

PACKAGE INSERT FOR GLAUMIDE-CO OPHTHALMIC SOLUTION

SCHEDULING STATUS S3

PROPRIETARY NAME AND DOSAGE FORM

Glaumide-Co Ophthalmic Solution

COMPOSITION

Each ml of GLAUMIDE-CO Ophthalmic Solution contains 22,26 mg dorzolamide hydrochloride equivalent to 20 mg dorzolamide base and 6,83 mg timolol maleate equivalent to 5,0 mg timolol base.

Preservative : Benzalkonium chloride 0,0075 % *m/v*.

Other ingredients are: hydroxyethylcellulose, mannitol, sodium citrate dihydrate and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A. 15.4 Ophthalmic Preparations, other.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

GLAUMIDE-CO contains dorzolamide hydrochloride and timolol maleate.

Dorzolamide hydrochloride and timolol maleate both decrease aqueous humour secretions and thus intraocular pressure, but do so by different modes of action.

Dorzolamide hydrochloride:

Dorzolamide hydrochloride is a carbonic anhydrase inhibitor used topically in the management of open-angle glaucoma and ocular hypertension. Carbonic anhydrase is an enzyme which is widely distributed throughout the body including the eyes. Carbonic anhydrase catalyses the rapid conversion of carbon dioxide and water to hydrogen and carbonate ions. Carbonic anhydrase inhibitors thus reduce the formation of hydrogen and bicarbonate ions from carbon dioxide and water by non-competitive, reversible inhibition of carbonic anhydrase, thereby reducing the availability of these ions for active transport into secretions.

In humans, carbonic anhydrase exists in several isoforms (isoenzymes).

Carbonic anhydrase II (CA-II) is the most active isoform of the enzyme, found primarily in erythrocytes (red blood cells) but also in other tissues including the secretory cells of the ciliary process, where its main function is to regulate the secretion of aqueous humour.

Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour secretion, probably by slowing the formation of bicarbonate ions with a subsequent reduction in sodium and fluid transport and thus intra-ocular pressure.

Timolol maleate:

Timolol maleate, a non-selective beta-adrenergic receptor blocker, reduces intraocular pressure by decreasing the production of aqueous humour.

The combined effect of dorzolamide hydrochloride and timolol maleate results in additional intraocular pressure reduction compared to either component administered alone.

Pharmacokinetic properties:

Dorzolamide hydrochloride:

Following topical application, dorzolamide hydrochloride reaches the systemic circulation.

During chronic dosing, dorzolamide hydrochloride accumulates in erythrocytes as a result of selective binding to carbonic anhydrase II (CA-II), while a low concentration of free dorzolamide in the plasma is maintained.

Dorzolamide hydrochloride is metabolised in the liver by cytochrome P-450 isoenzymes to form N-desethyldorzolamide hydrochloride, which inhibits CA-II less potently than the dorzolamide hydrochloride but also inhibits carbonic anhydrase I (CA-I). The metabolite also accumulates in erythrocytes where it binds primarily to CA-I.

Plasma protein binding of dorzolamide hydrochloride is approximately 33 %. While both dorzolamide and its metabolite are excreted in urine, it is excreted principally (about 80 %) unchanged.

Following discontinuation of the medicine, dorzolamide hydrochloride is eliminated from the erythrocytes in a nonlinear manner with an initial rapid decline of dorzolamide concentration, followed by a slower elimination phase with a half-life of approximately 120 days.

Timolol maleate:

In a study of plasma timolol concentration, the systemic exposure to timolol was determined following a twice daily topical administration of timolol maleate ophthalmic solution 0,5 %. The mean peak plasma concentration following the morning dosing was 0,46 ng/ml and following the afternoon dosing was 0,35 ng/ml.

INDICATIONS

GLAUMIDE-CO is indicated in the treatment of elevated intra-ocular pressure in patients with:

- ocular hypertension.
- open angle glaucoma.
- pseudoexfoliative glaucoma and other secondary open-angle glaucomas when concurrent therapy is appropriate.

CONTRA-INDICATIONS

- Hypersensitivity to dorzolamide hydrochloride, timolol maleate or any of the ingredients of GLAUMIDE-CO.
- Bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- Sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, cardiogenic shock.
- Pregnancy and lactation.
- Safety and efficacy in children has not been established.

(See WARNINGS AND SPECIAL PRECAUTIONS)

WARNINGS AND SPECIAL PRECAUTIONS

As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.

The preservative in GLAUMIDE-CO, benzalkonium chloride, may be absorbed by soft contact lenses.

GLAUMIDE-CO should therefore not be administered while wearing soft contact lenses.

Remove lenses before administration and re-insert 15 minutes after application of the drops.

Immunology and Hypersensitivity:

GLAUMIDE-CO contains dorzolamide hydrochloride which is a sulphonamide and topical administration can result in systemic absorption. Side-effects pertaining to sulphonamides may be experienced. These include Stevens-Johnson Syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anaemia and other blood dyscrasias. If signs of serious reactions or hypersensitivity occur, discontinue the use of GLAUMIDE-CO.

In clinical studies, local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of ophthalmic solutions containing dorzolamide hydrochloride (as contained in GLAUMIDE-CO). Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of therapy. If such reactions occur, treatment with GLAUMIDE-CO should be discontinued and the patient evaluated before restarting the medicine.

While taking beta-blockers, including timolol (as contained in GLAUMIDE-CO), patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to accidental, diagnostic, or therapeutic repeated challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions.

Concomitant Therapy:

There is a potential for an additive effect on the systemic effects of the inhibition of carbonic anhydrase in patients taking an oral carbonic anhydrase inhibitor and GLAUMIDE-CO concomitantly.

The concomitant administration of GLAUMIDE-CO and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

Patients who are currently receiving treatment with a beta-adrenergic blocker and who are given GLAUMIDE-CO should be observed for a possible additive effect either on the intraocular pressure or on the known systemic effects of beta-blockade. The use of two topical beta-adrenergic blocking agents is not recommended.

(See INTERACTIONS)

Cardio-respiratory reactions:

GLAUMIDE-CO may be absorbed systemically. Timolol maleate is a beta-blocker and therefore the same types of adverse reactions found with systemic administration of beta-blockers may occur with GLAUMIDE-CO.

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

Respiratory and cardiac adverse effects, including death due to bronchospasm in patients with asthma and death in association with cardiac failure, have been reported following administration of ophthalmic solutions containing timolol maleate (as contained in GLAUMIDE-CO).

Renal and Hepatic Impairment:

GLAUMIDE-CO has not been studied in patients with severe renal impairment (CrCl less than 30 millilitre/min). Due to dorzolamide hydrochloride and its metabolite being excreted primarily by the kidney, GLAUMIDE-CO is not recommended in such patients. GLAUMIDE-CO has not been studied in patients with hepatic impairment.

Use in Elderly:

No differences in efficacy or safety were observed between older patients and younger patients, but greater sensitivity of some of the older individuals cannot be ruled out.

Other:

GLAUMIDE-CO has not been studied in patients with acute angle-closure glaucoma. The management of patients with acute angle-closure glaucoma requires therapeutic intervention in addition to ocular hypotensive agents. Choroidal detachment has been observed with the use of aqueous suppressant therapy (e.g. timolol, acetazolamide, dorzolamide hydrochloride) after filtration procedures.

Effects on ability to drive and use machines:

GLAUMIDE-CO causes visual disturbances. Patients should be advised not to drive or operate machines until their vision is clear.

INTERACTIONS

Specific interaction studies with GLAUMIDE-CO have not been performed. However, in clinical studies dorzolamide-timolol ophthalmic solution was used concomitantly with the following medicines without evidence of adverse interactions: ACE-Inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs (including aspirin), hormones (e.g. oestrogen, insulin, thyroxine).

However there is a potential for additive effects and the development of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution and oral calcium channel blockers, catecholamine-depleting medicines or beta-adrenergic blocking medicines are used concurrently.

Dorzolamide hydrochloride is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In clinical studies, dorzolamide hydrochloride ophthalmic solution was not associated with acid-base disturbances. However these disturbances have been reported with oral carbonic anhydrase inhibitors and have in some cases resulted in interactions (e.g. toxicity associated with high-dose salicylate therapy). Thus the potential for such interactions in patients using GLAUMIDE-CO should be considered.

Oral beta-adrenergic blocking agents (such as contained in GLAUMIDE-CO) may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

Potentiated systemic beta-blockade (e.g. decreased heart rate) has been observed during concurrent treatment with quinidine and timolol (as contained in GLAUMIDE-CO), possibly as quinidine inhibits the metabolism of timolol via the P450 enzyme, CYP2D6.

PREGNANCY AND LACTATION

(See CONTRA-INDICATIONS)

The safety of GLAUMIDE-CO in pregnant and lactating women has not been established.

There are no adequate and controlled studies in pregnant women.

According to studies timolol maleate is excreted into human milk.

DOSAGE AND DIRECTIONS FOR USE

Benzalkonium chloride is known to cause eye irritation, discolour soft lenses and may be absorbed by soft contact lenses. Patients wearing soft contact lenses should be instructed to remove their lenses prior to using GLAUMIDE-CO and to wait at least 15 minutes after instilling GLAUMIDE-CO to insert soft contact lenses (See WARNINGS AND SPECIAL PRECAUTIONS).

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

The dose is one drop of GLAUMIDE-CO in the affected eye(s) two times a day.

When substituting GLAUMIDE-CO for another ophthalmic anti-glaucoma medicine, discontinue the other medicine after proper dosing on one day, and start GLAUMIDE-CO on the next day.

SIDE EFFECTS

The following adverse reactions have been reported with GLAUMIDE-CO ophthalmic solution.

Adverse reactions marked with an asterisk (*) were also observed with dorzolamide-timolol ophthalmic solution during post marketing experience.

Eye disorders:

GLAUMIDE-CO:

Frequent: Burning and stinging, conjunctival injection, blurred vision, tearing, corneal erosion, ocular itching.

Dorzolamide hydrochloride ophthalmic solution:

Frequent: Eyelid irritation, superficial punctuate keratitis, eyelid inflammation.

Less frequent: Iridocyclitis, transient myopia, eyelid crusting, signs and symptoms of local reactions including palpebral reaction, choroidal detachment (following filtration surgery).

Timolol maleate ophthalmic solution:

Frequent: Conjunctivitis, signs and symptoms of ocular irritation including blepharitis, keratitis, decreased corneal sensitivity, dry eyes.

Less frequent: Visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, choroidal detachment (following filtration surgery)*, ptosis.

Immune system disorders:

Dorzolamide hydrochloride ophthalmic solution:

Less frequent: Systemic allergic reactions including urticaria, angioedema, pruritus and bronchospasm.

Timolol maleate ophthalmic solution:

Less frequent: Systemic lupus erythematosus, signs and symptoms of allergic reactions including anaphylaxis, localised and generalised rash, urticaria and angioedema.

Ear and labyrinth disorders:

Timolol maleate ophthalmic solution:

Less frequent: Tinnitus.

Nervous system disorders:

Dorzolamide hydrochloride ophthalmic solution:

Frequent: Headache.

Less frequent: Paraesthesia, dizziness.

Timolol maleate ophthalmic solution:

Frequent: Headache.

Less frequent: Depression, dizziness, syncope, nightmares, insomnia, paraesthesia, memory loss, increase in signs and symptoms of myasthenia gravis, cerebrovascular accident, decreased libido.

Cardiac disorders:

Timolol maleate ophthalmic solution:

Less frequent: Bradycardia*, palpitation, chest pain, congestive heart failure, dysrhythmia, heart block*, cerebral ischaemia, cold hands and feet, Raynaud's phenomenon, claudication.

Vascular disorders:

Less frequent: Hypotension, oedema.

Respiratory, thoracic and mediastinal disorders:

GLAUMIDE-CO:

Less frequent: Respiratory failure.*

Dorzolamide hydrochloride ophthalmic solution:

Less frequent: Epistaxis.

Timolol maleate ophthalmic solution:

Less frequent: Dyspnoea*, cough, bronchospasm (predominantly in patients with pre-existing bronchospastic disease).

Gastro-intestinal disorders:

GLAUMIDE-CO:

Frequent: Taste perversion.

Dorzolamide hydrochloride ophthalmic solution:

Frequent: Nausea.*

Less Frequent: Dry mouth, throat irritation.

Timolol maleate ophthalmic solution:

Less frequent: Dyspepsia, nausea*, dry mouth, diarrhoea.

Skin and subcutaneous tissue disorders:

GLAUMIDE-CO:

Less frequent: Contact dermatitis.*

Dorzolamide hydrochloride ophthalmic solution:

Less frequent: Rash.

Timolol maleate ophthalmic solution:

Less frequent: Exacerbation of psoriasis or psoriasiform rash or, alopecia.

Renal and urinary disorders:

GLAUMIDE-CO:

Less frequent: Urolithiasis.

Reproductive system and breast disorders:

Timolol maleate ophthalmic solution:

Less frequent: Peyronie's disease.

General disorders and administrative site disorders:

Dorzolamide hydrochloride ophthalmic solution:

Frequent: Fatigue/asthenia.

Timolol maleate ophthalmic solution:

Less frequent: Fatigue/asthenia.

Laboratory findings:

GLAUMIDE-CO was not associated with clinically meaningful electrolyte disturbances.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

(See SIDE-EFFECTS)

Overdosage of dorzolamide hydrochloride can be expected to result in electrolyte imbalances, systemic acidosis and possibly central nervous system effects.

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

Treatment is supportive and symptomatic.

Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol maleate does not dialyse readily.

IDENTIFICATION

GLAUMIDE-CO is a slightly opalescent, nearly colourless, slightly viscous solution.

PRESENTATION

Cardboard carton containing a sterile, white, 10 ml, low density polyethylene container with a sterile, white low density polyethylene under-cap dropper and a sterile, white high density polyethylene cap.

Each container contains 5 ml of GLAUMIDE-CO ophthalmic solution.

STORAGE INSTRUCTIONS

Store at or below 25 °C in a well closed container.

Protect from light.

Do not remove the container from the carton until required for use.

Do not use more than 28 days after opening.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

46/15.4/0684

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Actor Pharma (Pty) Ltd¹

Unit 7, Royal Palm Business Estate

646 Washington Street

Halfway House, Midrand, 1685

Gauteng, South Africa

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