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.
COSOPT®
dorzolamide hydrochloride-timolol maleate ophthalmic solution

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.

COSOPT® (dorzolamide hydrochloride-timolol maleate ophthalmic solution)
Initial U.S. Approval: 1998

1 INDICATIONS AND USAGE

- COSOPT is a carbonic anhydrase inhibitor with a beta-adrenergic receptor blocking agent indicated for the reduction of elevated intraocular 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.

2 DOSAGE AND ADMINISTRATION

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

3 DOSAGE FORMS AND STRENGTHS

Solution containing 20 mg/mL dorzolamide and 5 mg/mL timolol.

4 CONTRAINDICATIONS

COSOPT is contraindicated in patients with:

- Bronchial asthma or a history of bronchial asthma, severe chronic obstructive pulmonary disease. (4.1)
- Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock. (4.2)
- Hypersensitivity to any component of this product. (4.3, 5.3)

5 WARNINGS AND PRECAUTIONS

- Potentiation of Respiratory Reactions Including Asthma (5.1)
- Cardiac Failure (5.2)

6 ADVERSE REACTIONS

- Sulfonamide Hypersensitivity (5.3)
- Obstructive Pulmonary Disease (5.4)
- Increased Reactivity to Allergens (5.5)
- Potentiation of Muscle Weakness (5.6)
- Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus (5.7)
- Masking of Thyrotoxicosis (5.8)
- Renal and Hepatic Impairment (5.9)
- Impairment of Beta-Adrenergically Mediated Reflexes During Surgery (5.10)

7 DRUG INTERACTIONS

- Potential additive effect of oral carbonic anhydrase inhibitor with COSOPT. (7.1)
- Potential acid-base and electrolyte disturbances. (7.2)
- Concomitant use with systemic beta-blockers may potentiate systemic beta-blockade. (7.3)
- Oral or intravenous calcium antagonists may cause atriocentric conduction disturbances, left ventricular failure, and hypotension. (7.4)
- Catecholamine-depleting drugs may have additive effects and produce hypotension and/or marked bradycardia. (7.5)
- Digitalis and calcium antagonists, may have additive effects in prolonging atriocentric conduction time. (7.6)
- CYP2D6 inhibitors may potentiate systemic beta-blockade. (7.7)

8 USE IN SPECIFIC POPULATIONS

- Calcium Antagonists (7.4)
- Catecholamine-Depleting Drugs (7.5)
- Digitalis and Calcium Antagonists (7.6)
- CYP2D6 Inhibitors (7.7)
- Clonidine (7.8)

9 CLINICAL PHARMACOLOGY

- Mechanism of Action (12.1)
- Pharmacodynamics (12.3)

10 OVERDOSAGE

- Impairment of Beta-Adrenergically Mediated Reflexes During Surgery (5.10)
- Contact Lens Use (17.7)

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

COSOPT® is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time). The IOP-lowering of COSOPT administered twice a day was slightly less than that seen with the concomitant administration of 0.5% timolol administered twice a day and 2% dorzolamide administered three times a day.

2 DOSAGE AND ADMINISTRATION

The dose is one drop of COSOPT in the affected eye(s) two times daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Solution containing 20 mg/mL dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg/mL timolol (6.83 mg timolol maleate).

4 CONTRAINDICATIONS

4.1 Asthma, COPD

COSOPT is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease.

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock

COSOPT is contraindicated in patients with sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, and cardiogenic shock.

4.3 Hypersensitivity

COSOPT contains dorzolamide, a sulfonamide; and although administered topically, it is absorbed systematically. Therefore, the same types of adverse reactions that are attributable to systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.

5 WARNINGS AND PRECAUTIONS

5.1 Potentiation of Respiratory Reactions Including Asthma

COSOPT contains timolol maleate, a beta-adrenergic blocking agent; and although administered topically, is absorbed systematically. Therefore, the same types of adverse reactions that are attributable to systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.

5.2 Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In patients without a history of cardiac failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, COSOPT should be discontinued.

5.3 Sulfonamide Hypersensitivity

COSOPT contains dorzolamide, a sulfonamide; and although administered topically, it is absorbed systematically. Therefore, the same types of adverse reactions that are attributable to beta-adrenergic blocking agents such as angioneurotic edema, urticaria, and other allergic reactions, may occur with COSOPT.

ADVERSE REACTIONS

The most frequently reported adverse reactions were taste perversion (bitter, sour, or unusual taste) or ocular burning and/or stinging in up to 30% of patients. Conjunctival hyperemia, blurred vision, superficial punctate keratitis or eye itching were reported between 5% to 15% of patients.

To report SUSPECTED ADVERSE REACTIONS, contact Akorn, Inc., at 1-800-932-5676 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

COSOPT® is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP determined after multiple measurements over time).

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

2 DOSAGE AND ADMINISTRATION

The dose is one drop of COSOPT in the affected eye(s) two times daily. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

3 DOSAGE FORMS AND STRENGTHS

Solution containing 20 mg/mL dorzolamide and 5 mg/mL timolol.

4 CONTRAINDICATIONS

- Cardiac Failure (5.2)

5 WARNINGS AND PRECAUTIONS

- Potentiation of Respiratory Reactions Including Asthma (5.1)
- Cardiac Failure (5.2)

6 ADVERSE REACTIONS

- Sulfonamide Hypersensitivity (5.3)
- Obstructive Pulmonary Disease (5.4)
- Increased Reactivity to Allergens (5.5)
- Potentiation of Muscle Weakness (5.6)
- Masking of Hypoglycemic Symptoms in Patients with Diabetes Mellitus (5.7)
- Masking of Thyrotoxicosis (5.8)
- Renal and Hepatic Impairment (5.9)
- Impairment of Beta-Adrenergically Mediated Reflexes During Surgery (5.10)

7 DRUG INTERACTIONS

- Potential additive effect of oral carbonic anhydrase inhibitor with COSOPT. (7.1)
- Potential acid-base and electrolyte disturbances. (7.2)
- Concomitant use with systemic beta-blockers may potentiate systemic beta-blockade. (7.3)
- Oral or intravenous calcium antagonists may cause atriocentric conduction disturbances, left ventricular failure, and hypotension. (7.4)
- Catecholamine-depleting drugs may have additive effects and produce hypotension and/or marked bradycardia. (7.5)
- Digitalis and calcium antagonists, may have additive effects in prolonging atriocentric conduction time. (7.6)
- CYP2D6 inhibitors may potentiate systemic beta-blockade. (7.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

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to sulfonamides may occur with topical administration of COSOPT. Fatalities have occurred, although rarely, due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation [see Contraindications (4.3) and Patient Counseling Information (17.2)].

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 bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which COSOPT is contraindicated) should, in general, not receive beta-blocking agents, including COSOPT [see Contraindications (4.1) and Patient Counseling Information (17.1)].

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 accidental, diagnostic, 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 myasthenia symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported 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 those with 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 thyrotoxicity. Patients suspected of developing 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 evaluated in patients with severe renal impairment (CrCl <30 mL/min). Because dorzolamide and its metabolite are excreted predominantly by the kidney, COSOPT is not recommended in such patients.

5.10 Impairment of Beta-Adrenergically Mediated Reflexes During Surgery The necessity 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. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents. If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

5.11 Corneal Endothelium Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing COSOPT to this group of patients.

5.12 Bacterial Keratitis 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 [see Patient Counseling Information (17.4)].

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.2 Post-Marketing Experience The following adverse reactions have been identified during post-approval use of COSOPT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

6.3 Overdose Experience An accidental overdose of COSOPT may not reflect the rates observed in practice.

6.4 Drug Interactions The following drug interactions have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; Body as a Whole: Extremity pain, decreased exercise tolerance, weight loss; Cardiovascular: Worsening of arterial insufficiency, vasodilatation; Digestive: Gastrointestinal pain, hematemesis, mesenteric arterial ischemia, urolithiasis, and vomiting.

7.4  Calciym Antagonists The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.5  Catecholamine-Depleting Drugs Close observation of the patient is recommended when a beta-blocker is administered to patients receiving catecholamine-depleting drugs, such as reserpine, because of possible additive effects of beta-blockade, both systemic and ocular. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.6  Calcium Antagonists Caution should be used in the coadministration of beta-adrenergic blocking agents, such as COSOPT, and oral or intravenous calcium antagonists because of possible atriocentrical constriction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

7.7  CYP2D6 Inhibitors The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

7.8  Chloralaine Depleting Drugs Close observation of the patient is recommended when a beta-blocker is administered to patients receiving chloralaine-depleting drugs, such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Teratogenic Effects. Pregnancy Category C. Developmental toxicity studies with dorzolamide hydrochloride in rabbits at oral doses of 2.5 mg/kg/day (37 times the recommended human ophthalmic dose) revealed malformations of the vertebral bodies. These malformations occurred at doses that caused metabolic acids with decreased body weight gain in dams.
and decreased weight. No treatment-related malformations were seen at 1 mg/kg/day (15 times the recommended human ophthalmic dose).

Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1,000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

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.

8.3 Nursing Mothers

It is not known whether dorzolamide is excreted in human milk. Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from COSOPT 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.

8.4 Pediatric Use

The safety and effectiveness of dorzolamide hydrochloride ophthalmic solution and timolol maleate ophthalmic solution have been established when administered individually in pediatric patients aged 2 years and older. Use of these drug products in children is supported by evidence from adequate and well-controlled studies in children and adults. Safety and efficacy in pediatric patients below the age of 2 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

10 OVERDOSAGE

Symptoms consistent with systemic administration of beta-blockers or carbonic anhydrase inhibitors may occur, including electrolyte imbalance, development of an acidic state, dizziness, headache, shortness of breath, bradycardia, bronchospasm, cardiac arrest and possible central nervous system effects. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. [See Adverse Reactions (6)].

A study of patients with renal failure showed that timolol did not dialyze readily.

11 DESCRIPTION

11.1 Description

COSOPT (dorzolamide hydrochloride-timol maleate ophthalmic solution) is the combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent.

Dorzolamide hydrochloride is described chemically as: (4S-trans)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide monohydrochloride. Dorzolamide hydrochloride is optically active. The specific rotation is:

\[ \left[ \alpha \right]_{25^\circ C}^\mathrm{C} = -17^\circ \]

Its empirical formula is \( C_{18}H_{22}N_{3}O_{5}S \cdot HCl \) and its structural formula is:

\[\text{COSOPT (dorzolamide hydrochloride-timol maleate ophthalmic solution) is the combination of a topical carbonic anhydrase inhibitor and a topical beta-adrenergic receptor blocking agent.}\]

Dorzolamide hydrochloride has a molecular weight of 360.91. It is a white to off-white, crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

Timolol maleate is described chemically as: (-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanoic maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon in its structure and is provided as the levo-isomer. The optical rotation of timolol maleate is:

\[ \left[ \alpha \right]_{25^\circ C}^\mathrm{C} = 12.2^\circ \ (11.7^\circ \text{ to } 10.5^\circ) \]

Its molecular formula is \( C_{18}H_{22}N_{3}O_{5}S \cdot C_{8}H_{10}O_{4} \) and its structural formula is:

\[\text{Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a beta_{1} and beta_{2} (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity. The combined effect of these two drugs administered as COSOPT twice daily results in additional intraocular pressure reduction compared to either component administered alone, but the reduction is not as much as when dorzolamide administered three times daily and timolol twice daily are administered concomitantly. [See Clinical Studies (14)].}\]

12.3 Pharmacokinetics

**Dorzolamide Hydrochloride**

When topically applied, 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 binding to CA-II. The parent drug forms a single N-desethyl metabolite, which inhibits CA-II less potently than the parent drug but also inhibits CA-I. The metabolite also accumulates in RBCs where it binds primarily to CA-I. Plasma concentrations of dorzolamide and metabolite concentrations generally below the assay limit of quantitation (15nM). Dorzolamide binds moderately to plasma proteins (approximately 33%).

Dorzolamide is primarily excreted unchanged in the urine; the metabolite also is excreted in urine.

After dosing is stopped, dorzolamide washes out of RBCs nonlinearly, 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 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 2 mg twice daily closely approximates the amount of drug delivered by topical ocular administration of dorzolamide 2% three times daily. Steady state was reached within 8 weeks. The inhibition of CA-II and total carbonic anhydrase activities was below the degree of inhibition anticipated to be necessary for a pharmacological effect on renal function and respiration in healthy individuals.

**Timolol Maleate**

In a study of plasma drug concentrations in six subjects, the systemic exposure to timolol was determined following twice daily topical administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL.

**13 NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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 recommended human ophthalmic dose). Papillomas were not seen in rats given oral doses equivalent to approximately 12 times the 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 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. Rats are particularly prone to developing bladder papillomas in response to foreign bodies, compounds causing crystalluria, and diverse sodium salts.

No changes in bladder urothelium were seen in dogs given oral dorzolamide hydrochloride for one year at 2 mg/kg/day (25 times the recommended human ophthalmic dose) or monkeys dosed topically to the eye at 0.4 mg/kg/day (~5 times the recommended human ophthalmic dose) for one year.

In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adenral pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose for one year.

In a lifetime oral study of timolol maleate in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female rats, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who 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) alkaline elution assay; (4) V-79 assay; and (5) Ames test.

Timolol maleate was devoid of mutagenic potential when tested in vivo (mouse) in the microun الصحفي test and cytogenetic assay (doses up to 800 mg/kg) and in vivo in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response was observed.
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 month durations 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® (dorzolamide hydrochloride-timolol maleate ophthalmic solution) is supplied in 10 mL white LDPE plastic dropper bottles with white LDPE tips and blue P/P caps as follows:
NDC 17478-605-10 10 mL capacity bottle.

Storage
Store COSOPT at 20° to 25°C (68° to 77°F). [see USP Controlled Room Temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information).

17.1 Potential for Exacerbation 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 Sulfonamide Reactions
COSOPT contains dorzolamide (which 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 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 reinseted 15 minutes following administration of COSOPT.