

Sterile Ophthalmic Solution

COSOPT^{®†}

(dorzolamide hydrochloride and timolol maleate
ophthalmic solution, MSD)

I. THERAPEUTIC CLASS

COSOPT Ophthalmic Solution (dorzolamide hydrochloride and timolol maleate, MSD) is the first combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent.

II. INDICATIONS

COSOPT is indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension, open-angle glaucoma, pseudoexfoliative glaucoma or other secondary open-angle glaucomas when concomitant therapy is appropriate.

III. DOSAGE AND ADMINISTRATION

The dose is one drop of COSOPT in the affected eye(s) two times daily.

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

If another topical ophthalmic agent is being used, COSOPT and the other agent should be administered at least ten minutes apart.

Safety and efficacy in pediatric patients below the age of 2 years have not been established. (For information regarding use in pediatric patients ≥ 2 years of age see section VIII)

IV. CONTRAINDICATIONS

COSOPT is contraindicated in patients with:

- bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease
- sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock
- hypersensitivity to any component of this product

The above are based on the components and are not unique to the combination.

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V. PRECAUTIONS

Cardio-respiratory Reactions

As with other topically-applied ophthalmic agents, this drug may be absorbed systemically. The timolol component is a beta-blocker. Therefore, the same types of adverse reactions found with systemic administration of beta-blockers may occur with topical administration.

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with COSOPT. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

Respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and rarely death in association with cardiac failure, have been reported following administration of timolol maleate ophthalmic solution.

Renal and Hepatic Impairment

COSOPT has not been studied in patients with severe renal impairment (CrCl < 30 milliliter/min). Because dorzolamide hydrochloride and its metabolite are excreted predominantly by the kidney, COSOPT is not recommended in such patients.

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

Immunology and Hypersensitivity

As with other topically-applied ophthalmic agents, this drug may be absorbed systemically. The dorzolamide component is a sulfonamide. Therefore, the same types of adverse reactions found with systemic administration of sulfonamides may occur with topical administration, such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

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

While taking β -blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to accidental, diagnostic, or therapeutic repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Concomitant Therapy

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving oral and topical carbonic anhydrase inhibitors concomitantly. The

concomitant administration of COSOPT and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Patients who are already receiving a beta-adrenergic blocking agent systemically and who are given COSOPT should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade. The use of two topical beta-adrenergic blocking agents is not recommended.

Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. COSOPT has not been studied in patients with acute angle-closure glaucoma.

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

There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Precautions should be used when prescribing COSOPT to this group of patients.

Contact Lens Use

COSOPT contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, COSOPT should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use.

VI. PREGNANCY

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

VII. NURSING MOTHERS

It is not known whether dorzolamide hydrochloride is excreted in human milk. Timolol maleate does appear in human milk. Because of the potential for serious adverse reactions on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

VIII. PEDIATRIC USE

Safety and effectiveness in children have not been established. The safety and efficacy of 2% dorzolamide hydrochloride ophthalmic solution has been established in a clinical study of children under the age of 6 years. In this study patients under 6 and greater than 2 years of age whose IOP was not controlled with monotherapy received COSOPT. In those patients COSOPT was generally well tolerated.

IX. DRUG INTERACTIONS

Specific drug interaction studies have not been performed with COSOPT.

In clinical studies, COSOPT was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics,

non-steroidal anti-inflammatory drugs including aspirin, and hormones (e.g., estrogen, insulin, thyroxine).

However, the potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium channel blockers, catecholamine-depleting drugs or beta-adrenergic blocking agents.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, SSRIs) and timolol.

The dorzolamide component of COSOPT is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, dorzolamide hydrochloride ophthalmic solution 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 COSOPT.

Oral β -adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine

X. SIDE EFFECTS

In clinical studies, COSOPT was generally well tolerated; no adverse experiences peculiar to this combination drug have been observed. Adverse experiences have been limited to those that were reported previously with dorzolamide hydrochloride and/or timolol maleate. In general, common adverse experiences were mild and did not cause discontinuation.

During clinical studies, 1035 patients were treated with COSOPT. Approximately 2.4% of all patients discontinued therapy with COSOPT because of local ocular adverse reactions. Approximately 1.2% of all patients discontinued because of local adverse reactions suggestive of allergy or hypersensitivity. The most frequently reported drug-related adverse effects were: ocular burning and stinging, taste perversion, corneal erosion, conjunctival injection, blurred vision, tearing, and ocular itching. Urolithiasis was reported rarely.

The following adverse reactions have been reported in post-marketing experience: dyspnea, respiratory failure, contact dermatitis, bradycardia, heart block, choroidal detachment following filtration surgery, nausea, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

XI. OVERDOSAGE

No data are available with regard to human overdosage by accidental or deliberate ingestion of COSOPT.

There have been reports of inadvertent overdosage with timolol maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. 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.

Treatment should be symptomatic and supportive. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyze readily.

XII. AVAILABILITY

Cosopt® 2%, 0.5% (dorzolamide hydrochloride and timolol maleate ophthalmic solution, MSD) is available in 5ml dispenser.

COSOPT is a clear, colorless to nearly colorless, slightly viscous solution.

XIIa. Storage

COSOPT Ophthalmic Solution:

Store at 15–30°C (59–86°F). Protect from light.