

PRODUCT MONOGRAPH

Pr **TRUSOPT**[®]

dorzolamide hydrochloride ophthalmic solution

dorzolamide 2% weight/volume

Sterile Ophthalmic Solution

Elevated Intraocular Pressure Therapy
(Topical Carbonic Anhydrase Inhibitor)

Purdue Pharma
575 Granite Court
Pickering, ON
L1W 3W8

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Pr TRUSOPT®

dorzolamide hydrochloride ophthalmic solution

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Ophthalmic	Solution, each mL contains 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride)	<i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

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.

A comparative crossover clinical trial consisting of two 6-week periods has been performed with TRUSOPT® preservative-free formulation and TRUSOPT® (with preservative) in 152 adult patients. 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 DOSAGE AND ADMINISTRATION section as well as to the PHARMACOLOGY - Clinical Studies section.

CONTRAINDICATIONS

TRUSOPT® (dorzolamide hydrochloride) is contraindicated in patients who are hypersensitive to any component of this product. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

TRUSOPT[®] has not been studied in patients with severe renal impairment (CrCl < 0.5 mL/s). Because TRUSOPT[®] and its metabolite are excreted predominantly by the kidney, TRUSOPT[®] is not recommended in such patients.

There is a potential for an additive effect with the known systemic effects of carbonic anhydrase inhibition in patients receiving oral carbonic anhydrase inhibitor and TRUSOPT[®]. The concomitant administration of TRUSOPT[®] and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

WARNINGS AND PRECAUTIONS

General

TRUSOPT[®] (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[®] has not been studied in patients with acute angle-closure glaucoma.

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.

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.

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.

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.

Hepatic**Hepatic Impairment**

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

Special Populations**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.

Nursing Women:

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).

Pediatrics:

Safety and effectiveness in children have not been established.

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.

Monitoring and Laboratory Tests

TRUSOPT[®] was not associated with clinically meaningful electrolyte disturbances.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In long-term studies of 1 108 patients treated with TRUSOPT[®] (dorzolamide hydrochloride) 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 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%.

Clinical Trial Adverse Drug Reactions

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.

Post-Market Adverse Drug 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.

Urogenital: Urolithiasis

DRUG INTERACTIONS

Overview

Specific drug interaction studies have not been performed with TRUSOPT[®] Ophthalmic Solution. 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).

Drug-Drug Interactions

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

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). Therefore, the potential for such drug interactions should be considered in patients receiving TRUSOPT[®].

Drug-Lifestyle Interactions

Effects on Ability to Drive and Use Machines

Possible side effects such as visual disturbances may affect the ability to drive and use machines (see DRUG INTERACTIONS and ADVERSE REACTIONS).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

When used as monotherapy, the dose is one drop of TRUSOPT[®] (dorzolamide hydrochloride) 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 CLINICAL TRIALS section.

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.

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.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 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/m² or 1 927 mg/kg (24 000 times the maximum recommended

human ophthalmic dose) and 3 960 mg/m² or 1 320 mg/kg (16 000 times the maximum recommended human ophthalmic dose), respectively.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

TRUSOPT[®] (dorzolamide hydrochloride) 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).

Pharmacokinetics

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. 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. 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%). 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.

STORAGE AND STABILITY

TRUSOPT® Ophthalmic Solution:

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

TRUSOPT® Preservative-free Formulation Ophthalmic Solution:

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

TRUSOPT® Ophthalmic Solution is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution of dorzolamide hydrochloride. Each mL of TRUSOPT® 2% contains 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride).

Non-medicinal ingredients: 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® (dorzolamide hydrochloride) sterile ophthalmic solution is a clear, colourless to nearly colourless, slightly viscous solution 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.

Ophthalmic Solution 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

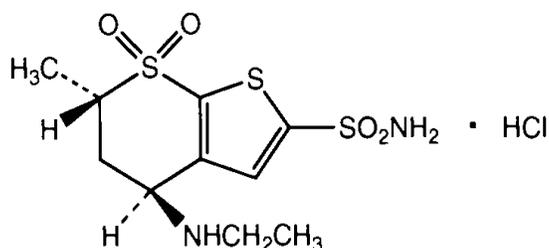
For patients who may be sensitive to the preservative benzalkonium chloride or when use of a preservative-free topical medication is advisable, a formulation of TRUSOPT® without the preservative benzalkonium chloride is available. This formulation is packaged in 4 pouches of 15 x 0.2 mL individual fill volume unit dose pipettes.

PART II: SCIENTIFIC INFORMATION

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: C₁₀H₁₆N₂O₄S₃·HCl
- Molecular mass: 360.9
- Structural formula:



Physicochemical properties:

Description: 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 α^{25° (C=1, water) = $\sim -17^\circ$.
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CLINICAL TRIALS

The efficacy of TRUSOPT[®] as monotherapy in patients with glaucoma or ocular hypertension (baseline IOP ≥ 23 mmHg) was demonstrated in clinical studies of up to one-year duration. The IOP-lowering effect of TRUSOPT[®] was demonstrated throughout the day and this effect was maintained during long-term administration.

In a small study, patients were treated for a total of twelve days. Patients (N=18) who received TRUSOPT[®] 2% t.i.d. for the last seven days of the study experienced the following mean percent reductions in IOP: 21% at morning trough (prior to first dose), 22% at peak (two hours post-dose), 18% at afternoon trough (eight hours post-dose) and 19% at the end of the day (four hours after the afternoon dose).

The efficacy of TRUSOPT[®] as monotherapy was further demonstrated in two large clinical trials. In a one-year controlled trial (N=523), 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 and afternoon trough (for TRUSOPT[®]), respectively, were as follows: TRUSOPT[®] = 23% and 17%; betaxolol = 21% and 15%; timolol = 25% and 20%. 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 ($p \leq 0.05$) than either TRUSOPT[®] or betaxolol, but no significant difference was observed between TRUSOPT[®] and betaxolol.

In 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 of 13% and 16%, respectively, which were significantly greater ($p \leq 0.01$) 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; mean percent reductions in IOP from prestudy at morning trough and peak were 15% and 18%, based on last evaluation on monotherapy.

Adjunctive Therapy to Beta-Blockers

The efficacy of TRUSOPT[®] as adjunctive therapy in patients with glaucoma or ocular hypertension (IOP ≥ 22 mmHg while receiving ophthalmic beta-blockers) was demonstrated in clinical studies of up to one-year duration. The IOP-lowering effect of TRUSOPT[®] as adjunctive therapy was demonstrated throughout the day and this effect was maintained during long-term administration.

In 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 the following additional mean percent reductions in IOP: 17% at morning trough, 21% at peak (one hour post-dose), 13% at evening trough (twelve hours post-dose).

In 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. The following additional mean percent reductions in IOP at morning trough and peak (two hours post-dose) were observed at six months: TRUSOPT[®] = 13% and 11%; pilocarpine = 10% and 10%.

Finally, over the course of one year in the beta-blocker comparison study described under Clinical Trials (N=523), 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%.

Preservative-Free Formulation Study

In a single, active-treatment, controlled, two 6-week period crossover, double-masked study of 152 male and female patients with an average age of 62.7 years (range:31-88) 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). The trough and peak IOP-lowering effects at six weeks ranged from 17.8% to 21.0% for TRUSOPT[®] preservative-free formulation and from 18.1% to 22.1% for TRUSOPT[®]. 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.

DETAILED PHARMACOLOGY

Mechanism of Action

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[®] (dorzolamide hydrochloride) 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.

TOXICOLOGY

Acute Toxicity

The oral LD₅₀ of the drug is 1 320 mg/kg (3 960 mg/m²) in mice and 1 927 mg/kg (11 369 mg/m²) in female rats.

Chronic Toxicity

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 \geq 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 \leq 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.

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 μ M); and (5) in the Ames test, in which the highest concentration of dorzolamide hydrochloride used, 10 000 μ g/plate, did not result in a two-fold or greater increase in revertants with tester strains of *S. typhimurium* and *E. coli*.

Reproduction

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.

Development

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 \geq 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 HCO₃⁻, 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).

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PART III: CONSUMER INFORMATION

Pr **TRUSOPT**[®]

dorzolamide hydrochloride ophthalmic solution

This leaflet is part III of a three-part "Product Monograph" published when TRUSOPT[®] was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TRUSOPT[®]. Contact your physician or pharmacist if you have any questions about the drug.

Read the following information carefully. **If you need any explanations, or further information, ask your physician or pharmacist.**

ABOUT THIS MEDICATION

What the medication is used for:

TRUSOPT[®] is the brandname for the medication dorzolamide hydrochloride available **only on prescription** through your physician. TRUSOPT[®] is an ophthalmic carbonic anhydrase inhibitor. TRUSOPT[®] is prescribed to lower the raised pressure in your eye(s) because you have increased pressure in your eye(s) or 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.

What it does:

TRUSOPT[®] inhibits the enzyme carbonic anhydrase to reduce production of the watery secretion of the eye, which helps reduce the pressure in your eye.

Remember - This medicine is prescribed for the particular condition that you have. Do not give this medicine to other people, nor use it for any other condition.

When it should not be used:

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

Do not use TRUSOPT[®] if you:

- are allergic to any of its components (see: What the important nonmedicinal ingredients are).
- have severe kidney problems.
- are taking oral carbonic anhydrase inhibitors.

What the medicinal ingredient is:

2% dorzolamide present as the hydrochloride salt, a sulfonamide-related compound.

What the important nonmedicinal ingredients are:

hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide and water for injection. Benzalkonium chloride is only added as a preservative to TRUSOPT[®] Ophthalmic Solution. TRUSOPT[®] preservative-free formulation does not contain benzalkonium chloride.

What dosage forms it comes in:

TRUSOPT[®] and TRUSOPT[®] preservative-free formulation ophthalmic solution 2% are sterile eye drops.

WARNINGS AND PRECAUTIONS

This medicine may not be suitable for some patients. So, tell your physician if you think **any** of the following applies to you:

- If you have any medical problems now or have had any in the past, including eye (corneal) defects, or previous eye surgery while using dorzolamide;
- If you are using any other medications (see INTERACTIONS WITH THIS MEDICATION);
- If you have any allergies to any medications;
- TRUSOPT[®] contains the preservative benzalkonium chloride. If you wear contact lenses, you should consult your physician before using TRUSOPT[®]. Do not administer while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use. TRUSOPT[®] preservative-free formulation has not been studied in patients wearing contact lenses;
- If you are pregnant or intend to become pregnant;
- If you are breast feeding or intend to breast feed;
- If you have now or have had in the past kidney or liver problems.

If any of the following occur during treatment with TRUSOPT[®], consult your physician immediately:

- if you suspect that TRUSOPT[®] is causing an allergic reaction such as skin rash or itching or other reactions in the eye, such as conjunctivitis;
- if you develop any eye infection or any eye irritation or any new eye problem such as redness of the eye or swelling of the eyelids;
- if you have any eye surgery or suffer eye injury;
- if you have severe skin reactions with symptoms such as blisters, peeling skin, red/purple rash, skin lesions and sores, and associated fever, sore throat.

TRUSOPT[®] IS NOT RECOMMENDED FOR CHILDREN.

In studies with TRUSOPT[®], the effect of TRUSOPT[®] was similar in both elderly and younger adult patients.

INTERACTIONS WITH THIS MEDICATION

Your physician also needs to know about drugs (including eye drops) that you are using or plan to use, including drugs obtained without a prescription, in particular, large doses of ASA (acetylsalicylic acid) or sulfa drugs.

PROPER USE OF THIS MEDICATION

- Do not start taking any other medicines unless you have discussed the matter with your physician.
- If more than one topical ophthalmic drug is being utilized, the drugs should be administered at least ten minutes apart.
- If your physician has recommended you use TRUSOPT[®] with a beta-blocker eye drop to lower eye pressure, then the dose is one drop of TRUSOPT[®] in the affected eye(s) in the morning and in the evening.
- Do not change the dosage of the drug without consulting your physician. If you must stop treatment, contact your physician immediately.
- Do not allow the tip of the container to touch the eye or areas around the eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface.

Usual Adult dose:

The appropriate dosage and duration of treatment will be established by your physician.

When TRUSOPT[®] is used alone, the dose is one drop in the affected eye(s) in the morning, in the afternoon and in the evening.

Missed Dose:

It is important to apply TRUSOPT[®] 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.

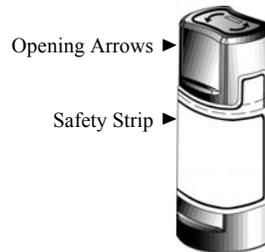
Overdose:

For management of a suspected drug overdose, particularly oral ingestion, contact your Regional Poison Control Centre even if there are no symptoms.

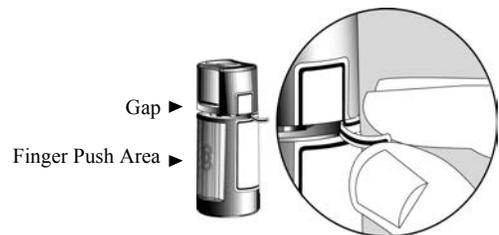
INSTRUCTIONS FOR USE

TRUSOPT[®] Ophthalmic Solution

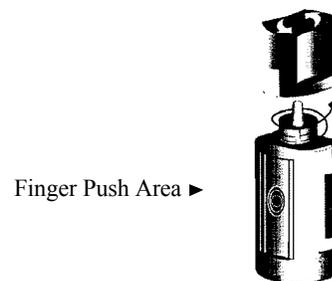
1. Before using the medication for the first time, be sure the Safety Strip on the front of the bottle is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.



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



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.



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



- 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 doctor.



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

Ophthalmic medications, if handled improperly, can become contaminated by common bacteria known to cause eye infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated ophthalmic medications. If you think your medication may be contaminated, or if you develop an eye infection, contact your doctor immediately concerning continued use of this bottle.

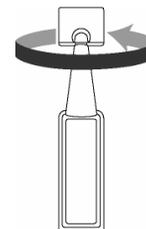
- If drop dispensing is difficult after opening for the first time, replace the cap on the bottle and tighten (DO NOT OVERTIGHTEN) and then remove by turning the cap in the opposite direction as indicated by the arrows on top of the cap.
- Repeat steps 4 & 5 with the other eye if instructed to do so by your doctor.
- Replace the cap by turning until it is firmly touching the bottle. Do not overtighten or you may damage the bottle and cap.
- The dispenser tip is designed to provide a single drop; therefore, do NOT enlarge the hole of the dispenser tip.
- 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 Formulation Ophthalmic Solution

The solution from one individual unit dose pipette of TRUSOPT[®] preservative-free formulation is to be used immediately after opening for administration to the affected eye(s). Since sterility cannot be maintained after the individual unit dose pipette is opened, any remaining contents must be discarded immediately after administration.

Usage Instructions

- Open the foil pouch which contains 15 individual unit dose pipettes. There are three strips of 5 pipettes each in the pouch.
- Break off one pipette from the strip and twist open the top of the pipette as shown in Figure 1.



- Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and eye as shown in Figure 2.



- Instill one drop in the affected eye(s) as directed by your physician. Each pipette contains enough solution for both eyes.
- After instillation, discard the used pipette even if there is solution remaining.
- Store the remaining pipettes in the foil pouch; the remaining pipettes must be used within 15 days.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Any medicine may have unintended or undesirable effects, so-called side effects.

You may experience eye symptoms such as burning and stinging, blurred vision, itching, tearing, redness of the eye (s), eye pain, or swelling or crusting of the eyelids. You may sense a bitter taste after putting in your eye drops.

Other side effects may include headache, nosebleed, dry mouth, nausea, tiredness, kidney stones and rarely, rash such as severe skin reactions. If you develop a severe skin reaction with symptoms such as blisters, peeling skin, red/purple rash, skin lesions and sores, and associated fever, sore throat, stop taking this medication immediately and contact your physician. There have been post-marketing experience reports of allergic reactions to TRUSOPT[®] with symptoms such as tissue swelling, difficulty in breathing, itching, and urticaria (raised

skin rash). If this occurs, stop taking this medication and contact your physician.

Your physician or pharmacist has a complete list of the possible side effects from this medication. Please tell your physician or pharmacist promptly about any unusual symptom.

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

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

This is not a complete list of side effects. For any unexpected effects while taking TRUSOPT[®], contact your physician or pharmacist.

HOW TO STORE IT

TRUSOPT[®] Ophthalmic Solution:

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

TRUSOPT[®] Preservative-free Formulation Ophthalmic Solution:

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

Keep all medicines safely away from children.

Reporting Side Effects

We encourage you to report serious or unexpected side effects to Health Canada. The information is used to check for new safety concerns about health products. As a consumer, your report contributes to the safe use of health products for everyone.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Should you require information related to the management of the side effects, please contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

<http://www.purdue.ca>

or by contacting the sponsor, Purdue Pharma, at: 1-800-387-4501.

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