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PROFESSIONAL INFORMATION FOR GLAUMIDE-CO OPHTHALMIC SOLUTION

SCHEDULING STATUS **S3**

1. NAME OF THE MEDICINE

Glaumide-Co 20 mg/ml + 5 mg/ml Ophthalmic Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of GLAUMIDE-CO Ophthalmic Solution contains 22,26 mg dorzolamide hydrochloride equivalent to 20,00 mg dorzolamide base and 6,83 mg timolol maleate equivalent to 5,00 mg timolol base.

Excipient with known effect:

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

For full list of excipients, see section 6.1.

3. PHARMACEUTIAL FORM

Ophthalmic solution.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Ocular hypertension.
- Open-angle glaucoma.
- Pseudoexfoliative glaucoma and other secondary open-angle glaucomas when concurrent therapy is appropriate.

4.2 Posology and method of administration

Posology:

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

Administration:

If more than one topical ophthalmic medicine is being used, the medicines should be administered at least 10 minutes apart.

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.

4.3 Contraindications

- 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 section 4.4)

4.4 Special warnings and precautions for use

The preservative in GLAUMIDE-CO, 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

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.

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 dyscrasis. 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 section 4.5).

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 millimetre/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.

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

(See section 4.3)

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.

4.7 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.

4.8 Undesirable 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.

GLAUMIDE-CO:	
Eye disorders:	
Frequent:	Burning and stinging, conjunctival injection, blurred vision, tearing, corneal erosion, ocular itching.
Respiratory, thoracic and mediastinal disorders:	
Less frequent:	Respiratory failure.*
Gastrointestinal disorders:	
Frequent:	Taste perversion.
Skin and subcutaneous tissue disorders:	
Less frequent:	Contact dermatitis.*
Renal and urinary disorders:	
Less frequent:	Urolithiasis.

***Dorzolamide hydrochloride ophthalmic solution*:**	
Eye disorders:	
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).
Immune system disorders:	
Less frequent:	Systemic allergic reactions including urticaria, angioedema, pruritus and bronchospasm.
Nervous system disorders:	
Frequent:	Headache.
Less frequent:	Paraesthesia, dizziness.
Respiratory, thoracic and mediastinal disorders:	

Less frequent:	Epistaxis.
Gastrointestinal disorders:	
Frequent:	Nausea.*
Less frequent:	Dry mouth, throat irritation.
Skin and subcutaneous tissue disorders:	
Less frequent:	Rash.
General disorders and administration site conditions:	
Frequent:	Fatigue/asthenia.

***Timolol maleate ophthalmic solution*:**	
Eye disorders:	
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:	
Less frequent:	Systemic lupus erythematous, signs and symptoms of allergic reactions including anaphylaxis, localised and generalised rash, urticaria and angioedema.
Ear and labyrinth disorders:	
Less frequent:	Tinnitus.
Nervous system disorders:	
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:	
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:	
Less frequent:	Dyspnoea*, cough, bronchospasm (predominantly in patients with pre-existing bronchospastic disease).

Gastrointestinal disorders:	
Less frequent:	Dyspepsia, nausea*, dry mouth, diarrhoea.
Skin and subcutaneous tissue disorders:	
Less frequent:	Exacerbation of psoriasis or psoriasiform rash or, alopecia.
Reproductive system and breast disorders:	
Less frequent:	Peyronie's disease.
General disorders and administration site conditions:	
Less frequent:	Fatigue/asthenia.

Laboratory findings:

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

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A.15.4 Ophthalmic preparations, other.

5.1 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 intraocular 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.

5.2 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

hydroxyethylcellulose
mannitol
sodium citrate dihydrate
water for injection
Preservative: 0,0075 % *m/v* benzalkonium chloride.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 2 years
Do not use more than 28 days after opening.

6.4 Special precautions for storage

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.
KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

No special requirements.
An unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Gen-Eye (Pty) Ltd[1]
Unit 7, Royal Palm Business Estate
646 Washington Street
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8. REGISTRATION NUMBER

46/15.4/0684

9. DATE OF FIRST AUTHORISATION

16 September 2015

10. DATE OF REVISION OF THE TEXT

Date of the most recently revised package insert as approved by SAHPRA: 07 October 2021

[1] Company Registration number: 2009/009360/07

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