PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]DORZOLAMIDE

Dorzolamide Eye Drops

Sterile Ophthalmic Solution, 2% weight/volume Dorzolamide (as Dorzolamide hydrochloride), ophthalmic

BP

Elevated Intraocular Pressure Therapy
(Topical Carbonic Anhydrase Inhibitor)

Date of Initial Approval:
June 14, 2022

Manufactured by:
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Bangalore– 560001
INDIA

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Mississauga, ON L4Z 1S1

Submission Control Number: 248994

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DORZOLAMIDE (Dorzolamide eye drops) 2% is indicated in the treatment of elevated intraocular pressure in patients with:

- ocular hypertension
- open-angle glaucoma

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 adult patients, but greater sensitivity of some older individuals to the product cannot be ruled out. See WARNINGS AND PRECAUTIONS – Special Populations – Geriatrics.

2 CONTRAINDICATIONS

DORZOLAMIDE is 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 the DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Dorzolamide eye drops has not been studied in patients with severe renal impairment (CrCl < 0.5 mL/s). Because dorzolamide hydrochloride and its metabolite are excreted predominantly by the kidney, DORZOLAMIDE 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 DORZOLAMIDE. The concomitant administration of dorzolamide eye drops and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

Adults (≥18 years of age): When used as monotherapy, the dose is one drop of DORZOLAMIDE in the affected eye(s) three times daily.

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

When substituting DORZOLAMIDE for another ophthalmic antiglaucoma agent, discontinue the other agent after proper dosing on one day, and start DORZOLAMIDE on the next day.

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

Pediatrics (<18 years of age): Safety and effectiveness in children have not been established. An indication for pediatric use has not been authorized

3.2 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.

4 OVERDOSAGE

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

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/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.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength	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.

DORZOLAMIDE eye drops is a sterile, isotonic, buffered, clear, colorless to nearly colorless and slightly viscous solution supplied in 5 mL LDPE ophthalmic dispenser with a sealed dropper tip. Tamper evidence is provided by a safety strip on the container label.

DORZOLAMIDE 2% eye drops, equivalent to 20 mg dorzolamide (22.3 mg of dorzolamide hydrochloride) per mL; in 5 mL dispenser.

6 WARNINGS AND PRECAUTIONS

General

DORZOLAMIDE 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. Dorzolamide eye drops has not been studied in patients with acute angle-closure glaucoma.

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
Dorzolamide eye drops 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 dorzolamide eye drops. 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 DORZOLAMIDE should be considered.

Monitoring and Laboratory Tests

Dorzolamide eye drops 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 DORZOLAMIDE.

Corneal Edema and Irreversible Corneal Decompensation
Corneal edema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using dorzolamide. DORZOLAMIDE 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
Dorzolamide eye drops has not been studied in patients wearing contact lenses. The preservative in DORZOLAMIDE eye drops, 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.

6.1 Special Populations

6.1.1 Pregnant Women

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

6.1.2 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 dorzolamide hydrochloride 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).

6.1.3 Pediatrics

Pediatrics (<18 years of age): Safety and effectiveness in children have not been established, therefore, an indication for pediatric use has not been authorized.

6.1.4 Geriatrics

Geriatrics (> 65 years of age): Of the total number of patients in clinical studies of dorzolamide eye drops, 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.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

In long-term studies of 1,108 patients treated with dorzolamide eye drops as monotherapy or as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3%) from treatment with dorzolamide eye drops 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.

The most frequently reported ocular drug related adverse effects for dorzolamide eye drops were burning and stinging 38%, taste perversion 13%, conjunctival injection 5%, corneal erosion 4%, follicular conjunctivitis 3%, and blurred vision 3%.

7.2 Clinical Trial Adverse Reactions

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

Adverse experiences that were reported during clinical studies as drug-related (possibly, probably, or definitely) in 1-5% of patients on dorzolamide eye drops 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.

7.3 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.

Urogenital: Urolithiasis

8 DRUG INTERACTIONS

8.1 Overview

Specific drug interaction studies have not been performed with dorzolamide eye drops. In clinical studies, dorzolamide eye drops 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).

8.2 Drug-Drug Interactions

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

Acid-base Disturbances: DORZOLAMIDE is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, dorzolamide eye drops 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 DORZOLAMIDE.

8.3 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 ADVERSE REACTIONS).

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

DORZOLAMIDE 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).

DORZOLAMIDE eye drops 2% contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide eye drops 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, dorzolamide eye drops reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction. Unlike topical beta-blockers, dorzolamide eye drops 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 dorzolamide eye drops 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.

9.2 Pharmacokinetics

Absorption: Unlike oral carbonic anhydrase inhibitors, topically-applied dorzolamide eye drops 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 dorzolamide eye drops 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.

10 STORAGE, STABILITY AND DISPOSAL

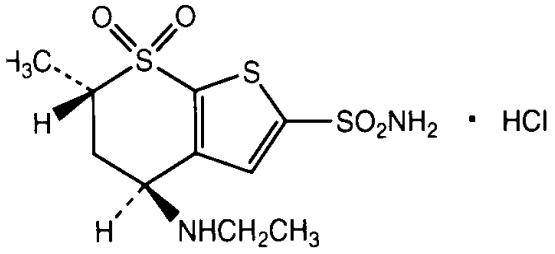
DORZOLAMIDE eye drops

Store at 15°-25°C (59° - 77°F). Protect from light. Once opened, the bottle may be stored at 15°-25°C for up to 28 days.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	dorzolamide hydrochloride
Chemical name:	(4S-*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 g/mol
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 α^{25° (C=1, water) = ~ -17°. 405

12 CLINICAL TRIALS

12.1 Trial Design and Study Demographics

The efficacy of dorzolamide eye drops as monotherapy in patients with glaucoma or ocular hypertension (baseline IOP $\geq$23 mmHg) was demonstrated in clinical studies of up to one-year duration. The IOP-lowering effect of dorzolamide eye drops 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 dorzolamide eye drops 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 dorzolamide eye drops as monotherapy was further demonstrated in two large clinical trials. In a one-year controlled trial (N=523), dorzolamide eye drops 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 dorzolamide eye drops), respectively, were as follows: dorzolamide eye drops = 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 dorzolamide eye drops or betaxolol, but no significant difference was observed between dorzolamide hydrochloride and betaxolol.

In a dose-response study (N=333), dorzolamide eye drops was compared with placebo during a six-week phase, followed by one year of treatment with dorzolamide eye drops. At six weeks, patients on dorzolamide eye drops 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 dorzolamide eye drops 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 dorzolamide eye drops 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 dorzolamide eye drops 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 dorzolamide eye drops 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 dorzolamide eye drops 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:
dorzolamide eye drops = 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.

Dorzolamide eye drops 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%.

13 NON-CLINICAL 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 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 ≥ 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.

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*.

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 ≥ 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).

14 SUPPORTING PRODUCT MONOGRAPHS

1. Trusopt® (ophthalmic solution, 2%), submission control 241417, Product Monograph, Elvium Life Sciences. (AUG 26, 2020).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr DORZOLAMIDE
Dorzolamide Eye Drops

Read this carefully before you start taking **DORZOLAMIDE** 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 **DORZOLAMIDE**.

What is DORZOLAMIDE used for?

DORZOLAMIDE lowers the pressure in the eye for conditions such as ocular hypertension or open-angle glaucoma.

How does DORZOLAMIDE work?

DORZOLAMIDE belongs to a group of medicines called carbonic anhydrase inhibitors. DORZOLAMIDE works by reducing the production of liquid in the eye. This helps lower the pressure in the eye.

What are the ingredients in DORZOLAMIDE?

Medicinal ingredients:	dorzolamide (present as the hydrochloride salt)
Non-medicinal ingredients:	hydroxyethyl cellulose, mannitol, sodium hydroxide, tri sodium citrate dihydrate, and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

DORZOLAMIDE comes in the following dosage forms:

DORZOLAMIDE eye drops 2% are sterile eye drops.

Do not use DORZOLAMIDE if:

- You are allergic to any of its components (see: What are the ingredients in DORZOLAMIDE).
- 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 DORZOLAMIDE. 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;
- DORZOLAMIDE contains the preservative benzalkonium chloride. If you wear contact lenses, you should consult your healthcare professional before using DORZOLAMIDE. Do not use DORZOLAMIDE while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use.
- 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 DORZOLAMIDE in your eye. Do not drive or use any tools or machines until your vision is clear.

DORZOLAMIDE is 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 DORZOLAMIDE:

- 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 DORZOLAMIDE:

- 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 DORZOLAMIDE with a beta-blocker eye drop, then the dose is one drop of DORZOLAMIDE 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.

DORZOLAMIDE Eye Drops

1. Before using the medication for the first time, be sure the tamper evident ring between the bottle and the cap is unbroken (See Figure A).

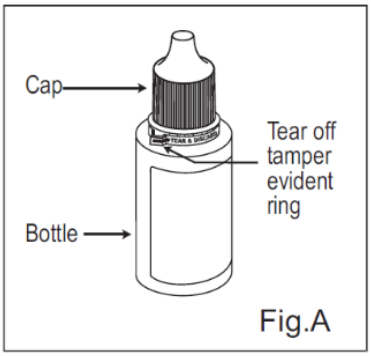


Fig.A

2. Wash your hands.

3. Before opening the bottle for the first time, tear off the tamper evident ring to break the seal (See Figure B).

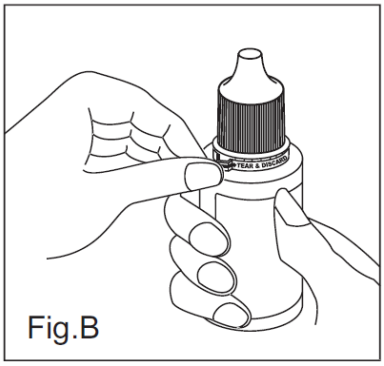


Fig.B

4. To open the bottle, remove the cap by turning it in the counterclockwise direction (See Figure C).

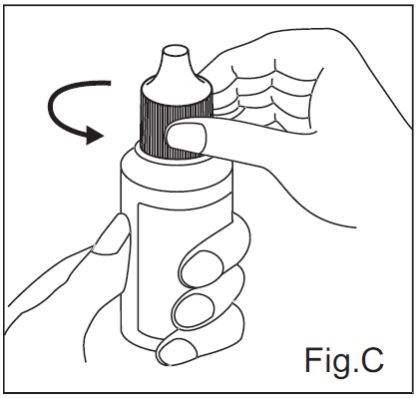
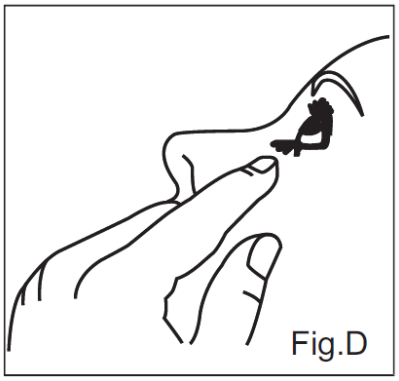


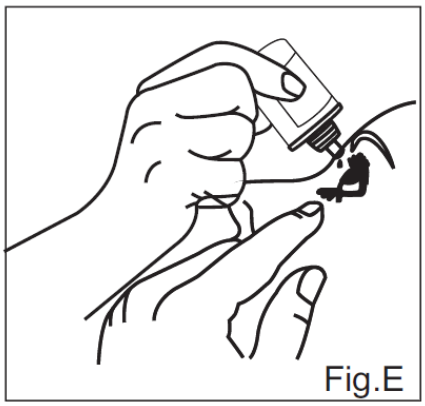
Fig.C

Giving your dorzolamide eye drops

5. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye. (See Figure D).



6. Invert the bottle upside down and hold and press gently middle of the bottle with your thumb until a single drop is placed in your eye as directed by your healthcare professional. (See 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.

7. 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.

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

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

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

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

Usual dose:

Your doctor will tell you the right dose and length of time to use DORZOLAMIDE.

When DORZOLAMIDE 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 DORZOLAMIDE, 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 DORZOLAMIDE 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 DORZOLAMIDE?

These are not all the possible side effects you may feel when taking DORZOLAMIDE. If you experience any side effects not listed here, contact 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.			√
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			√

This is not a complete list of side effects. For any unexpected effects while taking DORZOLAMIDE, contact your doctor or pharmacist.

Reporting Side Effects

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

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

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

Storage:

DORZOLAMIDE Eye Drops:
Store at 15°-25°C (59° - 77°F). Protect from light. Once opened, the bottle may be stored at 15°-25°C for up to 28 days.

Keep out of the reach and sight of children.

If you want more information about DORZOLAMIDE:

- 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); or by calling 1-(800) 715-6915.

This leaflet was prepared by Micro Labs Limited.

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