TRUSOPT® Merck Frosst Dorzolamide HCl Elevated Intraocular Pressure Therapy--Topical Carbonic Anhydrase Inhibitor

Action and Clinical

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).

Unlike oral carbonic anhydrase inhibitors, topically applied 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 nonlinear manner, resulting in a rapid decline of drug concentration initially, followed by a slower elimination phase with a half-life of about 4 months.

To simulate the maximum systemic exposure after long-term topical ocular administration, dorzolamide was given orally to 8 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 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 (15 nmol) indicating almost no free drug or metabolite;

In RBCs, dorzolamide concentrations approached the binding capacity of CA-II (20 to 25 µmol) and metabolite concentrations approached 12 to 15 µmol, well below the binding capacity of CA-I (125 to 155 µmol);

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.

**Indications And Clinical Uses:**

In the treatment of elevated intraocular pressure in patients with ocular hypertension, open-angle glaucoma.

**Contra-Indications:**

In patients who are hypersensitive to any component of this product.

Dorzolamide has not been studied in patients with severe renal impairment (CrCl <30 mL/min). Because dorzolamide and its metabolite are excreted predominantly by the kidney, the drug 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 an oral carbonic anhydrase inhibitor and dorzolamide. The concomitant administration of dorzolamide and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

**Warnings in Clinical States:**

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. 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 has not been studied in patients with acute angle-closure glaucoma.
Dorzolamide has not been studied in patients with hepatic impairment and should therefore be used with caution in such patients.

Dorzolamide 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 reinsert the lenses earlier than 15 minutes after use.

Children: Safety and effectiveness in children have not been established.

Pregnancy: 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.

Lactation: 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 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 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).

Precautions:

In clinical studies, local ocular adverse effects, primarily conjunctivitis and eyelid reactions, were reported with chronic administration of dorzolamide. 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.

Patients should be advised that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product and to communicate with the treating physician.
Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice about continuing treatment with dorzolamide.

There have been reports of bacterial keratitis associated with the use of multiple dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients should also be advised that if they develop an intercurrent ocular condition (e.g., trauma, ocular surgery or infection), they should immediately seek their physician's advice concerning the continued use of the present multi-dose container.

If more than one topical ophthalmic drug is being utilized, the drugs should be administered at least 10 minutes apart.

Geriatrics: Of the total number of patients in clinical studies of dorzolamide, 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.

**Drug Interactions:**

Specific drug interaction studies have not been performed with dorzolamide ophthalmic solution. In clinical studies, dorzolamide 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, nonsteroidal anti-inflammatory drugs including ASA, and hormones (e.g., estrogen, insulin, thyroxine).

Dorzolamide is a carbonic anhydrase inhibitor and although
administered topically, is absorbed systemically. In clinical studies, dorzolamide 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.

Occupational Hazards: Effects on Ability to Drive and Use Machines: Possible side effects such as visual disturbances may affect the ability to drive and use machines.

Laboratory Tests: Dorzolamide was not associated with clinically meaningful electrolyte disturbances.

**Adverse Reactions:**

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

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.

Adverse experiences that were reported as drug-related (possibly, probably or definitely) in 1 to 5% of patients on dorzolamide 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 1 report of urolithiasis.

**Symptoms And Treatment Of Overdose:**

Overdose No data are available in humans in regard to over dosage by accidental or deliberate ingestion.
Treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidic state, and possible CNS effects may occur. 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 HCl of 11 369 mg/m

Dosage And Administration:

When used as monotherapy, the dose is 1 drop of ophthalmic solution 2% in the affected eye(s) 3 times daily.

When used as adjunctive therapy with an ophthalmic beta-blocker, the dose is 1 drop in the affected eye(s) 2 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 1 topical ophthalmic drug is being used, the drugs should be administered at least 10 minutes apart.

Availability And Storage:

Each mL of sterile, clear, colorless to nearly colorless, isotonic, buffered, slightly viscous, aqueous ophthalmic solution contains: dorzolamide HCl 22.3 mg equivalent to dorzolamide 20 mg (2%). Nonmedicinal ingredients: benzalkonium chloride, hydroxyethyl cellulose, mannitol, sodium citrate dihydrate, sodium hydroxide and water for injection. White, opaque, plastic Ocumeter ophthalmic dispensers (with controlled drop tip) of 5 mL. Store at 15 to 25°C. Protect from light. The contents of the ophthalmic dispenser should not be used for more than 28 days after the date on which the container is first opened.