PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrTRUSOPT®

PrTRUSOPT® Preservative-Free

Dorzolamide Hydrochloride Ophthalmic Solution

Solution, dorzolamide 2% weight/volume, Ophthalmic

Elevated Intraocular Pressure Therapy

(Topical Carbonic Anhydrase Inhibitor)

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DEC 31, 1996

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RECENT MAJOR LABEL CHANGES

Not applicable.

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

TRUSOPT® (dorzolamide hydrochloride) ophthalmic solution 2% and TRUSOPT® preservative-free formulation are indicated in the treatment of elevated intraocular pressure in patients with:

- ocular hypertension
- open-angle glaucoma

TRUSOPT preservative-free formulation is indicated in patients who may be sensitive to a preservative, or for whom the use of a preservative-free formulation is otherwise advisable. For details please also refer to the 4 DOSAGE AND ADMINISTRATION section as well as to the 14 CLINICAL TRIALS section.

1.1 Pediatrics

Pediatrics (<18 years of age): Safety and effectiveness in children have not been established. No data are available to Health Canada; therefore, an indication for pediatric use has not been authorized.

1.2 Geriatrics

Geriatrics (>65 years of age): No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

TRUSOPT and TRUSOPT Preservative-Free are contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Patients with severe renal impairment (CrCl < 0.5 mL/s) as dorzolamide hydrochloride and its metabolite are excreted predominantly by the kidney. TRUSOPT and TRUSOPT preservative-free have not been studied in these patients and is not recommended.
- Patients taking oral carbonic anhydrase inhibitors, as there is potential for an additive effect with the known systemic effects of carbonic anhydrase inhibition. The concomitant administration of TRUSOPT or TRUSOPT preservative-free and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- When substituting TRUSOPT or TRUSOPT preservative-free formulation for another ophthalmic antiglaucoma agent, discontinue the other agent after proper dosing on one day, and start TRUSOPT or TRUSOPT preservative-free formulation on the next day.
- If more than one topical ophthalmic drug is being used, the drugs should be administered at least ten minutes apart.

4.2 Recommended Dose and Dosage Adjustment

- Adults (≥18 years of age): When used as monotherapy, the dose is one drop of TRUSOPT or TRUSOPT preservative-free formulation ophthalmic solution 2% in the affected eye(s) three times daily.

  When used as adjunctive therapy with an ophthalmic beta-blocker, the dose is one drop of TRUSOPT or TRUSOPT preservative-free formulation in the affected eye(s) two times daily.

  A comparative crossover clinical trial of 12 weeks duration (two 6-week periods) has been performed with TRUSOPT preservative-free formulation and TRUSOPT with preservative in adult patients. The total duration of exposure to TRUSOPT preservative-free formulation was for 6 weeks. The results have indicated that the efficacy and safety profile of these two formulations appear to be equivalent. No studies were conducted with TRUSOPT preservative-free formulation in special populations (pediatric, kidney or liver diseases, etc.). For details please also refer to the 14 CLINICAL TRIALS section.
- Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use (see 1.1 Pediatrics).

4.4 Administration

Do not allow the pipette to touch the eye or areas around the eye.

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

4.5 Missed Dose

If a dose is missed, it should be applied as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken as usual.

5 OVERDOSAGE

No data are available in humans in regard to overdosage by accidental or deliberate ingestion. The most common signs and symptoms to be expected with overdosage of dorzolamide are

electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects (see 8 ADVERSE REACTIONS).

Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Significant lethality was observed in female rats and mice after single oral doses of dorzolamide hydrochloride of 11 369 mg/m^2 or 1 927 mg/kg (24 000 times the maximum recommended human ophthalmic dose) and 3 960 mg/m^2 or 1 320 mg/kg (16 000 times the maximum recommended human ophthalmic dose), respectively.

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
Ophthalmic	Solution, each mL contains 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride)	Hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide (to adjust pH) and water for injection. Benzalkonium chloride 0.0075% is added as a preservative. The Preservative-Free formulation does not contain benzalkonium chloride.

TRUSOPT Ophthalmic Solution is a sterile, clear, colourless to nearly colourless, isotonic, buffered, slightly viscous, aqueous solution of dorzolamide hydrochloride. Each mL of TRUSOPT 2% contains 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride).

TRUSOPT Ophthalmic Solution

TRUSOPT sterile ophthalmic solution is supplied in translucent, high- density polyethylene ophthalmic dispensers, with a sealed dropper tip, a flexible fluted side area which is depressed to dispense the drops, and a 2-piece cap assembly. The opaque, white, 2-piece cap mechanism punctures the dropper tip seal upon initial use, then locks to provide a single cap during the usage period. Tamper evidence is provided by a safety strip on the container label.

TRUSOPT 2%, equivalent to 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride) per mL; in 5 mL dispensers.

TRUSOPT preservative-free formulation Ophthalmic Solution

For patients who may be sensitive to the preservative benzalkonium chloride or when use of a preservative-free topical medication is advisable, a formulation of TRUSOPT without the

preservative benzalkonium chloride is available.

This formulation is packaged in 4 pouches of 15 x 0.2 mL individual fill volume unit dose pipettes.

7 WARNINGS AND PRECAUTIONS

General

Dorzolamide hydrochloride is a sulfonamide and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. TRUSOPT and TRUSOPT preservative-free have not been studied in patients with acute angle-closure glaucoma.

Carcinogenesis and Mutagenesis

Carcinogenicity

In a two-year study of dorzolamide hydrochloride administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day (250 times the maximum recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately twelve times the maximum recommended human ophthalmic dose. No treatment-related tumors were seen in a 21-month study in female and male mice given oral doses up to 75 mg/kg/day (~900 times the maximum recommended human ophthalmic dose).

The increased incidence of urinary bladder papillomas seen in the high-dose male rats is a class-effect of carbonic anhydrase inhibitors in rats and is secondary to increased urinary sodium, potassium, pH and crystals, all changes induced by carbonic anhydrase inhibitors. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria and sodium salts of diverse compounds that are inert when given as calcium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide for one year at 2 mg/kg/day or monkeys given oral dorzolamide for one month at 50 mg/kg/day (the urothelial changes in the bladder occurred with oral dosing in rats within one month). In addition, monkeys dosed topically to the eye with 0.4 mg/kg/day (~5 times the maximum recommended human ophthalmic dose) for one year had no urothelial changes in the bladder.

Mutagenicity

Dorzolamide hydrochloride was devoid of mutagenic potential when evaluated in the following 5 tests: (1) *in vivo* (mouse) in the cytogenetic assay at doses up to 500 mg/kg/day (6 250 times the maximum recommended human ophthalmic dose); (2) *in vitro* in the

chromosomal aberration assay; (3) in the alkaline elution assay; (4) in the V-79 assay (doses up to 10 μM); and (5) in the Ames test, in which the highest concentration of dorzolamide hydrochloride used, 10 000 μg/plate, did not result in a two-fold or greater increase in revertants with tester strains of *S. typhimurium* and *E. coli*.

Please see 16 NON-CLINICAL TOXICOLOGY, Carcinogenicity and Mutagenicity.

Contamination

To minimize the contamination potential, patients should not touch the eye, the area around the eye, or any other surface with the tip of the container. It may become contaminated with bacteria. This can cause eye infections and could lead to serious damage of the eye including loss of vision. Keep the tip of the container away from contact with any surface.

Driving and Operating Machinery

Possible side effects such as visual disturbances may affect the ability to drive and use machines.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

TRUSOPT has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Immune

Immunology and Hypersensitivity

In clinical studies, local ocular adverse effects, primarily conjunctivitis and eyelid reactions, were reported with chronic administration of TRUSOPT. Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. If such reactions are observed, discontinuation of treatment with TRUSOPT should be considered.

Monitoring and Laboratory Tests

TRUSOPT was not associated with clinically meaningful electrolyte disturbances.

Ophthalmologic

Corneal Edema

There is an increased risk of developing irreversible corneal edema in a subset of glaucoma patients with endothelial abnormalities including cellular density and/or morphology. In this group of patients evaluation of the cornea with particular attention to the corneal endothelium is recommended prior and during treatment with TRUSOPT.

Corneal Edema and Irreversible Corneal Decompensation

Corneal edema and irreversible corneal decompensation has been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. TRUSOPT should be used with caution in such patients.

Contact Lenses

TRUSOPT has not been studied in patients wearing contact lenses. The preservative in TRUSOPT Ophthalmic Solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients should be instructed to remove their lenses before application of the drops and not to re-insert the lenses earlier than 15 minutes after use. TRUSOPT preservative-free formulation does not contain the preservative benzalkonium chloride.

Choroidal Detachment

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

Management of eyes with chronic or recurrent choroidal detachment should include stopping all forms of aqueous suppressant therapy and treating endogenous inflammation vigorously.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women. TRUSOPT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

7.1.2 Breast-feeding

It is not known whether dorzolamide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions from TRUSOPT 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.

In a study of dorzolamide hydrochloride in lactating rats, decreases in body weight gain of 5 to 7% in offspring at an oral dose of 7.5 mg/kg/day (94 times the maximum recommended human ophthalmic dose) were seen during lactation. A slight delay in postnatal development (incisor eruption, vaginal canalization and eye openings), secondary to lower fetal body weight, was noted at 7.5 mg/kg/day (94 times the maximum recommended human ophthalmic dose).

7.1.3 Pediatrics

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

7.1.4 Geriatrics

Geriatrics (>65 years of age): Of the total number of patients in clinical studies of TRUSOPT, 44% were 65 years of age and over, while 10% were 75 years of age and over. No overall differences in effectiveness or safety were observed between these patients and younger patients, but greater sensitivity of some older individuals to the product cannot be ruled out.

In a clinical study comparing TRUSOPT preservative-free formulation and TRUSOPT, 48% of all patients were over the age of 65, while 12% were over 75 years of age. No statistical analysis was performed based upon age, but greater sensitivity of some older individuals to the product cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

In long-term studies of 1108 patients treated with TRUSOPT as monotherapy or as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3%) from treatment with TRUSOPT was drug-related ocular adverse effects, primarily conjunctivitis and eyelid reactions (see 7 WARNINGS AND PRECAUTIONS).

In clinical studies, the most common ocular complaints were burning and stinging, blurred vision, itching and tearing. Bitter taste was also frequently reported. If these local symptoms were considered clinically important by investigators they also appear as adverse experiences in the listing below.

In an active treatment, controlled, crossover clinical study of 12 weeks duration, 152 patients received TRUSOPT preservative-free formulation for 6 weeks and TRUSOPT for 6 weeks. Approximately 1.3% of patients receiving TRUSOPT preservative-free formulation discontinued therapy due to adverse experiences. Approximately 0.7% of all patients receiving TRUSOPT preservative-free formulation discontinued therapy because of adverse reactions suggestive of allergy and/or hypersensitivity.

The most frequently reported ocular drug related adverse effects for TRUSOPT preservative-free formulation were burning and stinging 41%, taste perversion 13%, corneal erosion 5%, follicular conjunctivitis 3%, conjunctival injection 3%, and blurred vision 1%. For TRUSOPT ophthalmic solution the most frequently reported ocular drug related adverse events were burning and stinging 38%, taste perversion 13%, conjunctival injection 5%, corneal erosion 4%, follicular conjunctivitis 3%, and blurred vision 3%.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse experiences that were reported during clinical studies as drug-related (possibly,

probably, or definitely) in 1-5% of patients on TRUSOPT were in decreasing order of frequency:

Ocular:

Burning and stinging, conjunctivitis, eyelid inflammation, eye itching, eyelid irritation.

Systemic:

Headache, bitter taste, nausea, asthenia/fatigue.

Iridocyclitis and rash were each reported rarely. There was one report of urolithiasis.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been reported in post-marketing experience:

***Hypersensitivity**:* Signs and symptoms of local reactions including palpebral reactions and systemic allergic reactions including angioedema, bronchospasm, urticaria and pruritus

***Nervous System**:* Dizziness, paresthesia.

***Ocular**:* Pain, redness, superficial punctate keratitis, transient myopia (which resolved upon discontinuation of therapy), eyelid crusting, choroidal detachment following filtration surgery, corneal edema in glaucoma patients with endothelial abnormalities including cellular density and/or morphology.

***Skin/Mucous Membranes**:* Contact dermatitis, epistaxis, throat irritation, dry mouth, Stevens-Johnson syndrome, toxic epidermal necrolysis.

***Urogenita*l**: Urolithiasis

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Specific drug interaction studies have not been performed with TRUSOPT Ophthalmic Solution or TRUSOPT preservative-free formulation.

In clinical studies, TRUSOPT was used concomitantly with the following medications without evidence of adverse interactions: timolol ophthalmic solution, betaxolol ophthalmic solution and systemic medications, including ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs including ASA, and hormones (e.g. estrogen, insulin, thyroxine).

9.4 Drug-Drug Interactions

The following drug interaction has been associated with the dorzolamide component of TRUSOPT or with other sulfonamides:

Table 2 - Established or Potential Drug-Drug Interactions

[Proper/Common name]	Source of Evidence	Effect	Clinical comment
High-dose salicylate therapy	CS	Acid-base Disturbances: TRUSOPT is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, TRUSOPT was not associated with acid-base disturbances. However, these disturbances have been reported with oral carbonic anhydrase inhibitors and have, in some instances, resulted in drug interactions (e.g. toxicity associated with high-dose salicylate therapy).	The potential for such drug interactions (e.g. toxicity associated with high-dose salicylate therapy) should be considered in patients receiving TRUSOPT.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

TRUSOPT is a carbonic anhydrase inhibitor formulated for topical ophthalmic use.

Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. It catalyzes the reversible reaction involving the hydration of carbon dioxide and the dehydration of carbonic acid. In humans, carbonic anhydrase exists as a number of isoenzymes, the most

active being carbonic anhydrase II (CA-II) found primarily in red blood cells (RBCs) but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. The result is a reduction in intraocular pressure (IOP).

TRUSOPT ophthalmic solution 2% contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, TRUSOPT reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. Unlike miotics, TRUSOPT reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction. Unlike topical beta-blockers, TRUSOPT has minimal or no effect on pulse rate or blood pressure.

Topically applied beta-adrenergic blocking agents also reduce IOP by decreasing aqueous humor secretion but by a different mechanism of action. Studies have shown that when TRUSOPT is added to a topical beta-blocker, additional reduction in IOP is observed; this finding is consistent with the reported additive effects of beta-blockers and oral carbonic anhydrase inhibitors.

10.3 Pharmacokinetics

Absorption:

Unlike oral carbonic anhydrase inhibitors, topically-applied TRUSOPT exerts its effects at substantially low doses and therefore with less systemic exposure.

When applied topically, dorzolamide reaches the systemic circulation.

Distribution:

To assess the potential for systemic carbonic anhydrase inhibition following topical administration, drug and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while extremely low concentrations of free drug in plasma are maintained.

Metabolism:

The parent drug forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent drug but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33%).

Elimination:

Dorzolamide is excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs in a non-linear manner, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life

of about four months.

To simulate the maximum systemic exposure after long term topical ocular administration, dorzolamide was given orally to eight healthy subjects for up to 20 weeks. The oral dose of 4 mg/day closely approximates the maximum amount of dorzolamide delivered by topical ocular administration of TRUSOPT 2% t.i.d. Dorzolamide and metabolite reached steady state by 4 and 13 weeks, respectively, and the following observations were noted:

- In plasma, concentrations of dorzolamide and metabolite were generally below the assay limit of quantitation (15nM) indicating almost no free drug or metabolite;
- In RBCs, dorzolamide concentrations approached the binding capacity of CA-II (20-25 µM) and metabolite concentrations approached 12-15 µM, well below the binding capacity of CA-I (125-155 µM);
- In RBCs, inhibition of CA-II activity and total carbonic anhydrase activity was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration.

11 STORAGE, STABILITY AND DISPOSAL

TRUSOPT Ophthalmic Solution

Store at 15° - 25°C (59° - 77°F). Protect from light.

Keep out of sight and reach of children.

TRUSOPT Preservative-free Formulation Ophthalmic Solution

Store at 15° - 25°C (59° - 77°F). Protect from light. Store in protective foil pouch.

Keep out of sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

Keep the tip of the container away from the eye, area around the eye, or contact with any surface.

If using TRUSOPT Preservative-free, the container and any remaining contents must be discarded after each application.

See 4.1 Dosing Considerations, 4.4 Administration, 7 WARNINGS AND PRECAUTIONS, Contamination and 7 WARNINGS AND PRECAUTIONS, Contact Lenses.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

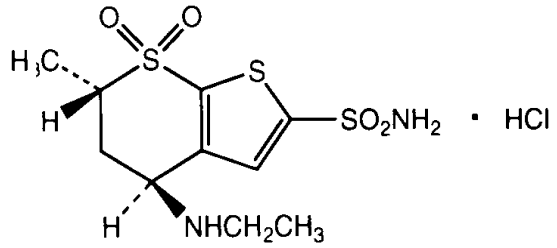
Drug Substance

Proper name: dorzolamide hydrochloride

Chemical name: (4*S*-*trans*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno[2,3-*b*] thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride. Dorzolamide hydrochloride is optically active.

Molecular formula and molecular mass: $C_{10}H_{16}N_2O_4S_3.HCl$
360.9

Structural formula:



Physicochemical properties: Dorzolamide hydrochloride is a white to off-white, free flowing crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol and has a melting point of about 264°C.

The specific rotation is $\alpha^{25^\circ}_{405}$ (C=1, water) = ~ -17°.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Elevated Intraocular Pressure Therapy

Table 3 - Summary of patient demographics for clinical trials in the treatment of elevated intraocular pressure as monotherapy

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 1	Two-period, crossover, randomized, double-masked, multiple-dose study	2% tid dorzolamide ophthalmic solution, 12 days	18	57.3 (34 to 83)	33% M; 67% F

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 2	Parallel, double-masked, randomized, active-controlled study	2% tid dorzolamide vs 0.5% timolol bid vs 0.5% betaxolol bid, ophthalmic solutions, 1 year	523	62.2 (17 to 85)	46% M; 54% F
Study 3	Parallel, double-masked, randomized, placebo-controlled, dose-response study with a double-masked, parallel extension.	2% tid dorzolamide ophthalmic solution, 6 weeks plus 1 year open label.	333	60.5 (23 to 81)	48 % M; 52% F

Table 4 - Summary of patient demographics for clinical trials in the treatment of elevated intraocular pressure as Adjunctive Therapy to Beta-Blockers

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 4	Parallel, randomized, double-masked, placebo controlled, multiclinic, multiple-dose study	2% bid dorzolamide ophthalmic solution + 0.5% timolol bid ophthalmic solution, 7 days	32	61.1 (28 to 86)	53% M 47% F

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 5	Parallel, randomized, double-masked, placebo-controlled, active-controlled, multicenter, multidose study followed by an active-controlled extension	0.5% timolol bid + 2% bid dorzolamide ophthalmic solution vs pilocarpine 2% qid, 6 months	261	60.6 (29 to 81)	50% M; 50% F

Table 5 - Summary of patient demographics for clinical trials in the treatment of elevated intraocular pressure with preservative-free formulation

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
Study 6	Active-Treatment, randomized, double-masked, crossover study	2% tid dorzolamide ophthalmic solution vs 2% tid preservative-free dorzolamide ophthalmic solution, 6 weeks per arm	152	62.7 yr (31 to 88)	(not available)

Clinical trials of TRUSOPT as a monotherapy were conducted in patients with glaucoma or ocular hypertension with a baseline intraocular pressure (IOP) >23 mmHg. Clinical trials of TRUSOPT as an adjunctive therapy were conducted in patients with glaucoma or ocular hypertension with a baseline IOP ≥ 22 mmHg while receiving ophthalmic beta-blockers.

Table 6 - Results of study 1 in the treatment of elevated intraocular pressure

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo
Mean Percent reductions in IOP	21.4% morning trough (0 h), 21.8% 2 h post-dose, 18.0% 8 h post-dose 19.4% 12 h post-dose	0.3% (P<0.01) 8.2% (p<0.01) 0.8% (p<0.01) 0.5% (p<0.01)

In Study 1, patients were treated for a total of twelve days. Patients who received TRUSOPT 2% t.i.d. for the last seven days of the study experienced reductions in IOP at morning trough (prior to first dose), at peak (two hours post-dose), at afternoon trough (eight hours post-dose) and at the end of the day (four hours after the afternoon dose).

Table 7 - Results of study 2 in the treatment of elevated intraocular pressure

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Mean Percent reductions in IOP	22.9% (2 h post-dose, month 12) 16.9% (8 h post-dose, month 12)	Betaxolol 0.5%: 20.8% (2 h, month 12) (p=NS) 15.1% (8 h, month 12); (p=NS) Timolol 0.5%: 25.3% (2 h, month 12) (p=NS) 20.4% (8 h, month 12) (p<0.05)

In Study 2, a one-year controlled trial, TRUSOPT 2% t.i.d. (N=313) was compared with betaxolol 0.5% (N=107) and timolol 0.5% (N=103) administered b.i.d. At the end of the trial, the mean percent reductions in IOP at peak did not differ significantly among treatment groups. At afternoon trough, the mean percent reduction in IOP for timolol was significantly greater ($p < 0.05$) than either TRUSOPT or betaxolol, but no significant difference was observed between TRUSOPT and betaxolol.

Table 8 - Results of study 3 in the treatment of elevated intraocular pressure

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo
Mean Percent reductions in IOP (6 weeks)	Morning Trough: 13.2%; Morning Peak: 16.3% (6 weeks)	Morning Trough: 5.6%, p<0.05 Morning Peak: 5.5%, p<0.05
Mean Percent reductions in IOP (1 year)	Morning Trough: 14.6%; Morning Peak: 17.9% (1 year)	There is no placebo or comparator in the 1 year study

In Study 3, a dose-response study (N=333), TRUSOPT was compared with placebo during a six-week phase, followed by one year of treatment with TRUSOPT. At six weeks, patients on TRUSOPT 2% t.i.d. (N=86) had mean percent reductions in IOP at morning trough and peak which were significantly greater ($p < 0.01$) than those observed with placebo. During extension treatment (N=160) with TRUSOPT 2% t.i.d. as monotherapy for up to one year, efficacy was consistent with the six week findings.

Table 9 - Results of study 4 in the treatment of elevated intraocular pressure

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for Placebo or active control
Mean Percent reductions in IOP	Timolol plus Trusopt 16.8% (Morning Trough, 0 h) 21.0% (Morning Peak, 1 h post-dose) 13.2% (12 h post-dose)	Timolol plus placebo 3.4% (0h), p<0.01 4.5% (1 h), p<0.01 6.6 (12 h), p<0.01

In Study 4, a one-week placebo-controlled study (N=32), when patients (N=16) on timolol 0.5% b.i.d. had TRUSOPT 2% b.i.d. added to their treatment regimen, they experienced additional mean percent reductions in IOP at morning trough, at peak (one hour post-dose), and at evening trough (twelve hours post-dose).

Table 10 - Results of study 5 in the treatment of elevated intraocular pressure

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for active control
Mean Percent reductions in IOP	12.8% (h0, morning trough, 6 months) 10.9% (h2 morning peak, 6 months)	Pilocarpine 2% qid: 10.2% (h0, Morning Trough), p=NS 10.4% (h2, morning peak) p=NS

In Study 5, a six-month dose-comparison study (N=261) in patients receiving timolol 0.5% b.i.d., the additive ocular hypotensive effect of TRUSOPT 2% b.i.d. (N=89) was compared to that of pilocarpine 2% q.i.d (N=44). Both drugs showed comparable efficacy as adjunctive therapy over the six-month treatment period. Additional mean percent reductions in IOP at morning trough and peak (two hours post-dose) were observed at six months.

Finally, over the course Study 2, a subset of 59 patients receiving timolol or betaxolol required additional medication for IOP reduction. TRUSOPT 2% b.i.d. was added and at the end of the study these patients had experienced additional mean percent reductions at peak (two hours post-dose) of 14 to 19%, and eight hours post-dose of 13 to 14%.

Table 11 - Results of study 6 in the treatment of elevated intraocular pressure (Preservative-Free)

Primary Endpoints	Associated value and statistical significance for Drug at specific dosages	Associated value and statistical significance for active control
Mean Percent reductions in IOP	Morning Trough (0 h): 17.8%; Morning Peak (2 h): 21.0%	Morning Trough (0h): 18.1%; (p=NS) Morning Peak (2 h): 22.1% (p=NS)

In Study 6, a single, active-treatment, controlled, two 6-week period crossover, double-masked study of 152 patients with intraocular pressure >22 mmHg in one or both eyes, TRUSOPT preservative-free formulation and TRUSOPT (with preservative) were compared for relative ocular hypotensive effect at morning trough (hour 0) and peak (hour 2). At both trough and peak, the differences between the IOP-lowering effect demonstrated during studies of TRUSOPT preservative-free formulation and TRUSOPT were less than 0.3 mmHg. Therefore, the treatments were found to be clinically equivalent. The safety and tolerability of TRUSOPT preservative-free formulation and TRUSOPT were also compared. No statistically significant

differences between the treatments were reported with respect to type or frequency of specific adverse experiences, serious adverse experiences, discontinuation due to adverse experience, or drug-related adverse experiences. Exposure to TRUSOPT preservative-free formulation was only studied for a total of 6 weeks.

15 MICROBIOLOGY

TRUSOPT® contains the preservative benzalkonium chloride as an antimicrobial preservative.

TRUSOPT® preservative-free is a formulation without benzalkonium chloride.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Acute Toxicity

The oral LD_{50} of the drug is 1 320 mg/kg (3 960 mg/m^2) in mice and 1 927 mg/kg (11 369 mg/m^2) in female rats.

Chronic Toxicology

In repeated oral dose toxicity studies of dorzolamide hydrochloride in rodents, dogs and monkeys, the following effects were noted.

An increased incidence of urothelial hyperplasia was noted in rats and mice. This is a class-effect of carbonic anhydrase inhibitors (CAIs) specific to rodents and is secondary to increased urinary sodium, potassium, pH and crystals.

Another class effect of CAIs seen only in rodents was renal papillary cytoplasmic granularity associated with potassium depletion in the kidney. No-effect levels for these microscopic changes were not observed. However, these findings are rodent specific and not seen in monkeys at oral doses up to 50 mg/kg/day (625 times the maximum recommended human ophthalmic dose).

Metabolic acidosis and the related gastric mucous neck cell hyperplasia were seen in dogs and monkeys. In dogs, the gastric change was seen at a dose as low as 0.2 mg/kg/day in a one-month study, but disappeared with continued dosing and was absent at one year at a dose as high as 2 mg/kg/day. In monkeys in a one-month study, the gastric change was seen at a dose of 50 mg/kg/day orally, but no effects were seen at 10 mg/kg/day orally, or when 0.4 mg/kg/day (~5 times the maximum recommended human ophthalmic dose) was applied topically to the eye for one year.

Another high dose phenomenon observed in dogs and monkeys (doses ≥ 1.5 mg/kg/day and 50 mg/kg/day, respectively) in short term studies was decreased remodeling of bone, probably as a result of inhibition of carbonic anhydrase in osteoclasts. Longer term studies in dogs showed the change was transient.

Marginal nonprogressive decreases in some erythroid parameters were seen in dogs and monkeys at dorzolamide plasma levels of 50 ng/mL in dogs and 1660 ng/mL in monkeys. The

plasma levels of dorzolamide in humans given the maximum recommended ophthalmic dose are generally ≤ 5 ng/mL.

Carcinogenicity:

In a two-year study of dorzolamide hydrochloride administered orally to male and female Sprague-Dawley rats, urinary bladder papillomas were seen in male rats in the highest dosage group of 20 mg/kg/day (250 times the maximum recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately twelve times the maximum recommended human ophthalmic dose. No treatment-related tumors were seen in a 21-month study in female and male mice given oral doses up to 75 mg/kg/day (~900 times the maximum recommended human ophthalmic dose).

The increased incidence of urinary bladder papillomas seen in the high-dose male rats is a class-effect of carbonic anhydrase inhibitors in rats and is secondary to increased urinary sodium, potassium, pH and crystals, all changes induced by carbonic anhydrase inhibitors. Rats are particularly prone to developing papillomas in response to foreign bodies, compounds causing crystalluria and sodium salts of diverse compounds that are inert when given as calcium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide for one year at 2 mg/kg/day or monkeys given oral dorzolamide for one month at 50 mg/kg/day (the urothelial changes in the bladder occurred with oral dosing in rats within one month). In addition, monkeys dosed topically to the eye with 0.4 mg/kg/day (~5 times the maximum recommended human ophthalmic dose) for one year had no urothelial changes in the bladder.

Genotoxicity

Dorzolamide hydrochloride was devoid of mutagenic potential when evaluated in the following 5 tests: (1) in vivo (mouse) in the cytogenetic assay at doses up to 500 mg/kg/day (6 250 times the maximum recommended human ophthalmic dose); (2) in vitro in the chromosomal aberration assay; (3) in the alkaline elution assay; (4) in the V-79 assay (doses up to 10 μM); and (5) in the Ames test, in which the highest concentration of dorzolamide hydrochloride used, 10 000 μg/plate, did not result in a two-fold or greater increase in revertants with tester strains of S. typhimurium and E. coli.

Reproductive and Developmental Toxicology:

In reproduction studies of dorzolamide hydrochloride in rats, there were no adverse effects on males or females at doses up to 188 or 94 times, respectively, the maximum recommended human ophthalmic dose.

There were no treatment-related fetal malformations in developmental toxicity studies with dorzolamide hydrochloride in rats at oral doses up to 10 mg/kg/day (125 times the maximum recommended human ophthalmic dose). Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of ≥ 2.5 mg/kg/day (31 times the maximum recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred only at doses that caused metabolic acidosis with resultant decreased body weight gain in dams and decreased fetal weights. These malformations, seen

only at maternotoxic doses, appear to be a class-effect related to a combination of electrolyte and acid-base changes: decreased venous HCO_3-, decreased venous pH and decreased serum potassium. No treatment-related malformations were seen at 1.0 mg/kg/day (13 times the maximum recommended human ophthalmic dose). Acetazolamide, an oral carbonic anhydrase inhibitor, causes skeletal malformations in rats and rabbits by a similar mechanism.

In a study of dorzolamide hydrochloride in lactating rats, decreases in body weight gain of 5 to 7% in offspring at an oral dose of 7.5 mg/kg/day (94 times the maximum recommended human ophthalmic dose), were seen during lactation. A slight delay in postnatal development (incisor eruption, vaginal canalization and eye openings), secondary to lower fetal body weight, was noted at 7.5 mg/kg/day (94 times the maximum recommended human ophthalmic dose).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrTRUSOPT®
PrTRUSOPT® Preservative-free
Dorzolamide hydrochloride ophthalmic solution

Read this carefully before you start taking **TRUSOPT or TRUSOPT Preservative-free** 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 **TRUSOPT or TRUSOPT Preservative-free**.

What is TRUSOPT and TRUSOPT Preservative-free used for?

TRUSOPT and TRUSOPT Preservative-free lower the pressure in the eye for conditions such as ocular hypertension or open-angle glaucoma.

TRUSOPT Preservative-free does not contain a preservative. This may be prescribed to you if you are sensitive to a preservative.

How does TRUSOPT and TRUSOPT Preservative-free work?

TRUSOPT and TRUSOPT Preservative-free belong to a group of medicines called carbonic anhydrase inhibitors. TRUSOPT and TRUSOPT Preservative-free work by reducing the production of liquid in the eye. This helps lower the pressure in the eye.

What are the ingredients in TRUSOPT and TRUSOPT Preservative-free?

Medicinal ingredients: dorzolamide (present as the hydrochloride salt)

Non-medicinal ingredients: Hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide (to adjust pH) and water for injection.

Benzalkonium chloride is only added as a preservative to TRUSOPT. TRUSOPT Preservative-free does not contain benzalkonium chloride.

TRUSOPT and TRUSOPT Preservative-free come in the following dosage forms:

Solution: 2% dorzolamide (dorzolamide hydrochloride)

Do not use TRUSOPT or TRUSOPT Preservative-free if:

- You are allergic to any of its components (see: What are the ingredients in TRUSOPT and TRUSOPT and TRUSOPT Preservative-free).

- You have severe kidney problems.
- You are taking oral carbonic anhydrase inhibitors.

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

- Have any medical problems now or have had any in the past, including eye (corneal) problems, or previous eye surgery;
- Have any allergies to any medications;
- TRUSOPT contains the preservative benzalkonium chloride. If you wear contact lenses, you should consult your healthcare professional before using TRUSOPT. Do not use TRUSOPT while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use. TRUSOPT Preservative-free does not contain the preservative benzalkonium chloride;
- Are pregnant or intend to become pregnant;
- Are breast feeding or intend to breast feed;
- Have now or have had in the past liver problems;
- Have now or have had in the past kidney problems.

Other warnings you should know about:

You may find that your vision is blurred for a time just after you put TRUSOPT or TRUSOPT Preservative-free in your eye. Do not drive or use any tools or machines until your vision is clear.

TRUSOPT and TRUSOPT Preservative-free are not recommended for children under 18 years of age.

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 TRUSOPT or TRUSOPT Preservative-free:

- Other drugs (including eye drops) that you are using or plan to use;
- Other drugs obtained without a prescription;
- Other carbonic anhydrase inhibitors;
- Large dose of ASA (acetylsalicylic acid);
- A group of drugs known as “sulfa drugs”.

How to take TRUSOPT or TRUSOPT Preservative-free:

- Do not start taking any other medicines unless you have discussed the matter with your healthcare professional.
- If you use other eye drops, they should be used at least ten minutes apart.
- If you use TRUSOPT or TRUSOPT Preservative-free with a beta-blocker eye drop, then the dose is one drop of TRUSOPT or TRUSOPT Preservative-free in the affected eye(s) in the morning and in the evening.
- Do not change how you take this drug without talking to your healthcare professional. If you must stop taking this drug, contact your healthcare professional immediately.

TRUSOPT

1. Before using this drug for the first time, be sure the Safety Strip on the front of the bottle is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.

Figure A

2. Tear off the Safety Strip to break the seal.

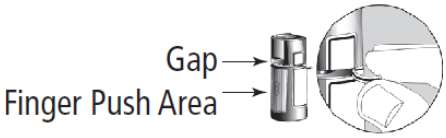


Figure B

3. To open the bottle, unscrew the cap by turning as indicated by the arrows on the top of the cap. Do not pull the cap directly up and away from the bottle. Pulling the cap directly up will prevent your dispenser from operating properly.

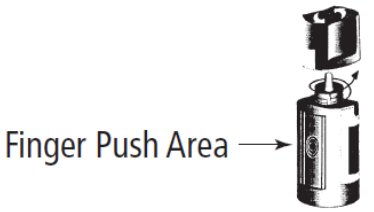


Figure C

4. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.

Figure D

5. Invert the bottle and press lightly with the thumb or index finger over the "Finger Push Area" (as shown) until a single drop is dispensed into the eye as directed by your healthcare professional.

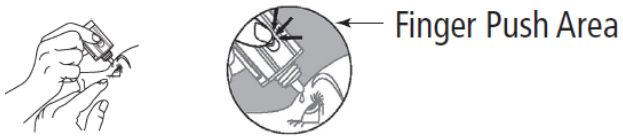


Figure E

DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.

Eye droppers can become contaminated with bacteria from touching the eye or around the eye area. This can cause eye infections leading to serious damage of the eye, even loss of vision. If you think your bottle may be contaminated, or if you develop an eye infection, contact your healthcare professional immediately concerning continued use of this bottle.

6. If drop dispensing is difficult after opening for the first time, replace the cap on the bottle and tighten (DO NOT OVERTIGHTEN). Then, remove by turning the cap in the opposite direction as indicated by the arrows on top of the cap.

7. Repeat steps 4 & 5 with the other eye if instructed to do so by your healthcare professional.

8. Replace the cap by turning until it is firmly touching the bottle. Do not overtighten or you may damage the bottle and cap.

9. The dispenser tip is designed to provide a single drop; therefore, do NOT enlarge the hole of the dispenser tip.

10. After you have used all doses, there will be some TRUSOPT left in the bottle. You should not be concerned since an extra amount of TRUSOPT has been added and you will get the full amount of TRUSOPT that your doctor prescribed. Do not attempt to remove excess medicine from the bottle.

TRUSOPT Preservative-free

Use the individual pipette of TRUSOPT preservative-free immediately after opening. Discard any remaining solution immediately after use.

Usage Instructions

1. Open the foil pouch which contains 15 individual unit dose pipettes. There are three strips of 5 pipettes each in the pouch.

2. Break off one pipette from the strip and twist open the top of the pipette as shown in Figure F.

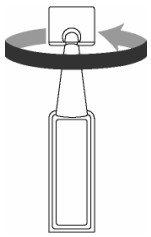


Figure F

3. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and eye as shown in Figure G.

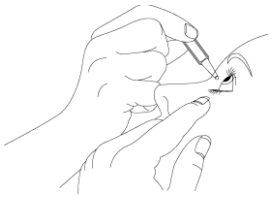


Figure G

4. Apply one drop in the affected eye(s) as directed by your healthcare professional. Each pipette contains enough solution for both eyes.

5. After application, discard the used pipette even if there is solution remaining.

6. Store the remaining pipettes in the foil pouch; the remaining pipettes must be used within 15 days.

Usual dose:

Your doctor will tell you the right dose and length of time to use TRUSOPT or TRUSOPT Preservative-free.

When TRUSOPT or TRUSOPT Preservative-free is used alone, the dose is one drop in the affected eye(s) in the morning, in the afternoon and in the evening.

Overdose:

If you think you, or a person you are caring for, have taken too much TRUSOPT or TRUSOPT Preservative-free, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important to apply TRUSOPT or TRUSOPT Preservative-free as prescribed by your physician. If you miss a dose, apply it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule.

What are possible side effects from using TRUSOPT or TRUSOPT Preservative-free?

These are not all the possible side effects you may have when taking TRUSOPT or TRUSOPT Preservative-free. If you experience any side effects not listed here, tell your healthcare professional.

You may experience eye symptoms such as:

- Burning and stinging
- Blurred vision
- Itching
- Tearing
- Redness of the eye(s)
- Eye pain
- Swelling of the eyelids
- Crusting of the eyelids
- Eyelid irritation
- Sensitivity to light
- A feeling of something in the eye

Other side effects may include:

- Bitter taste after putting in your eye drops
- Headache
- Nosebleed
- Dry mouth
- Throat irritation
- Nausea
- Tiredness
- Dizziness
- Numbness or tingling of the skin
- Itchy skin

If the contents of the container are swallowed, you should contact your healthcare professional immediately.

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: rash, hives, swelling of the mouth, throat, and lips, difficulty breathing, blue skin, shock, loss of consciousness, low blood pressure			✓

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**	
Stevens-Johnson syndrome (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands			✓
Toxic Epidermal Necrolysis (severe skin reaction): redness, blistering and/or peeling of large areas of the skin			✓
Urolithiasis (Kidney stones): pain when urinating, severe pain in the side and back, below the ribs			✓

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

TRUSOPT:

Store at 15°-25°C. Protect from light.

TRUSOPT Preservative-free:

Store at 15°-25°C. Protect from light. Store in protective foil pouch.

Do not use this medicine after the date shown on the container.

Keep out of reach and sight of children.

If you want more information about TRUSOPT or TRUSOPT Preservative-free:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.elvium.ca, or by calling 1-833-744-0005.

This leaflet was prepared by Elvium Life Sciences.

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