COSOPT® PF (dorzolamide hydrochloride-timolol maleate ophthalmic solution)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COSOPT PF safely and effectively. See full prescribing information for COSOPT PF.

COSOPT® PF (dorzolamide hydrochloride-timolol maleate ophthalmic solution) 2%/0.5%

Initial U.S. Approval: 1998

INDICATIONS AND USAGE
COSOPT PF 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. (1)

DOSAGE AND ADMINISTRATION
The dose is one drop of COSOPT PF in the affected eye(s) two times daily. (2)

DOSAGE FORMS AND STRENGTHS
Solution containing 20 mg/mL dorzolamide and 5 mg/mL timolol. (3)

CONTRAINDICATIONS
COSOPT PF 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)

WARNINGS AND PRECAUTIONS
- Potentiation of Respiratory Reactions Including Asthma (5.1)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
COSOPT® PF 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 (see Clinical Studies (14.1)).

2 DOSAGE AND ADMINISTRATION
The dose is one drop of COSOPT PF 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 [see Drug Interactions (7.3)]. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be maintained after the individual unit is opened, the remaining contents should be discarded immediately after administration.

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 PF is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease [see Warnings and Precautions (5.1)].

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock
COSOPT PF is contraindicated in patients with sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, and cardiogenic shock [see Warnings and Precautions (5.2)].

4.3 Hypersensitivity
COSOPT PF is contraindicated in patients who are hypersensitive to any component of this product [see Warnings and Precautions (5.3)].

5 WARNINGS AND PRECAUTIONS
5.1 Potentiation of Respiratory Reactions Including Asthma
COSOPT PF contains timolol maleate, a beta-adrenergic blocking agent; and although administered topically, is absorbed systemically. 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 [see Contraindications (4.1) and Patient Counseling Information (17.1)].
5.2 Cardiac Failure

Systolic hypertension may be essential for support of the circulation in individuals with diminished myocardial contractility, and its omission 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 PF should be discontinued [see Contraindications (4.2) and Patient Counseling Information (17.2)].

5.3 Sulfinamide Hypersensitivity

COSOPT PF contains dorzolamide, a sulfonamide; and although administered topically, it is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfinamides may occur with topical administration of COSOPT PF. Fatalities have occurred, although rarely, due to severe reactions to sulfinamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, anaphylactic shock, angioedema, and anaphylaxis. Sensitization may recur when a sulfinamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation [see Contraindications (4.1) and Patient Counseling Information (17.1)].

5.4 Obstructive Pulmonary Disease

Contraindications (4.3)

In patients without a history of cardiac failure continued depression of the myocardium and bronchoconstriction may precipitate more severe failure.

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

5.8 Masking of Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. 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 studied in patients with severe renal impairment (CrCl <30 mL/min). Because dorzolamide and its metabolite are excreted predominantly by the kidney, COSOPT PF is not recommended in such patients.

Dorzolamide has not been studied in patients with hepatic impairment and should therefore be used with caution 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 in patients receiving 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 PF to this group of patients.

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.

COSOPT and COSOPT PF

COSOPT and COSOPT PF were evaluated in patients with elevated intraocular pressure treated for open-angle glaucoma or ocular hypertension for up to 15 months. Approximately 5% of all patients discontinued treatment, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

COSOPT PF contains timolol maleate and dorzolamide hydrochloride, two topical carbonic anhydrase inhibitors with additive hypotensive effects. Therefore, the potential for such drug interactions should be considered in patients receiving COSOPT PF.

7 DRUG INTERACTIONS

7.1 Oral Carbonic Anhydrase Inhibitors

There is a potential for an additive effect on the known side effects of carbonic anhydrase inhibitors in patients receiving an oral carbonic anhydrase inhibitor and COSOPT PF. The concomitant administration of COSOPT PF and oral carbonic anhydrase inhibitors is not recommended.

7.2 High-Dose Salicylate Therapy

Although acid-base and electrolyte disturbances were not reported in the clinical trials with dorzolamide hydrochloride solution, 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 PF.

7.3 Beta-Adrenergic Blocking Agents

Patients who are receiving a beta-adrenergic blocking agent orally and COSOPT PF should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.4 Calcium Antagonists

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

7.5 Catecholamine-Depleting Drugs

Close observation of the patient is recommended when a beta-blocker is administered to patients receiving depletive agents (e.g., reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

7.6 Digitalis and Calcium Antagonists

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.
Pregnancy Category C. Developmental toxicity studies with tert-

5,6-dihydro-6-methyl-4

A study of patients with renal failure showed that timolol did not dialyze readily. timolol maleate. There is enough COSOPT PF in 1 single-use container for 1 or both of your eyes. The safety and effectiveness of dorzolamide hydrochloride ophthalmic solution and

1 drop of COSOPT PF fall into the

Dorzolamide binds moderately to plasma proteins (approximately 33%). Dorzolamide hydrochloride has a molecular weight of 360.91. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. Timolol maleate is stable at room temperature. COSOPT PF is supplied as a sterile, clear, colorless to nearly colorless, isotonic, buffered, slightly viscous, aqueous solution. The pH of the solution is approximately 5.65, and the osmolality is 242-323 mOsm. Each mL of COSOPT PF contains 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6.83 mg timolol maleate). Inactive ingredients are sodium, hydroxyethyl cellulose, sodium hydroxide, manitol, and water for injection. COSOPT PF does not contain a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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-deethyl 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 are 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 administered centrally 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 studies in which 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 papillomas in response to foreign bodies, compounds causing crystalluria, and diverse sodium salts.

No changes in bladder urethra 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 adrenal 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. 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 mice, 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 micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and in vitro in a neoplastic cell transformation assay (up to 100 µg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 µg/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 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

14.1 COSOPT Efficacy

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 2.0% dorzolamide twice and three times daily. The IOP-lowering effect of COSOPT twice daily was greater (1-3 mmHg) than that of monotherapy with either 2.0% 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 2.0% 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.

14.2 COSOPT PF Equivalence Study

In an active-treatment controlled, parallel, double-masked study in 261 patients with elevated intraocular pressure >22 mmHg in one or both eyes, COSOPT PF had an IOP-lowering effect equivalent to that of COSOPT.

16 HOW SUPPLIED/STORAGE AND HANDLING

COSOPT PF is supplied in a foil pouch containing 15 low density polyethylene 0.2 ml single-use containers.

NDC 17478-604-30, package of 60 single-use vials.

NDC 17478-604-90, package of 180 single-use vials.

Store COSOPT PF at 20° to 25°C (68° to 77°F). Do not freeze.

Store in the original pouch. After the pouch is opened, store the remaining single-use containers in the foil pouch to protect from light. Write down the date you open the foil pouch in the space provided on the pouch. Discard any unused containers 15 days after first opening the pouch.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

17.1 Potential for Exacerbation of Asthma and COPD

COSOPT PF may cause severe worsening of asthma and COPD symptoms including death due to bronchoospasm. Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease should be advised not to take this product. [See Contraindications (4.1).]

17.2 Potential of Cardiovascular Effects

COSOPT PF may cause worsening of cardiac symptoms. Patients with sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. [See Contraindications (4.2).]

17.3 Sulfonamide Reactions

COSOPT PF 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. Patients should be advised 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).]