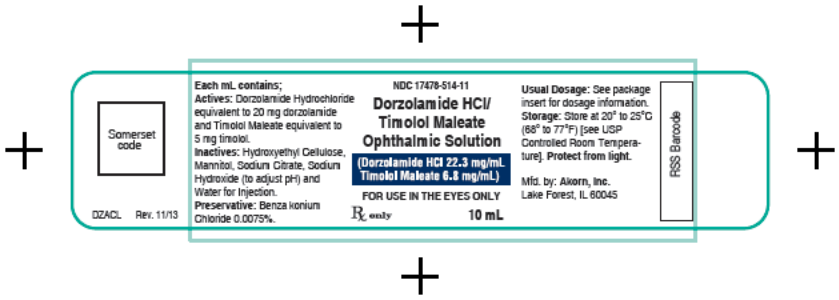
DRAWING #3580



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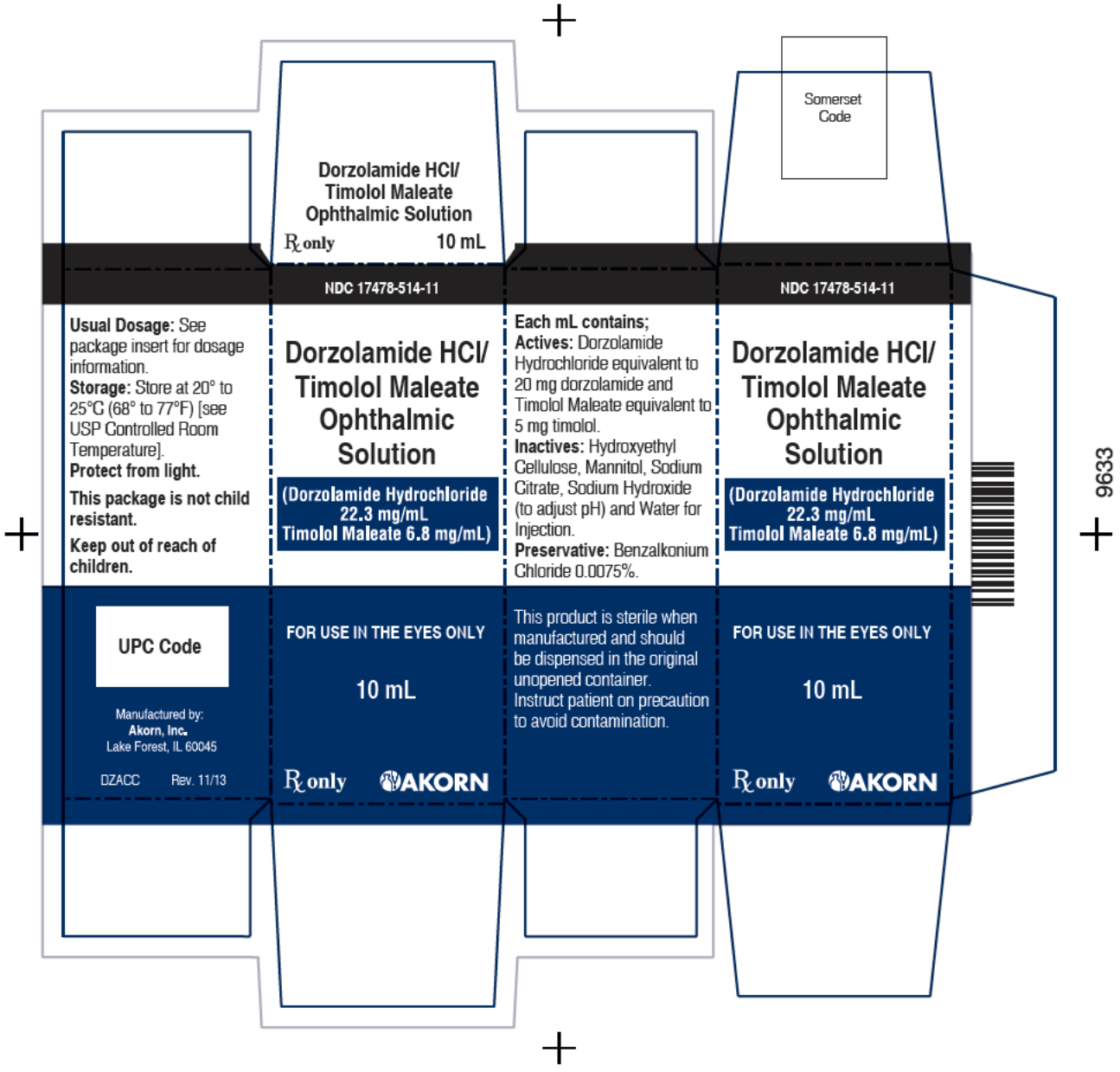
(b) (4)



Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution

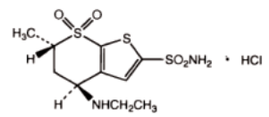
DESCRIPTION

Dorzolamide Hydrochloride-Timolol 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-4*H*-thieno [2,3-*b*] thiopyran-2-sulfonamide 7, 7-dioxide monohydrochloride. Dorzolamide hydrochloride is optically active. The specific rotation is:

[α] 25°C 405 nm (C=1, water) = ~ -17°.

Its empirical formula is $C_{10}H_{16}N_2O_4S_3$•HCl and its structural formula is:

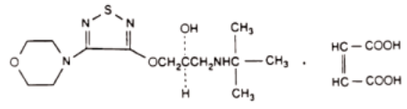


Dorzolamide hydrochloride has a molecular weight of 360.91. It is a white to off-white, crystalline powder, which is soluble in water and slightly soluble in methanol and ethanol.

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

[α] 25°C 405 nm in 1N HCl (C = 5) = -12.2° (-11.7° to -12.5°).

Its molecular formula is $C_{13}H_{24}N_4O_3S$•$C_4H_4O_4$ and its structural formula is:



Timolol maleate has a molecular weight of 432 50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. Timolol maleate is stable at room temperature.

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution. The pH of the solution is approximately 5.65, and the osmolarity is 242-323 mOsM. Each mL of Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution contains 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6 83 mg timolol maleate). Inactive ingredients are sodium citrate, hydroxyethyl cellulose, sodium hydroxide, mannitol, and water for injection. Benzalkonium chloride 0.0075% is added as a preservative.

CLINICAL PHARMACOLOGY

Mechan sm of Act on

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure, whether or not associated with glaucoma, by reducing aqueous humor secretion. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous field loss and optic nerve damage.

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 agents administered as Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution b.i.d. results in additional intraocular pressure reduction compared to either component administered alone, but the reduction is not as much as when dorzolamide t i d. and timolol b.i.d. are administered concomitantly (see Clinical Studies).

Pharmacok net cs/Pharmacodynam cs

Dorzolam de Hydrochlor de

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 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 (half-life of 4 months) and a slower elimination phase with a half-life of about four months.

Reference ID: 3408444

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 b i d. closely approximates the amount of drug delivered by topical ocular administration of dorzolamide 2% t i d. 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.

T molol 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.

Cl n cal Stud es

Clinical studies of 3 to 15 months duration were conducted to compare the IOP-lowering effect over the course of the day of Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0 5% timolol (b.i.d.) and 2.0% dorzolamide (b.i.d. and t.i d.). The IOP-lowering effect of Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution b.i.d. was greater (1-3 mmHg) than that of monotherapy with either 2.0% dorzolamide t.i.d. or 0.5% timolol b.i.d. The IOP-lowering effect of Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution b.i.d. was approximately 1 mmHg less than that of concomitant therapy with 2.0% dorzolamide t i d. and 0.5% timolol b.i.d.

Open-label extensions of two studies were conducted for up to 12 months. During this period, the IOP-lowering effect of Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution b.i.d. was consistent during the 12 month follow-up period.

INDICATIONS AND USAGE

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure 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 Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution b.i.d. was slightly less than that seen with the concomitant administration of 0 5% timolol b.i.d. and 2.0% dorzolamide t.i d. (see CLINICAL PHARMACOLOGY, Clinical Studies).

CONTRAINDICATIONS

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

System c Exposure

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution contains dorzolamide, a sulfonamide, and 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 sulfonamides and/or systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe 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 systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS). 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 *preparat on*

Card ac Fa lure

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 Pat ents W thout a H story of Card ac Fa lure 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, Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution should be discontinued.

Obstruct ve Pulmonary D sease

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 Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is contraindicated [see CONTRA NDICATIONS]) should, in general, not receive beta-blocking agents, including Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution.

Major 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.

f necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

D abetes Mell tus

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.

Thyrotox cos s

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.

PRECAUTIONS

General

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, Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution 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.

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.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution. Many of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of drug therapy. f such reactions are observed, Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution should be discontinued and the patient evaluated before considering restarting the drug. (See ADVERSE REACTIONS.)

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution has not been studied in patients with acute angle-closure glaucoma.

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

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.

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 PRECAUTIONS, *Informat on for Pat ents*)

There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Precautions should be used when prescribing Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution to this group of patients.

Informat on for Pat ents

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution 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 (see WARN NGS).

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should discontinue use and seek their physician's advice.

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 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 PRECAUTIONS, General.)

Patients also should be advised 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.

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

Patients should be advised that Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution 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 Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution.

Drug Interact ons

Carbon c anhydrase nh b tors: There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution. The concomitant administration of Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution and oral carbonic anhydrase inhibitors is not recommended.

Ac d-base d sturbances: Although acid-base and electrolyte disturbances were not reported in the clinical trials with dorzolamide hydrochloride ophthalmic 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 Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution.

Beta-adrenerg c block ng agents: Patients who are receiving a beta-adrenergic blocking agent orally and Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution 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.

Calc um antagon sts: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution, 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.

Catecholam ne-deplet ng 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 and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

D g tal s and calc um antagon sts: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 nh b tors: 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.

Clon d ne: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable Ep nephr ne: (See PRECAUTIONS, General, Anaphylaxis.)

Patient Information About
Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution

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

What is Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution?

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is an eye drop. 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.

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution 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 eye drop 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. f you have high pressure in your eye, you will need your pressure checked and your eyes examined regularly.

Who should not use Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution?

Do not use Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution if you have:

- asthma or have ever had asthma,
- severe lung problems,
- slow or irregular heartbeat or heart failure,
- allergies to any of its ingredients. See the list at the end of the leaflet.

f you are not sure whether you should use Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution, contact your doctor or pharmacist.

What should I tell my doctor be ore and during treatment with Dorzolamide Hydrochloride - Timolol Maleate Ophthalmic Solution?

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 Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution?

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution is an eye drop. 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.

f you are using Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution with another eye drop, the eye drops should be used at least 10 minutes apart. t is very important to use your medication exactly as directed by your doctor. If you stop using your medicine, contact your doctor immediately.

Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution contains a preservative called benzalkonium chloride. This preservative may be absorbed by soft contact lenses. Contact lenses should be removed before using Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution. The lenses can be placed back into your eyes 15 minutes after using the eye drops.

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.

INSTRUCTIONS FOR USE

Please follow these instructions carefully when using Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution. Use Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution as prescribed by your doctor.

1. If you use other topically applied ophthalmic medications, they should be administered at least 10 minutes before or after Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution.

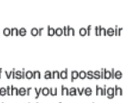


Fig. 1

2. Wash hands before each use.

3. Before using the medication for the first time, be sure the plastic sealing tape between the bottle and the cap is unbroken (Fig. 1).


Fig. 2

4. To break the seal and open the bottle, unscrew the cap by turning as indicated by the arrow (Fig. 2).


Fig. 3

5. Tilt your head back and pull your lower eyelid down slightly to form a pocket between your eyelid and your eye (Fig. 3).

6. Invert the bottle, and press lightly (as shown in Fig. 4) until a single drop is dispensed into the eye as directed by your doctor.


Fig. 4

Carc nogenes s Mutagenes s Impa rment of Fert l ty

n a wo-year s udy o dorzolamide hydrochloride adminis ered orally o male and emale Sprague- Dawley ra s urinary bladder papillomas were seen in male ra s in he highes dosage group o 20 mg/kg/day (250 imes he recommended human oph halmic dose) Papillomas were no seen in ra s given oral doses equivalen o approxima ely 12 imes he recommended human oph halmic dose No rea men -rela ed umors were seen in a 21-mon h s udy in emale and male mice given oral doses up o 75 mg/kg/day (~900 imes he recommended human oph halmic dose)

he increased incidence o urinary bladder papillomas seen in he high-dose male ra s is a class-e ec o carbonic anhydrase inhibi ors in ra s Ra s are par icularly prone o developing papillomas in response o oreign bodies compounds causing crys alluria and diverse sodium sal s

No changes in bladder uro helium were seen in dogs given oral dorzolamide hydrochloride or one year a 2 mg/kg/day (25 imes he recommended human oph halmic dose) or monkeys dosed opically o he eye a 0 4 mg/kg/day (~5 imes he recommended human oph halmic dose) or one year

n a wo-year s udy o imolol malea e adminis ered orally o ra s here was a s a is ically signi ican increase in he incidence o adrenal pheochromocy omas in male ra s adminis ered 300 mg/kg/day (approxima ely 42 000 imes he sys emic exposure ollowing he maximum recommended human oph halmic dose) Similar di erences were no observed in ra s adminis ered oral doses equivalen o approxima ely 14 000 imes he maximum recommended human oph halmic dose

n a li e ime oral s udy o imolol malea e in mice here were s a is ically signi ican increases in he incidence o benign and malignan pulmonary umors benign u erine polyps and mammary adenocarcinomas in emale mice a 500 mg/kg/day (approxima ely 71 000 imes he sys emic exposure ollowing he maximum recommended human oph halmic dose) bu no a 5 or 50 mg/kg/day (approxima ely 700 or 7 000 respec ively imes he sys emic exposure ollowing he maximum recommended human oph halmic dose) n a subsequen s udy in emale mice in which pos -mor em examina ions were limi ed o he u erus and he lungs a s a is ically signi ican increase in he incidence o pulmonary umors was again observed a 500 mg/kg/day

he increased occurrence o mammary adenocarcinomas was associa ed wi h eleva ions in serum prolac in which occurred in emale mice adminis ered oral imolol a 500 mg/kg/day bu no a doses o 5 or 50 mg/kg/day An increased incidence o mammary adenocarcinomas in roden s has been associa ed wi h adminis ra ion o several o her herapeu ic agen s ha eleva e serum prolac in bu no correla ion be ween serum prolac in levels and mammary umors has been es ablished in humans ur hermore in adul human emale subjec s who received oral dosages o up o 60 mg o imolol malea e (he maximum recommended human oral dosage) here were no clinically meaning ul changes in serum prolac in

he ollowing es s or mu agenic po en ial were nega ive or dorzolamide

(1) *n v vo* (mouse) cy ogene ic assay (2) *n v tro* chromosomal aberra ion assay (3) alkaline elu ion assay (4) V-79 assay and (5) Ames es

imolol malea e was devoid o mu agenic po en ial when es ed *n v vo* (mouse) in he micronucleus es and cy ogene ic assay (doses up o 800 mg/kg) and *n v tro* in a neoplas ic cell rans orma ion assay (up o 100 µg/mL) n Ames es s he highes concen ra ions o imolol employed 5 000 or 10 000 µg/pla e were associa ed wi h s a is ically signi ican eleva ions o rever an s observed wi h es er s rain A100 (in seven replica e assays) bu no in he remaining hree s rains n he assays wi h es er s rain A100 no consis en dose response rela ionship was observed and he ra io o es o con rol rever an s did no reach 2 A ra io o 2 is usually considered he cri erion or a posi ive Ames es

Reproduc ion and er ili y s udies in ra s wi h ei her imolol malea e or dorzolamide hydrochloride demons ra ed no adverse e ec on male or emale er ili y a doses up o approxima ely 100 imes he sys emic exposure ollowing he maximum recommended human oph halmic dose

Pregnancy

Teratogen c Effects Pregnancy Ca egory C Developmen al oxici y s udies wi h dorzolamide hydrochloride in rabbi s a oral doses o ≥2 5 mg/kg/day (31 imes he recommended human oph halmic dose) revealed mal orma ions o he ver ebral bodies hese mal orma ions occurred a doses ha caused me abolic acidosis wi h decreased body weigh gain in dams and decreased e al weigh s No rea men -rela ed mal orma ions were seen a 1 0 mg/kg/day (13 imes he recommended human oph halmic dose)

era ogenici y s udies wi h imolol in mice ra s and rabbi s a oral doses up o 50 mg/kg/day (7 000 imes he sys emic exposure ollowing he maximum recommended human oph halmic dose) demons ra ed no evidence o e al mal orma ions Al hough delayed e al ossi ica ion was observed a his dose in ra s here were no adverse e ec s on pos na al developmen o o spring Doses o 1000 mg/kg/day (142 000 imes he sys emic exposure ollowing he maximum recommended human oph halmic dose) were ma erno oxic in mice and resul ed in an increased number o e al resorp ions ncreased e al resorp ions were also seen in rabbi s a doses o 14 000 imes he sys emic exposure ollowing he maximum recommended human oph halmic dose in his case wi hou apparen ma erno oxici y

here are no adequa e and well-con rolled s udies in pregnan women Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion should be used during pregnancy only i he po en ial bene i jus i ies he po en ial risk o he e us

Nurs ng Mothers

is no known whe her dorzolamide is excre ed in human milk imolol malea e has been de ec ed in human milk ollowing oral and oph halmic drug adminis ra ion Because o he po en ial or serious adverse reac ions rom Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion in nursing in an s a decision should be made whe her o discon inue nursing or o discon inue he drug aking in o accoun he impor ance o he drug o he mo her

Ped atr c Use

he sa e y and e ec iveness o dorzolamide hydrochloride oph halmic solu ion and imolol malea e oph halmic solu ion have been es ablished when adminis ered individually in pedia ric pa ien s aged 2 years and older Use o hese drug produc s in hese children is suppor ed by evidence rom adequa e and well-con rolled s udies in children and adul s Sa e y and e icacy in pedia ric pa ien s below he age o 2 years have no been es ablished

Ger atr c Use

No overall di erences in sa e y or e ec iveness have been observed be ween elderly and younger pa ien s

ADVERSE REACTIONS

Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion was evalua ed or sa e y in 1035 pa ien s wi h eleva ed in raocular pressure rea ed or open-angle glaucoma or ocular hyper ension Approxima ely 5% o all pa ien s discon inued herapy wi h Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion because o adverse reac ions he mos requen ly repor ed adverse even s were as e perversion (bi er sour or unusual as e) or ocular burning and/or s inging in up o 30% o pa ien s Conjunc ival hyperemia blurred vision super icial punc a e kera i is or eye i ching were repor ed be ween 5-15% o pa ien s he ollowing adverse even s were repor ed in 1-5% o pa ien s abdominal pain back pain blephari is bronchi is cloudy vision conjunc ival discharge conjunc ival edema conjunc ival ollicles conjunc ival injec ion conjunc ivi is corneal erosion corneal s aining cor ical lens opaci y cough dizziness dryness o eyes dyspepsia eye debris eye discharge eye pain eye earing eyelid edema eyelid ery hema eyelid exuda e/scales eyelid pain or discom or oreign body sensa ion glaucoma ous cupping headache hyper ension in luenza lens nucleus colora ion lens opaci y nausea nuclear lens opaci y pharyngi is pos -subcapsular ca arac sinusi is upper respira ory in ec ion urinary rac in ec ion visual ield de ec vi reous de achmen

he ollowing adverse even s have occurred ei her a low incidence (<1%) during clinical rials or have been repor ed during he use o Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion in clinical prac ice where hese even s were repor ed volun arily rom a popula ion o unknown size and requency o occurrence canno be de ermined precisely hey have been chosen or inclusion based on ac ors such as seriousness requency o repor ing possible causal connec ion o Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion or a combina ion o hese ac ors bradycardia cardiac ailure cerebral vascular acciden ches pain choroidal de achmen ollowing il ra ion surgery (see PRECAU ONS General) depression diarrhea dry mou h dyspnea hear block hypo ension iridocycli is myocardial in arc ion nasal conges ion S evens-Johnson syndrome oxic epidermal necrolysis pares hesia pho ophobia respira ory ailure skin rashes uroli hiasis and vomi ing

O her adverse reac ions ha have been repor ed wi h he individual componen s are lis ed below

Dorzolam de - Allerg c/Hypersens t v ty: Signs and symp oms o local reac ions including palpebral reac ions and sys emic allergic reac ions including angioedema bronchospasm pruri us ur icaria *Body as a Whole:* As henia/ a igue *Sk n/Mucous Membranes:* Con ac derma i is epis axis hroa irri a ion *Spec al Senses:* Eyelid crus ing signs and symp oms o ocular allergic reac ion and ransien myopia

T molol (ocular adm n strat on) - Body as a Whole: As henia/ a igue Cardiovascular Arrhy hmia syncope cerebral ischemia worsening o angina pec oris palpi a ion cardiac arres pulmonary edema edema claudica ion Raynaud s phenomenon and cold hands and ee *D gest ve:* Anorexia *Immunolog c* Sys emic lupus ery hema osus *Nervous System/Psych atr c:* ncrease in signs and symp oms o myas henia gravis somnolence insomnia nigh mares behavioral changes and psychic dis urbances including con usion hallucina ions anxie y disorien a ion nervousness and memory loss *Sk n:* Alopecia psoriasi orm rash or exacerba ion o psoriasis *Hypersens t v ty* Signs and symp oms o sys emic allergic reac ions including anaphylaxis angioedema ur icaria and localized and generalized rash *Resp ratory* Bronchospasm (predominan ly in pa ien s wi h pre-exis ing bronchospas ic disease) *Endocr ne:* Masked symp oms o hypoglycemia in diabe ic pa ien s (see WARN NGS) *Spec al Senses* P osis decreased corneal sensi ivi y cys oid macular edema visual dis urbances including re rac ive changes and diplopia pseudopemphigoid and inni us *Urogen tal* Re roperi oneal ibrosis decreased libido impo ence and Peyronie s disease

he ollowing addi ional adverse e ec s have been repor ed in clinical experience wi h ORAL imolol malea e or o her ORAL be a-blocking agen s and may be considered po en ial e ec s o oph halmic imolol malea e *Allerg c* Ery hema ous rash ever combined wi h aching and sore hroa laryngospasm wi h respira ory dis ress *Body as a Whole:* Ex remi y pain decreased exercise olerance weigh loss *Card ovascular* Worsening o ar erial insu iciency vasodila a ion *D gest ve* Gas roin es inal pain hepa omegaly mesen eric ar erial hrombosis ischemic coli is *Hematolog c* Non hrombocy openic purpura hrombocy openic purpura agranulocy osis *Endocr ne* Hyperglycemia hypoglycemia Skin Pruri us skin irri a ion increased pigmen a ion swea ing *Musculoskeletal* Ar hralgia *Nervous System/Psych atr c* Ver igo local weakness diminished concen ra ion reversible men al depression progressing o ca a onia an acu e reversible syndrome charac erized by disorien a ion or ime and place emo ional labili y sligh ly clouded sensorium and decreased per ormance on neuropsychome rics *Resp ratory* Rales bronchial obs ruc ion *Urogen tal* Urina ion di icul ies

OVERDOSAGE

here are no human da a available on overdosage wi h Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion

Symp oms consis en wi h sys emic adminis ra ion o be a-blockers or carbonic anhydrase inhibi ors may occur including elec roly e imbalance developmen o an acido ic s a e dizziness headache shor ness o brea h bradycardia bronchospasm cardiac arres and possible cen ral nervous sys em e ec s Serum elec roly e levels (par icularly po assium) and blood pH levels should be moni ored (see also ADVERSE REAC ONS)

A s udy o pa ien s wi h renal ailure showed ha imolol did no dialyze readily

DOSAGE AND ADMINISTRATION

he dose is one drop o Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion in he a ec ed eye(s) wo imes daily

more han one opical oph halmic drug is being used he drugs should be adminis ered a leas en minu es apar (see also PRECAU ONS Drug n erac ions)

HOW SUPPLIED

Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion is a clear colorless o nearly colorless sligh ly viscous solu ion

Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion is supplied in 10 mL whi e LDPE bo les wi h pierced dropper ips and whi e shor skir caps as ollows

NDC 17478-514-11 10 mL

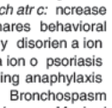
Storage S ore a 20° o 25°C (68° o 77°) [see USP Con rolled Room empera ure

Protect rom light.

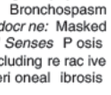
INSTRUCTIONS FOR USE

Please ollow hese ins ruc ions care ully when using Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion Use Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion as prescribed by your doc or

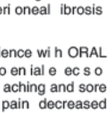
1 you use o her opically applied oph halmic medica ions hey should be adminis ered a leas 10 minu es be ore or a er Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion



2 Wash hands be ore each use

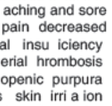


3 Be ore using he medica ion or he irs ime be sure he plas ic sealing ape be ween he bo le and he cap is unbroken (ig 1)



4 o break he seal and open he bo le unscrew he cap by urning as indica ed by he arrow (ig 2)

5 il your head back and pull your lower eyelid down sligh ly o orm a pocke be ween your eyelid and your eye (ig 3)



6 nver he bo le and press ligh ly (as shown in ig 4) un il a single drop is dispensed in o he eye as direc ed by your doc or

Reference ID: 3408444

DO NO OUCH YOUR EYE OR EYEL D W H HE DROPPER P

OPH HALM C MED CA ONS HANDLED MPROPERLY CAN BECOME CON AM NA ED BY COMMON BAC ER A KNOWN O CAUSE EYE N EC ONS SER OUS DAMAGE O HE EYE AND SUBSEQUEN LOSS O V S ON MAY RESUL ROM US NG CON AM NA ED OPH HALM C MED CA ONS YOU H NK YOUR MED CA ON MAY BE CON AM NA ED OR YOU DEVELOP AN EYE N EC ON CON AC YOUR DOC OR MMED A ELY CONCERN NG CON NUED USE O H S BO LE

7 Repea s eps 5 & 6 wi h he o her eye i ins ruc ed o do so by your doc or

8 Replace he cap by urning un il i is irmly ouching he bo le Do no over igh en he cap

9 he dispenser ip is designed o provide a single drop here ore do NO enlarge he hole o he dispenser ip

10 A er you have used all doses here will be some Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion le in he bo le You should no be concerned since an ex ra amoun o Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion has been added and you will ge he ull amoun o Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion ha your doc or prescribed Do no a emp o remove excess medicine rom he bo le

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Lake ores L 60045

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DO NO OUCH YOUR EYE OR EYEL D W H HE DROPPER P

OPH HALM C MED CA ONS HANDLED MPROPERLY CAN BECOME CON AM NA ED BY COMMON BAC ER A KNOWN O CAUSE EYE N EC ONS SER OUS DAMAGE O HE EYE AND SUBSEQUEN LOSS O V S ON MAY RESUL ROM US NG CON AM NA ED OPH HALM C MED CA ONS YOU H NK YOUR MED CA ON MAY BE CON AM NA ED OR YOU DEVELOP AN EYE N EC ON CON AC YOUR DOC OR MMED A ELY CONCERN NG CON NUED USE O H S BO LE

7 Repea s eps 5 & 6 wi h he o her eye i ins ruc ed o do so by your doc or

8 Replace he cap by urning un il i is irmly ouching he bo le Do no over igh en he cap

9 he dispenser ip is designed o provide a single drop here ore do NO enlarge he hole o he dispenser ip

10 A er you have used all doses here will be some Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion le in he bo le You should no be concerned since an ex ra amoun o Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion has been added and you will ge he ull amoun o Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion ha your doc or prescribed Do no a emp o remove excess medicine rom he bo le

Can I use Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution with other medicines?

ell your doc or or pharmacis abou all drugs ha you are using or plan o use his includes o her eye drops and drugs ob ained wi hou a prescrip ion his is par icularly impor an i you are aking medicine o lower blood pressure or o rea hear disease or i you are aking large doses o aspirin

Ask your doc or s advice abou aking Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion i you are also using

- oral carbonic anhydrase inhibi ors (or example ace azolamide Diamox®)
- oral be a-blockers (or example propranolol nderal®)
- calcium an agonis s (or example ni edipine Procardia®)
- ca echolamine-deple ing drugs (or example reserpine)
- digi alis in combina ion wi h calcium an agonis s (or example Lanoxin® wi h Procardia®)
- quinidine (or example Cardioquin®)
- clonidine (or example Ca apres®)
- injec able epinephrine (or example EpiPen®)
- SSR s (or example Prozac®)

Your doc or or pharmacis can ell you i any o he drugs you are using are in he above lis

What are the possible side e ects o Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution?

Any medicine may have unin ended or undesirable e ec s hese are called side e ec s Side e ec s may no occur bu i hey do occur you may need medical a en ion he mos common side e ec s you may experience are

- eye symp oms such as burning and s inging redness o he eye(s) blurred vision earing or i ching
- a bi er sour or unusual as e a er pu ing in your eye drops

O her side e ec s may occur rarely and some o hese may be serious ell your doc or righ away i you experience

- shor ness o brea h
- visual changes
- an irregular hear bea and/or a slowing o your hear ra e
- severe skin reac ions

he above lis is NO a comple e lis o side e ec s repor ed wi h Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion Your doc or can discuss wi h you a more comple e lis o side e ec s Please ell your doc or [or pharmacis promp ly abou any o hese or any o her unusual symp om

What should I do in case o an overdose?

you swallow he con en s o he bo le con ac your doc or immedia ely Among o her e ec s you may eel ligh -headed have di icul y brea hing or eel your hear ra e has slowed

How should I store Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution?

Keep your medicine in a sa e place where children canno reach i S ore Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion a 20° o 25°C (68° o 77°) [see USP Con rolled Room empera ure Pro ec rom ligh Do no use your medicine a er he expira ion da e on he bo le

What else should I know about Dorzolamide Hydrochloride-Timolol Maleate Ophthalmic Solution?

Do no use Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion or a condi ion or which i was no prescribed Do no give Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion o o her people even i hey have he same condi ion you have may harm hem

Inactive ingredients

he inac ive ingredien s o Dorzolamide Hydrochloride- imolol Malea e Oph halmic Solu ion are hydroxye hylcellulose manni ol sodium ci ra e sodium hydroxide wa er or injec ion and benzalkonium chloride added as a preserva ive

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Lake ores L 60045

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLEN E HWANG
11/18/2013

JOHN F GRACE
11/18/2013