PRODUCT MONOGRAPH

[Pr]Med-Dorzolamide

Dorzolamide Eye Drops, BP

2% weight/volume dorzolamide (as dorzolamide hydrochloride)

Sterile Ophthalmic Solution

Elevated Intraocular Pressure Therapy
(Topical Carbonic Anhydrase Inhibitor)

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[Pr]Med-Dorzolamide

Dorzolamide Eye Drops, BP

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 (22.260 mg of dorzolamide hydrochloride)	*This product contains: Benzalkonium chloride 0.0075% as a preservative.* *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Med-Dorzolamide (dorzolamide hydrochloride) ophthalmic solution 2% is indicated in the treatment of elevated intraocular pressure in patients with:

- ocular hypertension
- open-angle glaucoma

CONTRAINDICATIONS

Med-Dorzolamide (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.

Dorzolamide hydrochloride 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, Med-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 Med-Dorzolamide. The concomitant administration of dorzolamide hydrochloride and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

WARNINGS AND PRECAUTIONS

General

Med-Dorzolamide (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. Dorzolamide hydrochloride 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 dorzolamide hydrochloride. 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 Med-Dorzolamide 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 Med-Dorzolamide.

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. Med-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 hydrochloride has not been studied in patients wearing contact lenses. The preservative in Med-Dorzolamide 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.

Hepatic

Hepatic Impairment

Dorzolamide hydrochloride 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. Med-Dorzolamide 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 Med-Dorzolamide 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 dorzolamide hydrochloride, 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 of dorzolamide hydrochloride ophthalmic solution, 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

Dorzolamide hydrochloride was not associated with clinically meaningful electrolyte disturbances.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In long-term studies of 1108 patients treated with dorzolamide hydrochloride as monotherapy or

as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3%) from treatment with dorzolamide hydrochloride 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.

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 dorzolamide hydrochloride 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 dorzolamide hydrochloride Ophthalmic Solution. In clinical studies, dorzolamide hydrochloride 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 Med-Dorzolamide or with other sulfonamides:

Acid-base Disturbances
Med-Dorzolamide is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, dorzolamide hydrochloride 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 Med-Dorzolamide.

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 Med-Dorzolamide (dorzolamide hydrochloride) 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 Med-Dorzolamide in the affected eye(s) two times daily.

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

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/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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Med-Dorzolamide (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 Med-Dorzolamide 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 Med-Dorzolamide 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

Med-Dorzolamide Ophthalmic Solution:
Store at 15°C-30°C. Protect from light. Once opened, the bottle may be stored at 15°C-30°C for up to 40 days. Discard unused portion 40 days after opening.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Med-Dorzolamide Ophthalmic Solution is supplied as a sterile, slightly opalescent, nearly colorless, slightly viscous solution of dorzolamide hydrochloride. Each mL of Med-Dorzolamide 2% contains 20 mg dorzolamide (22.260 mg of dorzolamide hydrochloride).

Non-medicinal ingredients: hydroxyethyl cellulose, mannitol, sodium citrate, sodium hydroxide (to adjust pH) and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

Med-Dorzolamide (dorzolamide hydrochloride) sterile ophthalmic solution is a slightly opalescent, nearly colorless, slightly viscous solution supplied in a10 mL (with 5 mL fill volume) LDPE ophthalmic dispenser, with a sealed dropper tip.

Ophthalmic Solution Med-Dorzolamide 2%, equivalent to 20 mg dorzolamide (22.260 mg of dorzolamide hydrochloride) per mL; in 10 mL dispensers (with 5 mL fill volume).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

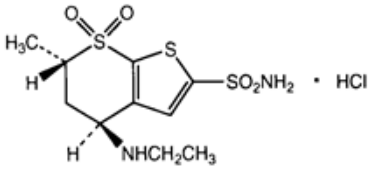
Proper name: dorzolamide hydrochloride

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

Molecular formula: $C_{10}H_{17}ClN_2O_4S_3$

Molecular mass: 360.9 g/mol

Structural formula:



Physicochemical properties:

Description: Dorzolamide hydrochloride is a white to off-white, free flowing crystalline powder, which is soluble in water, slightly soluble in methanol and very slightly soluble in anhydrous ethanol and has a melting point of about 283-285.5°C.

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

CLINICAL TRIALS

The efficacy of dorzolamide hydrochloride 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 dorzolamide hydrochloride 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 hydrochloride 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 hydrochloride as monotherapy was further demonstrated in two large clinical trials. In a one-year controlled trial (N=523), dorzolamide hydrochloride 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 hydrochloride), respectively, were as follows: dorzolamide hydrochloride = 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 hydrochloride or betaxolol, but no significant difference was observed between dorzolamide hydrochloride and betaxolol.

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

Med-Dorzolamide 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%.

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).

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

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10. Product Monograph, TRUSOPT (dorzolamide hydrochloride) ophthalmic solution, as marketed by Merck Frosst Canada Ltd. Submission Control No. 135834, Date of Revision: April 21, 2010.

PART III: CONSUMER INFORMATION
[Pr]Med-Dorzolamide
Dorzolamide Eye Drops, BP

This leaflet is part III of a three-part "Product Monograph" published when Med-Dorzolamide was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Med-Dorzolamide. 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:
Med-Dorzolamide is the brandname for the medication dorzolamide hydrochloride available **only on prescription** through your physician. Med-Dorzolamide is an ophthalmic carbonic anhydrase inhibitor. Med-Dorzolamide is prescribed to lower the raised pressure in your eye(s) because you have increased pressure in your eye(s) or glaucoma.

What it does:
Med-Dorzolamide 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 Med-Dorzolamide 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, sodium hydroxide and water for injection. Benzalkonium chloride is only added as a preservative to Med-Dorzolamide Ophthalmic Solution.

What dosage forms it comes in:
Med-Dorzolamide 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;
- Med-Dorzolamide contains the preservative benzalkonium chloride. If you wear contact lenses, you should consult your physician before using Med-Dorzolamide. Do not administer while wearing (soft) contact lenses. Remove lenses before application and reinsert no earlier than 15 minutes after use.
- 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 Med-Dorzolamide, consult your physician immediately:

- if you suspect that Med-Dorzolamide 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

MED-DORZOLAMIDE IS NOT RECOMMENDED FOR CHILDREN.

In studies with dorzolamide hydrochloride, the effect of dorzolamide hydrochloride 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 Med-Dorzolamide with a beta-blocker eye drop to lower eye pressure, then the dose is one drop of Med-Dorzolamide 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 Med-Dorzolamide 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 Med-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.

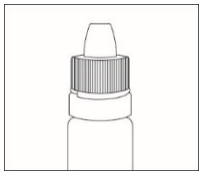
Overdose:

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

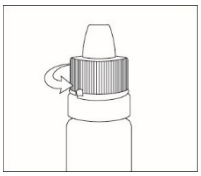
INSTRUCTIONS FOR USE

Med-Dorzolamide Ophthalmic Solution

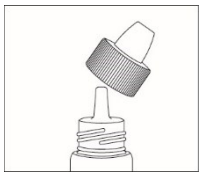
1. Before using the medication for the first time, be sure the safety seal on the bottle is unbroken.



2. Tear off the safety seal to break the seal.



3. To open the bottle, unscrew the cap by turning 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.

5. Invert the bottle and press lightly with the thumb or index finger (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.

6. 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.
7. Repeat steps 4 & 5 with the other eye if instructed to do so by your doctor.
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 Med-Dorzolamide left in the bottle. You should not be concerned since an extra amount of Med-Dorzolamide has been added and you will get the full amount of Med-Dorzolamide that your doctor prescribed. Do not attempt to remove excess medicine from the bottle.

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 dorzolamide hydrochloride 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 Med-Dorzolamide, contact your physician or pharmacist.

HOW TO STORE IT

Med-Dorzolamide Ophthalmic Solution:
Store at 15°C-30°C. Protect from light.

Once opened, the bottle may be stored at 15°C-30°C for up to 40 days. Discard unused portion 40 days after opening.

Keep all medicines safely away from children.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:
- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient 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 Patient Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: www.gmprx.com
or by contacting the sponsor, Generic Medical Partners Inc., at: 416-444-4467

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