = System Organ Class

^cPT = Preferred term

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

No clinical laboratory evaluations for the analysis of safety were performed during the clinical development of DUOTRAV PQ or DUOTRAV. The clinical laboratory adverse drug reactions

presented in Table 8 were based upon patient reports.

8.6 Post-Market Adverse Reactions

Ophthalmic solutions containing the individual components travoprost 0.004% and timolol (as timolol maleate) 0.1%, 0.25%, and 0.5% are registered in numerous countries. Based upon a review of spontaneous post-marketing reports of adverse events to date, travoprost and timolol maleate solutions are well-tolerated and safe for use as indicated.

No case of safety concern has been identified to date based on post-marketing experience since 2006 with DUOTRAV. No important information has been received which pertains to the safety of travoprost 0.04 mg/mL/ timolol 5 mg/mL containing products. Adverse events possibly associated with the use of DUOTRAV that have been reported are generally non-serious local ocular effects in concordance with the known safety profile of the product and its individual components.

The most frequently reported local ocular reactions were ocular hyperaemia, eye pain and eye irritation. These local effects are expected events associated with the ophthalmic use of travoprost /timolol maleate solutions. Unexpected ocular reactions such as ciliary body disorder and exophthalmos have also been reported. These reactions could be isolated events for which concomitant medication and/or intercurrent diseases should also be considered. Other unexpected events such as iris hyperpigmentation and diplopia are expected events for travoprost and timolol respectively.

The analysis of spontaneous events to date does not reveal new or potentially important safety findings associated with the ophthalmic use of DUOTRAV. Moreover, no previously unidentified toxicity or changes in the characteristics of known reactions of the product or its individual components has been identified.

No case of safety concern has been identified to date based on post-marketing experience since 2011 with DUOTRAV PQ. Adverse events possibly associated with the use of DUOTRAV PQ that have been reported are generally non-serious local ocular effects in concordance with the known safety profile of the product and its individual components. The most frequently reported local ocular reactions were ocular hyperemia, eye irritation, eye irritation, blepharal pigmentation, and eye pruritus. These local effects are expected events associated with the ophthalmic use of travoprost /timolol maleate solutions.

In post-market, a few reports of iritis/uveitis associated with the use of travoprost have been published. These cases occurred a few days after travoprost use in patients without a history of iritis/uveitis. All of these cases resolved after stopping travoprost with or without corticosteroid treatment.

As spontaneous event reports frequently provide incomplete data, report of a spontaneous event does not necessarily constitute an admission that travoprost solution or timolol solution caused or contributed to the event.

Additional adverse drug reactions that have been reported, in either subsequent clinical trials or via spontaneous post-market reporting, following use of DUOTRAV or DUOTRAV PQ, include the following:

Eye disorders: trichiasis; lid sulcus deepened; iris hyperpigmentation

Gastrointestinal disorders: dysgeusia;
Psychiatric disorders: hallucination, depression;
Respiratory, thoracic and mediastinal disorders: dysphonia;
Vascular disorders: peripheral edema.
Skin and subcutaneous tissue disorders: Rash

9 DRUG INTERACTIONS

9.2 Overview

No specific interaction studies have been performed with DUOTRAV PQ.

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 masked 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.

9.3 Drug-Drug Interactions

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and DUOTRAV PQ should be observed for potential additive effects of beta-blockade, both systemic and on IOP. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents, such as the timolol found in DUOTRAV PQ and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co administration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension, which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: See WARNINGS AND PRECAUTIONS, Anaphylaxis.

CNS Depressants: The possibility that DUOTRAV PQ may have an additive or potentiating effect with CNS depressants (alcohol, barbiturates, opiates, sedatives, or anaesthetics) should be considered.

Tricyclic Antidepressants: Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with DUOTRAV PQ can lead to interference in IOP lowering effect.

No data are available on the level of circulating catecholamines after DUOTRAV PQ is instilled. Caution, however, is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Epinephrine: Mydriasis resulting from concomitant use of timolol maleate and epinephrine has been reported occasionally.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

DUOTRAV PQ contains two active components, travoprost and timolol maleate, which lower intraocular pressure (IOP) by complementary mechanisms of action.

Travoprost free acid is a highly selective FP prostanoid receptor agonist that has been shown to reduce IOP by increasing uveoscleral and conventional outflow. Reduction of IOP starts within approximately two hours after administration, and the maximum effect is reached after 12 hours. Significant lowering of IOP can be maintained for periods exceeding 24 hours with a single dose. Repeated observations over a period of one year indicate that the IOP-lowering effect of travoprost is well maintained.

Timolol maleate is a beta₁ and beta₂ (non-selective) adrenergic receptor-blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilizing) activity. The precise mechanism of the ocular hypotensive action of timolol is not definitively established. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation. However in some studies, a slight increase in outflow facility was also observed. The onset of IOP reduction following administration of timolol can usually be detected within 30 minutes after a single dose. The maximum effect usually occurs in one to two hours, and significant lowering of IOP can be maintained for periods as long as 24 hours after a single dose. Repeated observations over a period of one year indicate that the IOP-lowering effect of timolol is well maintained.

10.2 Pharmacodynamics

Animal Pharmacology

No non-clinical ocular or systemic pharmacology studies were conducted on travoprost/timolol ophthalmic solution (0.004% /0.5% w/v) since the pharmacology of each has been well established previously in the medical and scientific literature. Previous studies have shown that the concomitant application of FP agonists with timolol results in an additional reduction in IOP compared to the administration of either single agent.

Human Pharmacology

The active components of *DUOTRAV PQ*, travoprost and timolol maleate, are approved therapeutic agents for the reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension, with different mechanisms of action. *DUOTRAV PQ* produces greater mean IOP reductions than those produced by either TRAVATAN® travoprost ophthalmic solution or timolol ophthalmic solution, 0.5% used alone.

DUOTRAV PQ, when applied topically to the eye, has the action of reducing elevated as well as normal IOP, whether or not accompanied by glaucoma. Elevated IOP is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the IOP level, the greater the likelihood of glaucomatous visual field loss and optic nerve damage. The Advanced Glaucoma Intervention Study (AGIS) established elevated IOP as a positive risk factor for glaucomatous visual field loss. Eyes with IOPs below 18 mmHg at all visits were found to have little to no visual field loss during the six-year monitoring period.

10.3 Pharmacokinetics

Animal Pharmacokinetics

POLYQUAD: Orally administered *POLYQUAD* is poorly absorbed in the gastrointestinal tract in rats. A study showed that only 0.9% of an oral dose of *POLYQUAD* was found in rat blood. Intravenously-administrated *POLYQUAD* appears to be eliminated in multi-phasic kinetics in rat plasma with a mean half-life of the terminal phase as 5.21 ± 2.21 hours.

Travoprost/timolol Combination: In rabbits, after a single topical ocular administration of *DUOTRAV PQ* or *DUOTRAV*, the concentration of travoprost free acid in the aqueous humour and iris-ciliary body slowly increased, reached the peak value at one or two hours post-dosing and then slowly decreased. At 6 hour post-dosing, mean concentrations of travoprost free acid in these ocular tissues were still >1 ng/g. In contrast, the timolol concentration in the rabbit aqueous humour and iris-ciliary body quickly increased immediately after dosing and reached the peak value about 30 minutes in rabbits treated with either *DUOTRAV PQ* or *DUOTRAV*.

DUOTRAV PQ was shown to have higher ocular bioavailability for both timolol and AL-5848 in rabbits than *DUOTRAV* after topical ocular administration. For bulbar conjunctiva, the differences were not significantly different.

After a single bilateral topical administration, *DUOTRAV PQ* resulted in significantly higher exposure to the active ingredients, timolol and AL-5848, in all ocular tissues compared to *DUOTRAV* in male rabbits (Figure 1). The increase as measured by mean AUC_{0-6h} was about 1.3 fold for timolol and 1.3 to 1.7 fold for AL-5848 with statistical significance ($P < 0.05$). Plasma

timolol exposure (per C_{max} and AUC) and travoprost free acid (per C_{max}) was higher for DUOTRAV PQ compared to DUOTRAV (Table 9). No ocular distribution data in female rabbits are available.

Figure 1 - Comparison of mean AUC_{0-6h} of timolol (left panel) and travoprost free acid (right panel) in different ocular tissues in male rabbits treated with a single topical ocular dose of DUOTRAV PQ (labelled as DUOTRAV APS in the figure) from the corresponding value of male rabbits treated with a single topical ocular dose of DUOTRAV

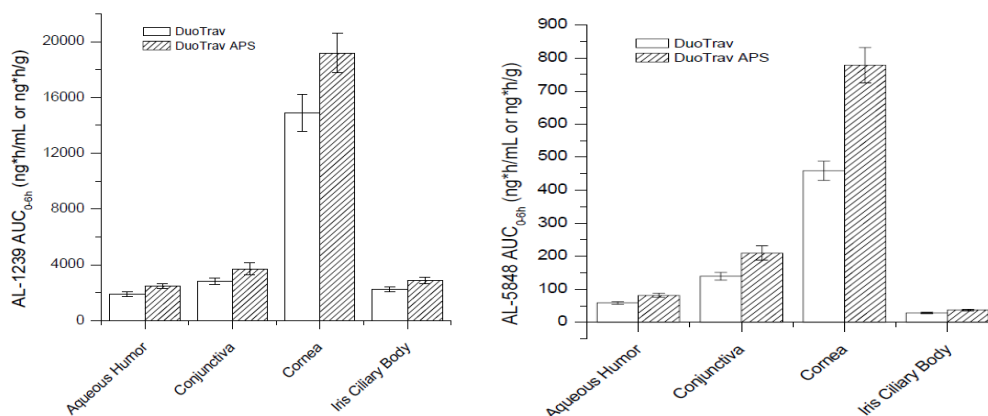


Table 9 - Systemic exposure (C_{max} and AUC) of DUOTRAV PQ at Day 1 and Day 90 was consistently higher than that of DUOTRAV in male rabbits (n=4)

PK Parameter	Treatment (N=4)	Timolol		AL-5848	
		Day 1	Day 90	Day 1	Day 90
Mean C_{max} (ng/mL)	DUOTRAV PQ	15.7	11.0	0.085	0.046
	DUOTRAV	8.3	7.1	0.033	0.025
	% Increase in Mean C_{max} (DUOTRAV PQ vs. DUOTRAV)	90.1	55.1	153.3	85.4
Mean AUC _{0-3 hr} (ng-hr/mL)	DUOTRAV PQ	17.2	13.5	n/a	n/a
	DUOTRAV	10.1	10.2	n/a	n/a
	% Increase in Mean AUC _{0-3 hr} (DUOTRAV PQ vs. DUOTRAV)	70.3	32.4	n/a	n/a

n/a: not analyzed

Human Pharmacokinetics

Topical ocular administration of DUOTRAV and DUOTRAV PQ once-daily in healthy subjects (C-09-009, N = 24) for 5 days in a randomized, two-way crossover study was undertaken to evaluate the steady state plasma pharmacokinetics of travoprost free acid and timolol.

Following topical ocular administration of DUOTRAV PQ or DUOTRAV, timolol was rapidly absorbed into blood. Peak timolol plasma concentrations were observed on average within approximately 30 minutes for DUOTRAV and approximately one hour for DUOTRAV PQ. Plasma timolol was then eliminated with mean half-lives of 5.16 ± 2.39 hours and 4.71 ± 2.15 hours following a single administration of DUOTRAV PQ or DUOTRAV, respectively. Plasma timolol mean half-lives at steady state were 5.38 ± 1.93 hours and 5.41 ± 1.94 hours after administration with DUOTRAV PQ or DUOTRAV respectively.

For DUOTRAV PQ, not only did the plasma timolol concentration peak significantly later, but the plasma timolol exposure level (as measured with mean C_{max} and mean $AUC_{0-tlast}$) was also consistently higher at the steady state compared to DUOTRAV. The C_{max} of plasma timolol was 1.34 ± 0.584 ng/mL and 1.11 ± 0.570 ng/mL for DUOTRAV PQ and DUOTRAV, respectively, while $AUC_{0-tlast}$ at steady state was 7.38 ± 3.53 ng-hr/mL and 6.25 ± 2.57 ng-hr/mL for DUOTRAV PQ and DUOTRAV, respectively. Compared to DUOTRAV, the systemic exposure to timolol, as measured by natural logarithm-transformed least squares mean plasma C_{max} values, were 4 and 23% higher after a single dose and at steady-state, respectively, following administration of DUOTRAV PQ. A similar trend was observed for plasma $AUC_{0-tlast}$, with the natural logarithm-transformed least squares mean ratio for DUOTRAV PQ being 18 and 16% higher following a single dose and at steady-state, respectively, compared to DUOTRAV. However, in this two-period, cross-over study, such difference in plasma C_{max} and $AUC_{0-tlast}$ of timolol between DUOTRAV PQ and DUOTRAV was observed only in the second treatment period, during which the C_{max} and $AUC_{0-tlast}$ of plasma timolol, as measured by natural logarithm-transformed least squares mean, was 25% to 55% higher or 62% to 77% higher, respectively, for DUOTRAV PQ than for DUOTRAV. The true magnitude of the bioavailability difference between the two formulations cannot be determined with certainty, as the study was not sufficiently powered to determine bioequivalence. Higher ocular and systemic exposure to the active ingredients in the DUOTRAV PQ treatment than that in the DUOTRAV treatment was also consistently observed in three rabbits studies after topical ocular administration (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Animal Pharmacokinetics).

For both DUOTRAV PQ and DUOTRAV, a gender difference in systemic timolol exposure was observed, with females having higher mean C_{max} and $AUC_{0-\infty}$ values compared to males. The extent of the gender difference for each of these formulations cannot be assessed in the study due to inadequate statistical power.

Absorption: Travoprost and timolol are absorbed through the cornea after topical ocular administration of DUOTRAV PQ. Travoprost undergoes rapid ester hydrolysis in the cornea to the active travoprost free acid (AL5848), which is the form absorbed into the eye and systemic circulation.

In a two-period crossover phase 1 study in healthy subjects (Study C-09-009), plasma pharmacokinetics of the active ingredients, timolol and AL-5848, were compared between DUOTRAV PQ and DUOTRAV after topical ocular administration⁴. The systemic absorption and elimination of AL-5848 were generally rapid with T_{max} ranging from 10 to 30 minutes for both DUOTRAV PQ and DUOTRAV. $T_{1/2}$ ranged from 0.46 to 0.82 hours and 0.60 to 2.06 hours for DUOTRAV PQ and DUOTRAV, respectively.

In Study C-09-009, timolol was also rapidly absorbed into the general circulation with an

⁴ DUOTRAV PQ is preserved with polyquaternium-1 (POLYQUAD®). DUOTRAV is preserved with benzalkonium chloride (BAK). These two products contain the same active ingredients at the same concentrations.

approximate T_{max} of 30 minutes and one hour for DUOTRAV and DUOTRAV PQ, respectively. The plasma timolol exposure level for DUOTRAV PQ was significantly higher at steady state (23% and 16% higher for C_{max} and AUC_{0-tlast}, respectively) compared to DUOTRAV. Plasma timolol was eliminated with mean half-lives of approximately 5 hours for both DUOTRAV PQ and DUOTRAV at steady state.

The significantly higher plasma timolol concentrations in humans in Study C-09-009 are consistent with the observations in the pharmacokinetic studies in rabbits where DUOTRAV PQ resulted in higher exposure to timolol in plasma as well as in ocular tissues compared to DUOTRAV after a single bilateral topical ocular administration (see ACTION AND CLINICAL PHARMACOLOGY, Animal Pharmacokinetics).

Distribution: Timolol can be measured in human aqueous humour up to 12 hour after topical ocular administration of timolol (Study C-02-35).

In rabbits, after a single topical ocular administration of DUOTRAV PQ or DUOTRAV, the concentration of travoprost free acid in aqueous humour and iris-ciliary body reached its maximum level at 1-2 hours post-dose and were still >1 ng/g at 6 hours. In contrast, timolol concentrations in these ocular tissues increased immediately after dosing, reaching maximum levels in about 30 minutes and decreased to ≤10 ng/g for aqueous humor and between approximately 10 and 30 ng/g for iris-ciliary body at 6 hours.

Studies in rabbits showed that after a single topical ocular dose, timolol and travoprost free acid exposure levels in all ocular tissues were higher for DUOTRAV PQ than for DUOTRAV. For timolol, the difference was not statistically significant for bulbar conjunctiva (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Animal Pharmacokinetics).

Metabolism: Travoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to its pharmacologically active free acid. Systemically, travoprost free acid is metabolized to inactive metabolites via beta-oxidation of the carboxylic acid side-chain to give the 1,2-dinor and 1,2,3,4-tetranor analogs, via oxidation of the 15-hydroxyl moiety, as well as via reduction of the 13,14 double bond in primates. There was no difference in plasma concentrations between Days 1 and 3, indicating steady-state was reached early and there was no accumulation.

In humans, timolol is primarily metabolized by two pathways involving ring-opening oxidation of the morpholine ring. One route yields an ethanolamine side chain on the thiaziazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen.

Elimination: Travoprost free acid and its metabolites are mainly excreted by the kidneys. In humans, < 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 is excreted in urine as metabolites.

Special Populations and Conditions

Pediatrics(<18 years of age): The use of DUOTRAV PQ in pediatric patients <18 years of age is currently not recommended. The safety and effectiveness of DUOTRAV PQ in these patients have not been established.

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

Pregnancy and Breast-feeding: No adequate and well controlled studies have been performed in pregnant women with DUOTRAV PQ. Studies in animals with travoprost have shown reproductive toxicity (see NON-TOXICOLOGY, Reproductive and Developmental Toxicology). Because travoprost has harmful effects on pregnancy and/or the fetus/newborn child, DUOTRAV PQ is contraindicated during pregnancy and in women planning to become pregnant (see CONTRAINDICATIONS).

Since prostaglandins are biologically active and 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 case of accidental contact with the contents of the bottle, thoroughly cleanse the exposed area with soap and water immediately.

Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Travoprost has been shown to be excreted in milk in animal studies; however, it is not known whether travoprost and/or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions from timolol maleate or travoprost in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

11 STORAGE, STABILITY AND DISPOSAL

Store at 2°C - 25° C. No refrigeration is required. Keep out of the reach and sight of children.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

DUOTRAV PQ is a combination of a topical prostaglandin analogue and a topical beta adrenergic receptor blocking agent.

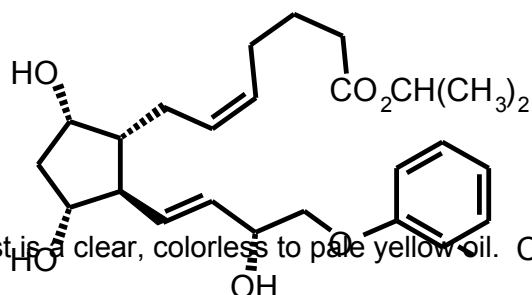
Drug Substance

Proper name: travoprost

Chemical Name: [1R-[1 α (Z),2 β (1E,3R*),3 α ,5 α]]-7-[3,5-Dihydroxy-2-[3-hydroxy-4-[3-(trifluoromethyl)phenoxy]-1-butenyl]cyclopentyl]-5-heptenoic acid, 1-methylethyl ester

Molecular formula and molecular mass: C₂₆H₃₅F₃O₆
500.56

Structural formula:



Physicochemical properties:

Description: Travoprost is a clear, colorless to pale yellow oil. CF₃

Solubility: Very soluble in acetonitrile, methanol, octanol, and chloroform.
Practically insoluble in water.

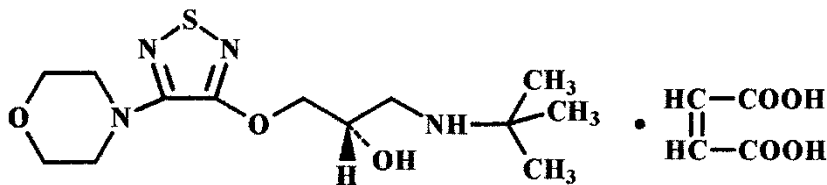
Drug Substance

Proper Name: timolol maleate

Chemical Name: (-)-1-(*tert*-Butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt)

Molecular formula and molecular mass: C₁₃H₂₄N₄O₃S•C₄H₄O₄
432.49

Structural Formula:



Physicochemical properties:

Description: Timolol maleate is a white, odorless, crystalline powder.

Solubility: Soluble in water, methanol, and alcohol.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Two Phase III safety and efficacy studies, (C-07-64/C-08-08), and 1 long term safety study (C-09-032) were conducted to establish that DUOTRAV PQ exhibited equivalent efficacy to DUOTRAV with the same overall safety profile for the product, regardless of the preservative used. In addition, 5 multicentre, randomised, double-masked, parallel-group, controlled clinical trials were conducted originally to assess the clinical efficacy and safety of DUOTRAV.

DUOTRAV PQ: Studies **C-07-64** and **C-08-08** were 2 multicentre, randomised, double-masked, parallel-group clinical trials. These studies were identical in design and were pre-planned to be combined for a single analysis.

Efficacy and safety data were collected at Week 2 and Week 6, and IOP was measured at 9 AM, 11 AM and 4 PM. The measurement of IOP at several time points at each visit is important to assess IOP throughout the day, as large diurnal fluctuations in IOP have been shown to be associated with visual field defect progression. All enrolled patients were followed for up to 6 weeks. Primary efficacy was based upon the mean IOP measurements pooled across all visits and time points.

DUOTRAV: Five multicentre, randomised, double-masked, parallel-group, controlled clinical trials were conducted to assess the clinical efficacy and safety of DUOTRAV.

Study C-02-03: One trial (C-02-03) compared DUOTRAV dosed once daily, in the morning, to DUOTRAV dosed once daily, in the evening, over a 6-week period. To qualify for the study, patients had to be diagnosed with open-angle glaucoma or ocular hypertension and had to be currently treated with one or more IOP-lowering medications. The primary efficacy endpoint was an assessment of mean IOP at the 9 AM, 11 AM and 4 PM time points at Week 2 and Week 6. The 2 dosing regimens were to be declared equivalent if the confidence interval limits were within ± 2.5 mmHg. Safety assessments included visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous cells and flare), ocular hyperemia, dilated fundus parameters (vitreous, retina/macula/choroid and optic nerve) and cardiovascular parameters (pulse rate, systolic and diastolic blood pressure).

Study C-01-69: A 3-month study (C-01-69) was designed to compare the safety and IOP-lowering efficacy of DUOTRAV to TRAVATAN® (travoprost 0.004%) alone or to timolol 0.5% alone. Patients enrolled could have been on previous IOP-lowering therapy or not on medication. The primary efficacy endpoint was an assessment of mean IOP at the 8 AM, 10 AM and 4 PM time points at Week 2, Week 6 and Month 3. A 3-month, planned, masked extension included a visit at Month 6 for additional safety follow-up.

Safety assessments included visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous cells and flare), ocular hyperemia, dilated fundus parameters (vitreous, retina/macula/choroid and optic nerve), iris/eyelash photography, cardiovascular parameters (pulse, systolic and diastolic blood pressures) and visual fields.

Studies C-01-70 and C-02-41: Two 3-month studies (C-01-70 and C-02-41) were designed to compare the IOP-lowering efficacy and safety of DUOTRAV to the concomitant administration of TRAVATAN® and timolol 0.5% in patients with open-angle glaucoma or ocular hypertension. Both studies were multicenter, double-masked, parallel group studies. The 2 treatment groups were: 1) DUOTRAV dosed once daily in the morning; and 2) Timolol 0.5% dosed once daily in the morning plus TRAVATAN® dosed once daily in the evening. The dosing regimens were to be declared similar if the confidence interval limits were within ± 1.5 mmHg. In Study C-02-41, a third treatment group, timolol 0.5% dosed twice daily, was also included. Patients enrolled could have been on previous IOP-lowering therapy or not on medication. The primary efficacy endpoint was an assessment of mean IOP at the 8 AM, 10 AM and 4 PM time points at Week 2, Week 6 and Month 3. A 3-month, planned, masked extension included a visit at Month 6 for additional safety follow-up.

Safety assessments included visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous cells and flare), ocular hyperemia, dilated fundus parameters (vitreous, retina/macula/choroid and optic nerve), iris/eyelash photography, cardiovascular parameters (pulse, systolic and diastolic blood pressures) and visual fields.

Study C-02-28: The long-term safety of DUOTRAV was evaluated in a 12-month study (C-02-28) comparing DUOTRAV and XALACOM® (latanoprost 0.005% / timolol 0.5%) ophthalmic solution in 407 patients with open-angle glaucoma or ocular hypertension. Safety assessments included visual acuity, ocular signs (cornea, iris/anterior chamber, lens, aqueous cells and flare), ocular hyperemia, dilated fundus parameters (vitreous, retina/macula/choroid and optic nerve), iris/eyelash photography, cardiovascular parameters (pulse, systolic and diastolic blood pressures) and visual fields.

14.2 Study Results

Studies C-07-64/C-08-08: DUOTRAV PQ and DUOTRAV produced statistically equivalent IOP-lowering efficacy.

Mean IOP reductions from baseline for DUOTRAV PQ and DUOTRAV were clinically relevant and statistically significant at all measurement times. Mean IOP reductions ranged from 7.5 to 8.3 mmHg for DUOTRAV PQ and from 8.1 to 8.5 mmHg for DUOTRAV in the protocol analysis and intent-to treat analysis when evaluated at the individual study visits and times.

The maximum mean IOP reduction in the DUOTRAV PQ group and DUOTRAV group were 8.3 mmHg at Week 6, 9 AM in the intent-to-treat data and 8.5 mmHg at Week 2, 4 PM in the per protocol data, respectively, corresponding to approximately 34% IOP reduction in each group.

Statistically significant differences were observed at Week 2, 4 PM Visit ($p = 0.0488$) and Week 6, 11 AM Visit ($p = 0.0155$). However, the difference in IOP lowering between DUOTRAV and DUOTRAV PQ at Week 2, 4 PM Visit was 0.6 mmHg and at Week 6, 11 AM Visit was 0.7 mmHg, neither of which is considered clinically relevant. Confidence limits for the treatment group differences in mean IOP reductions were within ± 1.5 mmHg at all 6 visits and times (Table 10).

Table 10: Comparison of Mean IOP Change from Baseline (mmHg) - C-07-64 and C-08-08 Combined (Per Protocol Data)

	Baseline ^a			Pooled	Combined			Week 2			Week 6		
	9AM	11AM	4PM		9AM	11AM	4PM	9AM	11AM	4PM	9AM	11AM	4PM
DUOTRAV PQ													
Mean	25.9	25.2	24.5	-8.0	-8.2	-7.7	-7.9	-8.2	-8.0	-7.9	-8.2	-7.5	-7.9
N	188	188	188	188	188	188	188	187	188	188	179	180	179
DUOTRAV													
Mean	25.8	24.9	24.2	-8.4	-8.4	-8.2	-8.4	-8.4	-8.3	-8.5	-8.4	-8.2	-8.3
N	184	184	184	183	183	181	181	183	180	181	176	176	177
Difference	0.2	0.3	0.3	0.4	0.2	0.5	0.5	0.2	0.3	0.6	0.2	0.7	0.4
P-value	0.5756	0.3355	0.2292	0.0943	0.4005	0.0530	0.0677	0.4589	0.2973	0.0488	0.4437	0.0155	0.1906
Upper 95% CI	0.7	0.8	0.9	0.8	0.7	1.0	1.0	0.8	0.8	1.1	0.8	1.2	0.9
Lower 95% CI	-0.4	-0.3	-0.2	-0.1	-0.3	-0.0	-0.0	-0.3	-0.3	0.0	-0.3	0.1	-0.2

DUOTRAV PQ = Travoprost 40 µg/mL + Timolol 5 mg/mL (POLYQUAD-preserved)

DUOTRAV = Travoprost 40 µg/mL + Timolol 5 mg/mL (Benzalkonium chloride-preserved)

^aBaseline is the average of the two Eligibility Visits if both values were not missing, otherwise the non-missing value of the two visits was used.

CI = Confidence interval

Combined = Results pooled across Week 2 and Week 6

Pooled = Results pooled across all time points for Week 2 and Week 6

Estimates based on least squares means using repeated measures analysis of covariance. Baseline estimates obtained from separate model.

P-values and confidence intervals were based on repeated measures analysis of covariance.

An additional measure of IOP-lowering was assessed by the percentage of patients whose on-therapy IOP decreased to less than 18 mmHg, representing a reduction from baseline of at least 30%. The percentage of patients with IOP < 18 mmHg or IOP percent reduction \geq 30% at each study visit ranged from 60% to 73% in the DUOTRAV PQ group and from 67% to 73% in the DUOTRAV group in the per protocol analysis.

A summary of all ocular and non-ocular adverse drug reactions from all 7 multicenter clinical trials with DUOTRAV PQ (2 studies) or DUOTRAV (5 studies) are presented in ADVERSE REACTIONS.

Study C-02-03: Participants included 92 adult patients (87% with open-angle glaucoma, which could include a pigmentary or exfoliative component, and 13% with ocular hypertension) with a baseline mean IOP of 25 to 27 mmHg following washout from previous IOP-lowering therapy. The results of this study indicate that the IOP-lowering efficacy of DUOTRAV is independent of time of dosing (morning vs. evening), providing clinically relevant and equivalent IOP control throughout the day. All of the two-sided 95% confidence limits were within \pm 2.5 mmHg. Mean IOP reductions ranged from approximately 8 to 10 mmHg, equating to IOP reductions of 32% to 38% relative to baseline.

The most frequent ocular adverse drug reactions to DUOTRAV in Study C-02-03 included ocular hyperemia (6 patients; 13.0%) and ocular pruritus (4 patients; 4.3%). The most frequent non-ocular adverse drug reaction was hypertension, occurring in 2 patients (2.2%). All other non-ocular adverse drug reactions occurred in 1 patient each. No clinically relevant differences were noted comparing the safety of morning and evening dosing (Table 11).

Table 11: Mean IOP (mmHg) Comparison of Morning and Evening Dosing with DUOTRAV solution (Per Protocol Data Set – Study C-02-03)

	Week 2			Week 6		
	9AM	11AM	4PM	9AM	11AM	4PM
DUOTRAV Morning Dosing	16.6	16.6	16.6	16.7	16.7	16.5
DUOTRAV Evening Dosing	17.2	16.7	16.1	17.0	16.9	16.3
Difference	-0.6 ^a	-0.1 ^a	0.5 ^a	-0.3 ^a	-0.2 ^a	0.2 ^a
Upper 95% Confidence Interval	0.9	1.3	2.0	1.1	1.3	1.7
Lower 95% Confidence Interval	-2.0	-1.6	-1.0	-1.8	-1.7	-1.2

^a p-value > 0.05

Study C-01-69: Participants included 263 adult and elderly patients with open-angle glaucoma (which could include a pigmentary or exfoliative component) (69%) or ocular hypertension (31%) with baseline mean IOPs, following washout from previous IOP-lowering therapy, if applicable, of 27 to 30 mmHg. The results of this study indicate that DUOTRAV produces statistically significant and clinically relevant reductions in IOP ranging from approximately 9 to 12 mmHg which equates to IOP reductions of 32% to 38% relative to baseline. IOP-lowering with DUOTRAV, dosed once-daily in the morning, was 2 to 3 mmHg greater than that of timolol ophthalmic solution, 0.5%, dosed twice-daily, at all visits and times, and was 1 to 2 mmHg greater than that of TRAVATAN® at all times of day (Table 12). This is most evident at the crucial 8 AM time point when IOP is highest and is 24 hours post-dosing of the fixed combination. Due to its complementary mechanisms of action (increased uveoscleral outflow and suppression of aqueous humour production), DUOTRAV solution produces large mean IOP reductions in all demographic subgroups.

In this study where baseline IOPs were 27 to 30 mmHg, 50% of patients receiving DUOTRAV solution achieved IOP below 18 mmHg on at least 1 time point for every visit (Table 13)

In clinical practice, the appropriate value of a target IOP (an IOP level that would be considered a clinical success) is determined by the physician for each patient. Information from the recent Advanced Glaucoma Intervention Study (AGIS) indicates that an IOP of less than 18 mmHg is correlated with reduced progression of visual field defects associated with glaucoma.

Table 12 - Mean IOP (mmHg) Comparison of DUOTRAV and Timolol 0.5% and of DUOTRAV and TRAVATAN® (Intent-to-Treat Data Set – Study C-01-69)

	Week 2			Week 6			Month 3		
	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
DUOTRAV	18.9	18.1	17.5	18.9	17.9	18.2	18.7	18.4	18.5
Timolol 0.5%	21.3	20.4	20.2	20.6	20.0	19.8	20.8	19.9	20.1
Difference	-2.4 ^a	-2.2 ^a	-2.7 ^a	-1.7 ^a	-2.1 ^a	-1.7 ^a	-2.1 ^a	-1.5 ^a	-1.5 ^a
Upper 95% CI	-1.3	-1.1	-1.6	-0.5	-1.0	-0.6	-0.9	-0.4	-0.4
Lower 95% CI	-3.5	-3.3	-3.8	-2.8	-3.2	-2.8	-3.2	-2.6	-2.6
DUOTRAV	18.9	18.1	17.5	18.9	17.9	18.2	18.7	18.4	18.5
TRAVATAN®	20.5	18.9	18.7	20.3	19.2	18.7	20.5	19.3	18.9
Difference	-1.6 ^b	-0.8	-1.2 ^b	-1.4 ^b	-1.3 ^b	-0.5	-1.8 ^b	-1.0	-0.4
Upper 95% CI	-0.5	0.4	-0.0	-0.3	-0.1	0.6	-0.6	0.2	0.8
Lower 95% CI	-2.8	-1.9	-2.3	-2.5	-2.4	-1.6	-2.9	-2.1	-1.5

^a p<0.05 DUOTRAV vs. Timolol 0.5%

^b p<0.05 DUOTRAV vs. TRAVATAN®

Table 13 - Percent of Patients with IOP < 18 mmHg on a Least One Time Point at Every Visit (Intent-to-Treat Data Set – Study C-01-69)

	Percent of Patients
DUOTRAV	50%
TRAVATAN®	29%
Timolol 0.5%	23%

The most frequent ocular adverse drug reactions with DUOTRAV in Study C-01-69 included ocular hyperemia (12 patients; 14.1%), ocular discomfort (6 patients; 7.1%), photophobia (4 patients; 4.7%), and changes in eyelash characteristics (4 patients; 4.7%). The most frequent non-ocular adverse drug reaction was headache, occurring in 2 patients (2.4%). All other non-ocular adverse drug reactions occurred in 1 patient each. No clinically relevant differences in safety were noted between the 3-month and 6-month data sets.

Studies C-01-70 and C-02-41: Participants included 316 (Study C-01-70) and 403 (Study C-02-41) adult and elderly patients with open-angle glaucoma, which could include a pigmentary or exfoliative component, (68% in C-01-70; 57% in C-02-41) or ocular hypertension (32% in C-01-70; 43% in C-02-41) with baseline mean IOPs, following washout from previous IOP-lowering therapy, if applicable, of 23 to 26 mmHg. The results of both studies indicate that DUOTRAV produces IOP-lowering that is similar to the concomitant administration of TRAVATAN® and timolol 0.5% and greater than timolol 0.5% dosed twice daily. Treatment-group differences in mean IOP were similar in the 2 studies and ranged from 0.1 to 1.1 mmHg, demonstrating the similarity of IOP reduction (see Table 14, Table 15, Table 16).

Table 14 - Mean IOP (mmHg) Comparison of DUOTRAV and TRAVATAN® + Timolol 0.5% for Test of Non-Inferiority (Per Protocol Dataset – Study C-01-70)

	Week 2			Week 6			Month 3		
	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
DUOTRAV	16.1	15.5	15.2	15.9	15.7	15.6	16.5	16.1	15.6
TRAVATAN® + Timolol 0.5%	16.0	15.2	14.8	15.8	14.8	14.7	16.1	15.1	14.8
Difference	0.1	0.3	0.5	0.1	1.0 ^a	0.9 ^a	0.5	0.9 ^a	0.8 ^a
Upper 95% CI	0.7	0.9	1.1	0.7	1.6	1.5	1.1	1.6	1.5
Lower 95% CI	-0.5	-0.4	-0.2	-0.5	0.3	0.3	-0.2	0.3	0.2

^a p<0.05 DUOTRAV vs. TRAVATAN® + Timolol 0.5%

Table 15 - Mean IOP (mmHg) Comparison of DUOTRAV and TRAVATAN® + Timolol 0.5% for Test of Non-Inferiority (Per Protocol Dataset – Study C-02-41)

	Week 2			Week 6			Month 3		
	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
DUOTRAV	17.4	16.8	16.2	17.0	16.6	16.2	17.1	16.5	16.3
TRAVATAN® + Timolol	16.8	15.7	15.4	16.6	15.5	15.4	16.7	15.8	15.5
Difference	0.6	1.1 ^a	0.8 ^a	0.4	1.0 ^a	0.7 ^a	0.4	0.7	0.8 ^a
Upper 95% CI	1.3	1.8	1.5	1.1	1.7	1.5	1.2	1.4	1.6
Lower 95% CI	-0.1	0.4	0.0	-0.4	0.3	0.0	-0.3	-0.1	0.1

^a p<0.05 DuoTrav vs. TRAVATAN® + Timolol

Table 16 - Mean IOP (mmHg) Comparison of DUOTRAV® and Timolol 0.5% for Test of Superiority (Intent-to-Treat Dataset – Study C-02-41)

	Week 2			Week 6			Month 3		
	8AM	10AM	4PM	8AM	10AM	4PM	8AM	10AM	4PM
DUOTRAV	17.5	16.8	16.2	17.0	16.6	16.2	17.2	16.5	16.4
Timolol 0.5%	18.3	18.0	18.3	18.8	17.9	17.9	18.8	17.8	17.5
Difference	-0.9 ^a	-1.3 ^a	-2.1 ^a	-1.8 ^a	-1.3 ^a	-1.7 ^a	-1.6 ^a	-1.3 ^a	-1.2 ^a
Upper 95% CI	-0.0	-0.4	-1.3	-0.9	-0.4	-0.8	-0.7	-0.5	-0.3
Lower 95% CI	-1.7	-2.1	-3.0	-2.7	-2.2	-2.6	-2.4	-2.2	-2.0

^a p<0.05 DUOTRAV solution versus Timolol 0.5%

In these studies where baseline IOPs were 23 to 26 mmHg, approximately 74% of patients receiving DUOTRAV achieved IOP below 18 mmHg on at least 1 time point at every visit.

Table 17 - Percent of Patients with IOP < 18 mmHg on at Least One Time Point at Every Visit (Intent-to-Treat Data Sets – Studies C-01-70 and C-02-41)

	Percent of Patients		
	C-01-70	C-02-41	Pooled
DUOTRAV	79%	70%	74%
TRAVATAN® + Timolol 0.5%	84%	80%	82%
Timolol 0.5%	---	52%	---

The most frequent ocular adverse drug reactions with DUOTRAV in Study C-01-70 included ocular hyperemia (20 patients; 12.4%), ocular discomfort (9 patients; 5.6%), ocular pruritus (6 patients; 3.7%), ocular dryness (5 patients; 3.1%), corneal staining (4 patients; 2.5%),

keratitis (3 patients; 1.9%), ocular allergic reaction (3 patients; 1.9%), and ocular pain (3 patients; 1.9%). The most frequent non-ocular adverse drug reaction was headache, occurring in 2 patients (1.2%). All other non-ocular adverse drug reactions (contact dermatitis, increased cough and skin discoloration) occurred in 1 patient each (0.6%).

The most frequent ocular adverse drug reactions with DUOTRAV in Study C-02-41 included ocular hyperemia (23 patients; 14.3%), ocular discomfort (20 patients; 12.4%), foreign body sensation (11 patients; 6.8%), ocular pruritus (7 patients; 4.3%), ocular dryness (5 patients; 3.1%), cells (4 patients; 2.5%), blurred vision (3 patients; 1.9%), lid erythema (3 patients; 1.9%), ocular pain (3 patients; 1.9%), and photophobia (3 patients; 1.9%). All non-ocular adverse drug reactions (abnormal urine, dyspnea, irritation throat, SGOT increased, SGPT increased and skin discoloration) occurred in 1 patient each (0.6%).

An analysis of the 6-month safety data from both Studies C-01-70 and C-02-41 confirmed that DUOTRAV has an acceptable safety profile with no clinically relevant differences noted between the 3-month and 6-month safety results.

In all 3-month studies, patients treated with DUOTRAV achieve sustainable IOP reduction after 2 weeks of therapy and the IOP reduction is maintained for 3 months.

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

Study C-02-28: The most frequent ocular adverse drug reactions with DUOTRAV in Study C-02-28 included ocular hyperemia (31 patients; 15.0%), ocular pruritus (14 patients; 6.8%), ocular discomfort (9 patients; 4.3%), changes in eyelash characteristics (5 patients; 2.4%), ocular dryness (4 patients; 1.9%), and ocular pain (3 patients; 1.4%). Increased iris pigmentation occurred at an incidence of 2.4% (4 patients) (see Table 4 in ADVERSE REACTIONS). The most frequent non-ocular adverse drug reaction was skin discoloration, occurring in 2 patients (1.0%). All other non-ocular adverse drug reactions (allergy, asthma, dizziness, dyspnea, hypertension and increased cough) occurred in 1 patient each (0.5%).

Summary: An analysis of the safety data obtained across all studies indicates that DUOTRAV is well tolerated with a safety profile similar to that obtained with the concomitant dosing of TRAVATAN® and timolol 0.5%. Studies conducted with the individual components of DUOTRAV indicate that the IOP-lowering effect of travoprost and of timolol are well maintained over a period of 1 year. Adverse drug reactions with DUOTRAV were consistent with those reported previously with TRAVATAN® and/or timolol 0.5%.

16 NON-CLINICAL TOXICOLOGY

GENERAL TOXICOLOGY

Single Dose Toxicity

Travoprost/Timolol Combination: DUOTRAV PQ was well tolerated after topical ocular administration of a single large dose in animals. After topical ocular administration of one drop in each eye every 30 minutes for a total of 10 doses in a single day, DUOTRAV PQ caused only minimal conjunctival congestion and discomfort. This result is similar to that of DUOTRAV in the same experimental system. However, the direct comparative acute ocular toxicity was not conducted between DUOTRAV PQ and DUOTRAV. Systemic single dose studies were not conducted with the combination.⁵

The poor oral bioavailability of travoprost mitigates the hazard of accidental ingestion. Timolol is orally bioavailable, but has a low order of toxicity (mouse/rat oral LD₅₀ ~ 1000 mg/kg).

Travoprost: Travoprost was demonstrated to have a low order of acute toxicity. An LD₅₀ of travoprost has not been established. No mortalities occurred in rats administered travoprost intravenously at a dose of 10 mg/kg (250,000-times the proposed clinical exposure) or in mice given up to 100 mg/kg/day (2,500,000-times the proposed clinical exposure). The most frequent clinical observations were discolored urine and red material around the nose in rats, and lethargy and diarrhea in mice.

Administration of travoprost ophthalmic solution, up to 0.01%, two drops every half-hour for five or six hours, did not result in any significant ocular or systemic effects.

Timolol: Acute oral dosing studies established an LD₅₀ of approximately 1000 mg/kg for mice and rats. The most frequent clinical observations were decreased activity and bradypnea. Oral acute interaction studies in mice in which timolol maleate was administered with probenecid, methyldopa, hydralazine, hydrochlorothiazide, or tolbutamide, showed that these drugs had no effect on the toxicity of timolol maleate. Timolol maleate had no effect on hypoprothrombinemia induced by bishydroxycoumarin in the dog.

POLYQUAD: The toxicity of POLYQUAD in animals appears to be low after topical ocular and oral administration. A single topical ocular POLYQUAD dose (32,000 times higher than that used in DUOTRAV PQ) was well tolerated in rabbits. Transient occurrences of soft stool and diarrhoea were the most common observations after oral administration of a single 1000 mg/kg dose of POLYQUAD in rats. The NOAEL for a single oral POLYQUAD dose in rats is estimated to be 100 mg/kg. The LD₅₀ for orally administered POLYQUAD in rats is higher than 1000 mg/kg. The maximum tolerated dose (MTD) of POLYQUAD in mice is estimated to be 5000 mg/kg.

Repeated Dose Toxicity

Travoprost/Timolol Combination: Similar to DUOTRAV, DUOTRAV PQ appears to be well tolerated following repeat-dose topical ocular administration in animals.

⁵ DUOTRAV PQ is preserved with polyquaternium-1 (POLYQUAD). DUOTRAV is preserved with benzalkonium chloride (BAK). These two products contain the same active ingredients at the same concentrations.

A 3-month topical ocular study in pigmented rabbits was conducted with DUOTRAV PQ. Study groups were exposed to the DUOTRAV PQ vehicle, DUOTRAV PQ and DUOTRAV, 3 times daily (TID). There was no difference identified in terms of ocular toxicity between DUOTRAV PQ and DUOTRAV.

All test articles were well tolerated. Biomicroscopic observations of the eyes of control and test article-treated rabbits were limited to minimal conjunctival congestion (hyperemia) with the exception of 1 male rabbit in Group 3 that displayed severe congestion and a mild subconjunctival hemorrhage in both eyes on Day 91, resulting from a non-treatment-related injury. One cataract was observed in a vehicle-treated rabbit (OD) on Day 91. There were no treatment-related macroscopic observations during necropsy on Day 92, and no clinically-relevant organ weight changes were observed in this study. None of the microscopic findings noted from the histopathology evaluation were interpreted to be treatment related. In addition, there were no findings in ocular tissues from the DUOTRAV PQ - treated animals that were distinctly different from animals treated with the POLYQUAD vehicle or with DUOTRAV.

Based on the data acquired from this 3-month topical ocular study in pigmented rabbits, DUOTRAV PQ does not demonstrate a cumulative ocular irritation potential or systemic toxicity potential that is different from DUOTRAV.

Travoprost: Topical ocular administration of travoprost ophthalmic solution, 0.01%, three times a day for six months, in rabbits, resulted in no significant ocular or systemic effects. Iris pigmentation and a species specific increase in palpebral fissure and increase in lid retraction was observed in some monkeys receiving 0.0015%, 0.004% or 0.012% travoprost ophthalmic solution for up to one year. No other significant ocular or systemic effects were seen.

The increased iridial pigmentation observed in monkeys and also in humans during chronic ocular treatment with travoprost is considered to be a class effect of prostaglandins. It is of particular interest that naturally occurring prostaglandins such as $\text{PGF}_{2\alpha}$ and PGE_2 also cause increased pigmentation of the iris in cynomolgus monkeys. It should also be noted that both cynomolgus monkey and human iridial melanocytes express FP receptors in their cell membrane, and since travoprost is a selective FP receptor agonist, it implies that the effect is mediated by FP receptors in the melanocytes.

Subchronic intravenous administration of travoprost in rats at all doses employed (100 to 1000 micrograms/kg/day) resulted in trace-to-moderate hyperostosis and bone fibrosis. Incidence and severity were dose related, and determined bone to be a target organ of toxicity in rats. Similar studies in mice resulted in no significant systemic effects at doses of up to 1000 $\mu\text{g}/\text{kg}/\text{day}$.

Chronic systemic administration (subcutaneous) of travoprost to rats at doses of 30 and 100 micrograms/kg/day resulted in dose-related hyperostosis and bone fibrosis similar to that observed in the subchronic study. No effect was observed in bone at 10 micrograms/kg/day (250 times the proposed clinical exposure), which was considered the no effect level.

Timolol: No adverse ocular effects were observed in rabbits and dogs administered timolol maleate ophthalmic solution topically in studies lasting one and two years, respectively.

Timolol was administered orally to rats at dose levels 5, 10 and 25 mg/kg/day for up to 67 weeks. No physical signs, ocular signs or deaths which could be attributed to the drug were evident.

In a 54 week oral study, timolol was administered to dogs at doses of 5, 10 and 25 mg/kg/day. Body weight and food consumption were normal and no physical signs attributable to treatment were evident. Slight focal hyperplasia of the transitional epithelium was seen in the renal pelvis of one dog receiving 25 mg/kg/day.

In rats treated with 100 to 400 mg/kg timolol maleate for seven weeks, excessive salivation seen 5 to 10 minutes after dosing has a dose related incidence in the first week of the study. At necropsy, organ weight studies revealed a significant increase in the kidneys, spleen and liver of some treated animals. Except for splenic congestion, there were no morphological changes to account for the increase in organ weights. Rats treated with 1 gram per day for eight weeks exhibited ptilyamism, muscle tremors and transient pale extremities.

In dogs, doses of 200 mg/kg timolol maleate or higher, were lethal to some animals. Low grade tubular nephrosis and trace amounts of hyaline casts in the collecting and convoluted tubules occurred in one of two dogs administered 100 mg/kg/day and in both dogs receiving 400 mg/kg/day. Small foci of tubular degeneration and regeneration occurred in the nephrotic areas. Similar slight multi focal degeneration of the collecting tubules in the medulla of both kidneys was evident in one of four dogs in a 15 day intravenous toxicity study.

POLYQUAD: POLYQUAD has been extensively studied in non-clinical models to evaluate ocular safety. In preclinical safety evaluations of up to one-year, POLYQUAD® at the concentration (0.001%) in DUOTRAV PQ, appears well tolerated in rabbits after long-term daily topical ocular administration.

CARCINOGENICITY

Two-year carcinogenicity studies in mice and rats at subcutaneous doses of 10, 30, or 100 µg/kg/day travoprost did not show any evidence of carcinogenic potential. However, at 100 µg/kg/day, male rats were only treated for 82 weeks, and the maximum tolerated dose (MTD) was not reached in the mouse study. The high dose (100 µg/kg/day) corresponds to exposure levels over 400 times the human exposure at the maximum recommended human ocular dose (MRHOD), based on plasma active drug levels.

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the MRHOD). This was not observed in rats administered oral doses equivalent to approximately 14,000 times the MRHOD.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps, and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the MRHOD), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the MRHOD). In a subsequent study in female mice, in which postmortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin, which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has

been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

No carcinogenicity studies were conducted with Travoprost/Timolol fixed combination solution.

No carcinogenicity studies were conducted with POLYQUAD.

MUTAGENICITY

Travoprost was not mutagenic in the Ames test, mouse micronucleus test and rat chromosome aberration assay. A slight increase in the mutant frequency was observed in one of two mouse lymphoma assays in the presence of rat S-9 activation enzymes.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 µg/mL). In Ames tests, the highest concentrations of timolol employed, 5,000 or 10,000 µg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

No mutagenicity studies were conducted with Travoprost/Timolol fixed combination solution.

POLYQUAD was not mutagenic and not genotoxic in the Ames test, chromosomal aberration test, forward mutation test, sister chromatid exchange test, BALB/3T3 cell transformation assay, and *in vivo* mouse micronucleus test.

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Travoprost did not affect mating or fertility indices in male or female rats at subcutaneous doses up to 10 µg/kg/day [250 times the MRHOD of 0.04 µg/kg/day]. At 10 µg/kg/day, the mean number of corpora lutea was reduced, and the post-implantation losses were increased. These effects were not observed at 3 µg/kg/day (75 times the MRHOD).

Travoprost was teratogenic in rats, at an intravenous (IV) dose of 10 µg/kg/day (250 times the MRHOD), evidenced by an increase in the incidence of skeletal malformations as well as external and visceral malformations, such as fused sternebrae, domed head and hydrocephaly. Travoprost was not teratogenic in rats at IV doses up to 3 µg/kg/day (75 times the MRHOD), or in mice at subcutaneous doses up to 1.0 µg/kg/day (25 times the MRHOD). Travoprost produced an increase in post-implantation losses and a decrease in foetal viability in rats at IV doses > 3 µg/kg/day (75 times the MRHOD) and in mice at subcutaneous doses > 0.3 µg/kg/day (7.5 times the MRHOD).

In the offspring of female rats that received travoprost subcutaneously from Day 7 of pregnancy to lactation Day 21 at the doses of ≥0.12 µg/kg/day (3 times the MRHOD), the incidence of postnatal mortality was increased, and neonatal body weight gain was decreased. Neonatal development was also affected, evidenced by delayed eye opening, pinna detachment and preputial separation, and by decreased motor activity.

Reproduction and fertility studies with timolol maleate in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the MRHOD.

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the MRHOD) demonstrated no evidence of foetal malformations. Although delayed foetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the MRHOD) were maternotoxic in mice and resulted in an increased number of foetal resorptions. Increased foetal resorptions were also seen in rabbits at doses of 14,000 times the MRHOD, in this case without apparent maternotoxicity.

No reproduction or teratology studies were conducted with Travoprost/Timolol fixed dose combination solutions such as DUOTRAV or DUOTRAV PQ.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrDUOTRAV® PQ
travoprost and timolol ophthalmic solution
with POLYQUAD® as preservative

Read this carefully before you start taking PrDUOTRAV® PQ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **DUOTRAV PQ**.

What is DUOTRAV PQ used for?

DUOTRAV PQ is used to decrease high pressure in the eye in patients with the following conditions:

- Open-angle glaucoma
- Ocular hypertension

High pressure in the eye(s). Your eyeballs contain a clear, watery liquid which feeds the inside of the eye. Liquid is always emptying out of the eye, and more liquid is always being produced. If the eye fills up faster than it empties, the pressure inside the eye builds up. If it gets too high, it can damage your sight.

How does DUOTRAV PQ work?

DUOTRAV PQ decreases the pressure in your eye through the action of travoprost (a prostaglandin analogue) and timolol (a beta-blocker). Travoprost increases the flow of fluid out of your eye. Timolol reduces the amount of fluid produced by your eye.

What are the ingredients in DUOTRAV PQ?

Medicinal ingredients: travoprost and timolol (as timolol maleate).

Non-medicinal ingredients: boric acid, mannitol, polyoxyethylene hydrogenated castor oil 40, polyquaternium-1 (POLYQUAD), propylene glycol, purified water and sodium chloride. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH.

DUOTRAV PQ comes in the following dosage forms:

Solution: travoprost 0.004% w/v and timolol 0.5% w/v (as timolol maleate)

Do not use DUOTRAV PQ if you:

- Have, or have ever had, an unusual or allergic reaction to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- Are pregnant or planning to become pregnant.
- Have, or have had, a lung condition. These can include asthma or chronic obstructive pulmonary disease (COPD).
- Have certain heart conditions, heart disease, or heart problems, such as slow heartbeat, heart failure, or heart rhythm disorder (irregular heartbeats).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DUOTRAV PQ. Talk about any health conditions or problems you may have, including if you:

- Have or have had diabetes or low blood sugar (hypoglycemia).
- Have or have had thyroid problems. This can include a condition called thyrotoxicosis.
- Have or have had kidney problems.
- Have muscle weakness or have a condition causing muscle weakness called myasthenia gravis.
- Have heart disease, low blood pressure, circulation problems such as Raynaud's syndrome or problems with blood circulation to the brain.
- Are breastfeeding or planning to breastfeed.
- Are planning to have surgery.
- Have had a severe allergic reaction.
- Have had cataract surgery.
- Have had a filtration procedure (a type of eye surgery). You may develop detachment of the internal layer of the eye.
- Have or have had an eye injury.
- Have or have had eye inflammation (iritis and/or uveitis).
- Have or have had distorted vision that is making things look blurry and colors look washed out. This can include a condition called macular edema.
- Are using other medicines called beta-blockers or prostaglandin analogues.

Other warnings you should know about:

Talk to your doctor if you develop an eye or eyelid infection while taking DUOTRAV PQ.

Not recommended to individuals under 18 years of age.

Pressure in your eye(s): Your doctor should check the pressure in your eye(s) regularly.

Eye color and eyelash changes: Using DUOTRAV PQ may cause your eye color to become more brown or cause your eyelashes to become thicker, longer and darker. These changes may be permanent. If you are using DUOTRAV PQ in only one eye, your two eyes may look different. Your doctor should examine you regularly to make sure your medication is working and look for changes in eye colour. Your doctor may stop treatment if needed.

Eyelid skin darkening: Using DUOTRAV PQ may cause darkening of your eyelid skin.

Contact lens wear: Do not wear contact lenses while applying DUOTRAV PQ. Remove your contact lenses before applying DUOTRAV PQ and wait at least 15 minutes before putting them back in.

Skin contact: DUOTRAV PQ contains propylene glycol and polyoxyethylene hydrogenated castor oil, which can cause skin reactions. Avoid accidental contact with your skin. Wipe up any spills and rinse the contacted areas with water.

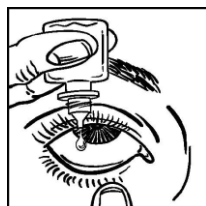
Driving and using machines: DUOTRAV PQ may cause you to become drowsy or your vision may become blurry for some time. If any of these happen to you, wait until they go away before driving or using machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

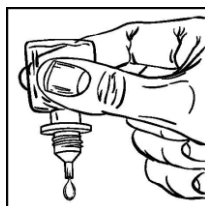
The following may interact with DUOTRAV PQ:

- Digitalis, a medicine used to treat congestive heart failure and heart rhythm problems.
- Calcium antagonists, used to treat high blood pressure.
- Catecholamine-depleting drugs, e.g. reserpine, used to treat high blood pressure.
- Quinidine, an antiarrhythmic used to treat heart conditions and some types of malaria.
- Injectable epinephrine, used to treat severe allergic reactions.
- Central nervous system depressants, used to treat insomnia, anxiety, panic attacks and seizures.
- Tricyclic antidepressants, used to treat depression.
- Other beta-blocking drugs, used to decrease blood pressure.

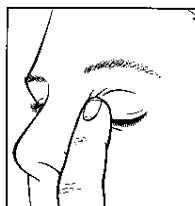
How to take DUOTRAV PQ:



1



2



3

- Get the DUOTRAV PQ bottle and a mirror.
- Wash your hands.
- Open the bottle being careful not to touch the dropper tip.
- Hold the bottle, pointing down, between your thumb and fingers.
- Tilt your head back. Pull down your eyelid with a clean finger, until there is a 'pocket' between the eyelid and your eye. The drop will go in there (see picture 1).
- Bring the bottle tip close to the eye. Use the mirror if it helps.
- Don't touch your eye or eyelid, surrounding areas or other surfaces with the bottle tip. It could contaminate the drops.
- Gently squeeze the bottle to release one drop of DUOTRAV PQ (see picture 2).
- After using DUOTRAV PQ, press a finger into the corner of your eye, by the nose (see picture 3). This helps to stop DUOTRAV PQ from getting into the rest of the body.
- If a drop misses your eye, wipe with a tissue and try again.
- If you take drops in both eyes, repeat the steps for your other eye.
- Close the bottle cap firmly immediately after use.
- Wash your hands after use.

If you are using more than one eye drop, wait at least 5 minutes between using DUOTRAV PQ and the other drop(s).

Usual dose:

Use one drop of DUOTRAV PQ in the affected eye(s) once daily.
Use DUOTRAV PQ either in the morning or in the evening.

Overdose:

If you use more DUOTRAV PQ than you should, rinse it all out with warm tap water. Using too many drops may cause your eyes to become red and irritated. Do not put in any more drops until it's time for your next regular dose.

If you accidentally ingest DUOTRAV PQ, contact your doctor or pharmacist for advice.

If you think you have used too much DUOTRAV PQ, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, wait until it is time for your next dose. Do not double dose to make up for a missed dose.

What are possible side effects from using DUOTRAV PQ?

These are not all the possible side effects you may feel when taking DUOTRAV PQ. If you experience any side effects not listed here, contact your healthcare professional.

Side effects in the eye(s) include:

- Redness.
- Itching.
- Dryness.
- Pain.
- Sensitivity to light.
- Abnormal sensation in eye or other eye irritations.
- Blurred vision.
- Temporary reduction of vision.
- Tearing.
- Growth of eyelashes and eyebrows hair.
- Abnormally positioned eyelashes.
- Eye swelling.
- Discomfort (burning and stinging).
- Changes in vision.
- Itching, swollen, heavy, painful or irritated eyelids.
- Inflammation of the eyelid glands.
- Increased eye pressure.
- Eyelid crusting.
- Sunken eyes (eyes appear more inset).
- Changes in the color of the iris (colored part of the eye).
- Skin darkening (around the eye).

Side effects in other areas of the body include:

- Headache.
- Postnasal drip.
- Thirst, cough or throat pain or irritation.
- A change in blood pressure or heart rate.
- Disturbance in attention.
- Dizziness.
- Nervousness.
- Seeing, feeling or hearing things that are not there (hallucination).
- Depression.
- Skin infection or irritation, skin reaction, skin redness.
- Ear infections.
- Pain in arms or legs.
- Shortness of breath, difficulty breathing
- Fatigue.
- Discomfort inside the nose.
- A change in urine color.
- Bad taste in the mouth.
- Strained talking or swelling in the limbs.
- Rash.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN Allergic reaction: swelling or inflammation of the eye, trouble breathing			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store between 2°C and 25°C. No refrigeration is required.

Do not use this medicine after the expiry date on the bottle or carton.
Discard 120 days after first opening.
Keep out of reach and sight of children.

If you want more information about DUOTRAV PQ:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

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