DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COSOPT® safely and effectively. See full prescribing information for COSOPT®.


INDICATIONS AND USAGE

- COSOPT® is a carbonic anhydrase inhibitor with a beta-adrenergic receptor blocking agent indicated for the reduction of elevated intracranial pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers.

- The IOP-lowering of COSOPT® twice daily was slightly less than that seen with the concomitant administration of 0.5% timolol twice daily, and 2% dorzolamide three times daily.

DOSE AND ADMINISTRATION

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

DOSE FORMS AND STRENGTHS

Solution containing 20 mg/mL dorzolamide and 5 mg/mL timolol. (3)

CONTRAINDICATIONS

COSOPT® is contraindicated in patients with:

- Bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease (4.1)

- Sinus Rhythms and degree of atrioventricular block, overt cardiac failure, cardionic shock. (4.2)

- Hypersensitivity to any component of this product. (4.3, 5.3)

WARNINGs AND PRECAUTIONs

- Potential of Respiratory Reactions Including Asthma (5.1)

- Cardiac Failure (5.2)

- Sulfonamide Hypersensitivity (5.3)

- Obstructive Pulmonary Disease (5.4)

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The most frequently reported adverse reactions were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging in up to 10% of patients. Conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching were reported in more than 5 to 15% of patients. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Akorn, Inc., at 1-800-932-0676 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Potential additive effect of oral carbamazepine with COSOPT® (7.1)

Potential acid-base and electrolyte disturbances. (7.2)

Concomitant use with systemic beta-blockers may potentiates systemic beta-blockade. (7.3)

Onset of cardiac failure may be hastened by beta-blockers. (7.4)

Digitalis and calcium antagonists, may have additive effects in prolonging atrioventricular conduction time. (7.5)

CYP2D6 inhibitors may potentiate systemic beta-blockade. (7.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
5.4 Obstructive Pulmonary Disease
Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchial asthma or a history of bronchial asthma, in which COSEPPT is considered to be of general use, not receive beta-blocking agents, including COSEPPT [see Contraindications (4.1) and Patient Counseling (17.4)].

5.5 Increased Reactivity to Allergens
While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated exposure to allergens, antigenic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

5.6 Potentiation of Muscle Weakness
Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

5.7 Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus
Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially with those labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

5.8 Masking of Thyrotoxicosis
Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents that might precipitate a thyroid storm.

5.9 Renal and Hepatic Impairment
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, COSEPPT is not recommended in such patients.

Dorzolamide has not been studied in patients with hepatic impairment and should therefore be used without knowledge of such conditions.

5.10 Impairment of Beta-Adrenergically Mediated Reflexes During Surgery
The potential for or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli, so the ability of the heart to respond to beta-adrenergically mediated reflex stimuli remains a consideration. Consider the following guidelines:

- Patients undergoing major surgery should have their surgery scheduled no later than 2 weeks after discontinuation of beta-blocking agents (unless there is a contraindication).
- Patients undergoing non-elective surgery should be monitored closely for the duration of their surgery.
- Patients undergoing elective surgery should be monitored closely for the duration of their surgery.

The following adverse reactions have been reported in clinical trials with dorzolamide hydrochloride in rabbits at oral doses of 2.5 mg/kg/day and in humans at oral doses of at least 0.5 mg/kg/day.
Dorzolamide hydrochloride is a topical carbonic anhydrase inhibitor that prevents the production of aqueous humor by inhibiting carbonic anhydrase II in the ciliary processes of the eye. It is available as dorzolamide hydrochloride ophthalmic solution, which contains dorzolamide hydrochloride, timolol maleate, sodium citrate, hydroxyethyl cellulose, sodium hydroxide, citric acid, and benzalkonium chloride. Dorzolamide hydrochloride is a white, odorless, crystalline powder which is soluble in water and slightly soluble in methanol and ethanol. Each milliliter of dorzolamide hydrochloride ophthalmic solution contains 20 mg of dorzolamide hydrochloride (22.26 mg of the parent drug) and 5 mg of timolol maleate (6.83 mg of timolol). It is a clear, colorless solution with a pH of 4.6. The molecular formula is $\text{C}_{10}\text{H}_{16}\text{N}_{2}\text{O}_{4}\text{S}_{3}•\text{HCl}$ and its structural formula is:

$$\text{C}_{10}\text{H}_{16}\text{N}_{2}\text{O}_{4}\text{S}_{3}•\text{HCl}$$

Dorzolamide hydrochloride has a molecular weight of 360.51. It is a white, odorous, crystalline powder which is soluble in water and slightly soluble in methanol and ethanol. Dorzolamide is a weak base with a pKa of approximately 8.6. It is used in the treatment of open-angle glaucoma and ocular hypertension. Dorzolamide is a non-competitive, potent carbonic anhydrase II inhibitor that reduces aqueous humor production by approximately 50%.
received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

The following tests for mutagenic potential were negative for dorzolamide: (1) in vivo (mouse) cytogenetic assay; (2) in vitro chromosomal aberration assay; (3) alkylation elution assay; (4) V-79 assay; and (5) Ames test. Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 mg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mg/mgplate, were associated with statistically significant elevations of revertants observed with tester strains TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats with either timolol maleate or dorzolamide hydrochloride demonstrated no adverse effect on male or female fertility at doses up to approximately 100 times the systemic exposure following the maximum recommended human ophthalmic dose.

14 CLINICAL STUDIES
Clinical studies of 3 to 15 months duration were conducted to compare the IOP-lowering effect over the course of the day of COSOPT twice daily (dosed morning and bedtime) to individually and concomitantly administered 0.5% timolol twice daily and 2% dorzolamide twice and three times daily. The IOP-lowering effect of COSOPT twice daily was greater (1 to 3 mmHg) than that of monotherapy with either 2% dorzolamide three times daily or 0.5% timolol twice daily. The IOP-lowering effect of COSOPT twice daily was approximately 1 mmHg less than that of concomitant therapy with 2% dorzolamide three times daily and 0.5% timolol twice daily.

Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of COSOPT twice daily was consistent during the 12 month follow-up period.

16 HOW SUPPLIED/STORAGE AND HANDLING
COSOPT Ophthalmic Solution is supplied in an OCUMETER® PLUS container: a white, translucent, HDPE plastic ophthalmic dispenser with a controlled drip tip and a white polystyrene cap with dark blue label as follows:
NDC 17478-605-10, 10 mL in an 18 mL capacity bottle.
Storage
Store COSOPT at 15° to 30°C (59° to 86°F). Protect from light.

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information).
17.1 Potential for Excereration of Asthma and COPD
COSOPT may cause severe worsening of asthma and COPD symptoms including death due to bronchospasm. Advise patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease not to take this product. (see Contraindications (4.1)).

17.2 Potential of Cardiovascular Effects
COSOPT may cause worsening of cardiac symptoms. Advise patients with sinus bradycardia, second or third degree atrioventricular block, or cardiac failure not to take this product. (see Contraindications (4.2)).

17.3 Sulphonamide Reactions
COSOPT contains dorzolamide (which is a sulphonamide) and, although administered topically, is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulphonamides may occur with topical administration, including severe skin reactions. Advise patients that if serious or unusual reactions or signs of hypersensitivity occur, they should discontinue the use of the product and seek their physician’s advice. (see Warnings and Precautions (5.3)).

17.4 Handling Ophthalmic Solutions
Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, 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. (see Warnings and Precautions (5.12)).

17.5 Intercurrent Ocular Conditions
Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician’s advice concerning the continued use of the present multidose container.

17.6 Concomitant Topical Ocular Therapy
If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

17.7 Contact Lens Use
Advise patients that COSOPT contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution, Lenses may be reinserted 15 minutes following administration of COSOPT.

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Read this information before you start using COSOPT and each time you refill your prescription. This is in case any information has changed. This leaflet provides a summary of certain information about COSOPT. Your doctor or pharmacist can give you more complete information about COSOPT. This leaflet does not take the place of careful discussions with your doctor. You and your doctor should discuss COSOPT when you start using your medicine at regular checkups. Only your doctor can prescribe COSOPT for you.

What is COSOPT?
COSOPT is an eyeldrop. It contains dorzolamide hydrochloride, which is an ophthalmic carbonic anhydrase inhibiting drug. It also contains timolol maleate, which is a beta-blocking drug. Both drugs work to lower pressure in the eye, but in different ways.

COSOPT is a medicine for lowering pressure in the eye in people with open-angle glaucoma or ocular hypertension. It is used when a beta-blocker eyedrop alone is not adequate to control eye pressure.

What should I know about high pressure in the eye?
People with open-angle glaucoma or ocular hypertension have pressures in one or both of their eye(s) that are too high for them.

High pressure in the eye may damage the optic nerve. This may lead to loss of vision and possible blindness. There generally are few symptoms that you can feel to tell you whether you have high pressure within your eye. Your doctor needs to examine your eyes to determine this. If you have high pressure in your eye, you will need your pressure checked and your eyes examined regularly.

Who should not use COSOPT?
Do not use COSOPT if you have:
• or have ever had asthma,
• severe lung problems (such as chronic obstructive pulmonary disease),
• heart problems, including slow or irregular heartbeat or heart failure,
• allergies to any of its ingredients. See the list at the end of the leaflet.

What should I tell my doctor before and during treatment with COSOPT?
Tell your doctor:
• if you are pregnant or plan to become pregnant,
• if you are breast-feeding or intend to breast-feed,
• about any medical problems you have now or had in the past, especially heart problems or breathing problems including asthma,
• if you now have or had in the past kidney or liver problems,
• if you have diabetes, thyroid disease or muscle weakness,
• about all medicines that you are taking or plan to take, including those you can get without a prescription,
• about any allergies including allergies to any medications, especially sulfa drugs,
• if you develop an eye infection, develop a red or swollen eye or eyelid, receive an eye injury, have eye surgery, or develop new or worsening eye symptoms,
• if you plan on having any type of surgery.

How should I use COSOPT?
COSOPT is an eyeldrop. The usual dose is one drop in the morning and one drop in the evening. Your doctor will tell you if just one or both eyes are to be treated.

If you are using COSOPT with another eyedrop, the eyedrops should be used at least 5 minutes apart. It is very important to use your medication exactly as directed by your doctor. If you stop using your medicine, contact your doctor immediately.

COSOPT contains a preservative called benzalkonium chloride. This preservative may be absorbed by soft contact lenses. Contact lenses should be removed before using COSOPT. The lenses can be placed back into your eyes 15 minutes after using the eyedrops. Do not allow the tip of the bottle to touch the eye or areas around the eye. The bottle may become contaminated with bacteria. This can cause eye infections leading to serious damage to the eye, even loss of vision. Keep the tip of the bottle away from contact with any surface to avoid contamination.

INSTRUCTION FOR USE
Please follow these instructions carefully when using COSOPT. Use COSOPT as prescribed by your doctor.

1. If you use other typically applied ophthalmic medications, they should be administered at least 5 minutes before or after COSOPT.
2. Wash hands before each use.
3. Before using the medication for the first time, be sure the Safety Strip on the front of the bottle is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.
4. Tear off the Safety Strip to break the seal.
5. To open the bottle, unscrew the cap by turning as indicated by the arrows on the top of the cap. Do not pull the cap directly up and away from the bottle. Pulling the cap directly up will prevent your dispenser from operating properly.
6. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye.  

7. Invert the bottle, and press lightly with the thumb or index finger over the “Finger Push Area” (as shown) until a single drop is dispensed into the eye as directed by your doctor.  

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

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

8. If drop dispensing is difficult after opening for the first time, replace the cap on the bottle and tighten (DO NOT OVERTIGHTEN) and then remove by turning the cap in the opposite direction as indicated by the arrows on the top of the cap.  

9. Repeat steps 6 & 7 with the other eye if instructed to do so by your doctor.  

10. Replace the cap by turning until it is firmly touching the bottle. The arrow on the left side of the cap must be aligned with the arrow on the left side of the bottle label for proper closure. Do not overtighten or you may damage the bottle and cap.  

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

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

Can I use COSOPT with other medicines?  

Tell your doctor or pharmacist about all drugs that you are using or plan to use. This includes other eyedrops and drugs obtained without a prescription. This is particularly important if you are taking medicine to lower blood pressure or to treat heart disease, medicines to treat diabetes, or if you are taking large doses of aspirin.  

Ask your doctor’s advice about taking COSOPT if you are also using:  

• oral carbonic anhydrase inhibitors (for example, acetazolamide, Diamox®)  
• oral beta-blockers (for example, propranolol, Inderal®)  
• calcium antagonists (for example, nifedipine, Procardia®)  
• catecholamine-depleting drugs (for example, reserpine)  
• digitalis in combination with calcium antagonists (for example, Lanoxin® with Procardia®)  
• quinidine (for example, Cardioquin®)  
• corticosteroids (for example, Kenalog®)  
• injectable epinephrine (for example, EpiPen®)  
• injectable ephrinphrine (for example, Epipen®)  
• certain antidepressants (for example, Prozac®)  
• oral beta-blockers (for example, propranolol, Inderal®)  
• certain antidepressants (for example, Prozac®)  

Your doctor or pharmacist can tell you if any of the drugs you are using are in the above list.  

What are the possible side effects of COSOPT?  

Any medicine may have unintended or undesirable effects. These are called side effects. Side effects may not occur, but if they do occur, you may need medical attention. The most common side effects you may experience are:  

• eye symptoms such as burning and stinging, redness of the eye(s), blurred vision, tearing or itching.  
• a bitter, sour or unusual taste after putting in your eyedrops.

Other side effects may occur rarely, and some of these may be serious. Tell your doctor right away if your experience:  

• shortness of breath  
• visual changes  
• an irregular heartbeat and/or a slowing of your heart rate  
• severe skin reactions

The above list is NOT a complete list of side effects reported with COSOPT. Your doctor can discuss with you a more complete list of side effects. Please tell your doctor [or pharmacist] promptly about any of these or any other unusual symptom.  

What should I do in case of an overdose?  

If you swallow the contents of the bottle, contact your doctor immediately. Among other effects, you may feel light headed, have difficulty breathing, or feel your heart rate has slowed.  

How should I store COSOPT?  

Keep your medicine in a safe place where children cannot reach it. Store COSOPT at room temperature 15° to 30°C (59° to 86°F). Protect the bottle from light. Do not use your medicine after the expiration date on the bottle.  

What else should I know about COSOPT?  

Do not use COSOPT for a condition for which it was not prescribed. Do not give COSOPT to other people, even if they have the same condition you have. It may harm them.  

Inactive ingredients:  

The inactive ingredients of COSOPT are sodium citrate, hydroxyethylcellulose, sodium hydroxide, mannitol, water for injection and benzalkonium chloride added as a preservative.  

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