PROFESSIONAL INFORMATION FOR GLAUTIDOR

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

GLAUTIDOR 20 mg/mL + 5 mg/mL eye drops.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 22,3 mg dorzolamide hydrochloride equivalent to 20 mg dorzolamide and 6,8 mg timolol maleate equivalent to 5 mg timolol.

Contains preservative (Benzalkonium chloride 0,0075 % *m/v*).

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Clear, colourless to nearly colourless, slightly viscous solution free from visible particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

GLAUTIDOR is indicated in the treatment of elevated intra-ocular pressure (IOP) in patients with ocular hypertension, open-angle glaucoma, pseudo-exfoliative glaucoma or other secondary open-angle glaucomas when concomitant therapy is appropriate.

4.2 Posology and method of administration

Posology:

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

When substituting GLAUTIDOR for another ophthalmic antiglaucoma medicine(s), discontinue the other medicine(s) after proper dosing on one day, and start GLAUTIDOR on the next day.

If another topical ophthalmic medicine is being used, GLAUTIDOR and the other medicine should be administered at least ten minutes apart.

Patients should be instructed to wash their hands before use and avoid allowing the tip of the container to come into contact with the eye or surrounding structures. Patients should also be instructed that ocular solutions, if handled improperly, 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. Patients should be informed of the correct handling of GLAUTIDOR.

Paediatric patients

Safety and efficacy in paediatric patients below the age of 2 years have not been established. GLAUTIDOR has been used in children 2 to 6 years of age, however data on safety and efficacy are insufficient to recommend a safe and effective dose (see section 5.2).

Method of administration

1. Wash your hands.
2. Open the container. Take special care that the tip of the dropper container does not touch your eye, the skin around your eye or your fingers.
3. Tilt your head backwards and hold the container upside down over the eye.
4. Pull the lower eyelid downwards and look up. Hold and gently squeeze the container on the sides of the container and let one drop fall into the space between the lower eyelid and the eye.
5. Press a finger into the corner of your eye, by the nose, or close your eyelids for 2 minutes. This helps to stops the medicine from getting into the rest of the body.
6. Repeat steps 3 to 5 with the other eye if instructed to do so by your doctor.
7. Put the cap back on and close the container tightly.

4.3 Contraindications

GLAUTIDOR is contraindicated in patient with:

- Hypersensitivity to dorzolamide, timolol or to any of the excipients listed in section 6.1.
- 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.

The above are based on the components and are not unique to the combination.

GLAUTIDOR contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, GLAUTIDOR should not be administered while wearing these lenses. The lenses should be removed before application of the drops and not be reinserted earlier than 15 minutes after use (see section 4.4).

Pregnancy

There are no adequate and well-controlled studies in pregnant women (see section 4.6).

4.4 Special warnings and precautions for use

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.

Cardio-respiratory reactions

GLAUTIDOR may be absorbed systemically. The timolol component is a beta-

blocker. Therefore, the same types of cardiovascular, pulmonary and other adverse reactions found with systemic administration of beta-blockers may occur with GLAUTIDOR.

Cardiac Disorders:

Because of the timolol maleate component, cardiac failure should be adequately controlled before beginning therapy with GLAUTIDOR. In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers should be critically assessed and the therapy with other active substances should be considered. In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

Due to its negative effect on conduction time, beta-blockers should only be given with caution to patients with first degree heart block.

Respiratory Disorders:

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 administration of timolol maleate ophthalmic solution.

GLAUTIDOR should be used with caution, in patients with mild/moderate chronic obstructive pulmonary disease (COPD).

Vascular Disorders:

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Immunology and hypersensitivity

GLAUTIDOR may be absorbed systemically. The dorzolamide component is a

sulfonamide. Therefore, the same types of adverse reactions found with systemic administration of sulfonamides may occur with GLAUTIDOR, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue use of this preparation.

Local ocular adverse effects, primarily conjunctivitis and lid reactions, were reported with chronic administration of dorzolamide hydrochloride ophthalmic solution. Some of these reactions had the clinical appearance and course of an allergic-type reaction that resolved upon discontinuation of therapy. Similar reactions have been reported with GLAUTIDOR. If such reactions are observed, discontinuation of treatment with GLAUTIDOR should be considered.

While taking beta-blockers, including timolol, as in GLAUTIDOR, 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 adrenaline (epinephrine) used to treat anaphylactic reactions.

Renal and hepatic impairment

GLAUTIDOR has not been studied in patients with severe renal impairment (CrCl less than 30 mL/min). Because dorzolamide hydrochloride and its metabolite are excreted predominantly by the kidney, GLAUTIDOR is not recommended in such patients.

GLAUTIDOR has not been studied in patients with hepatic impairment and should therefore, be used with caution in such patients.

Withdrawal of therapy

As with systemic beta-blockers, if discontinuation of ophthalmic timolol is needed in

patients with coronary heart disease, therapy should be withdrawn gradually.

Additional effects of beta-blockade

Hypoglycaemia/diabetes:

Beta-blockers should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile diabetes, as beta-blockers may mask the signs and symptoms of acute hypoglycaemia.

Hypothyroidism:

Beta-blockers may also mask the signs of hyperthyroidism. Abrupt withdrawal of beta-blocker therapy may precipitate a worsening of symptoms.

Corneal diseases:

Ophthalmic beta-blockers may induce dryness of eyes. Patients with corneal diseases should be treated with caution.

Surgical anaesthesia:

Beta-blocking ophthalmological preparations may block systemic beta-agonist effects e.g. of adrenaline (epinephrine). The anaesthesiologist should be informed when the patient is receiving timolol.

Myasthenia gravis:

Therapy with beta-blockers may aggravate symptoms of myasthenia gravis.

Additional effects of carbonic anhydrase inhibition

Therapy with oral carbonic anhydrase inhibitors has been associated with urolithiasis as a result of acid-base disturbances, especially in patients with a prior history of renal calculi. Although no acid-base disturbances have been observed with this medicine, urolithiasis has been reported infrequently. Because GLAUTIDOR contains a topical carbonic anhydrase inhibitor that is absorbed systemically, patients

with a prior history of renal calculi may be at increased risk of urolithiasis while using this medicine.

Use in the Elderly

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

Use in the paediatric population

See section 5.2.

Other

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive medicines. GLAUTIDOR has not been studied in patients with acute angle-closure glaucoma.

Corneal oedema and irreversible corneal decompensation have been reported in patients with pre-existing chronic corneal defects and/or a history of intra-ocular surgery while using dorzolamide. There is an increased potential for developing corneal oedema in patients with low endothelial cell counts. Precautions should be used when prescribing GLAUTIDOR to these groups of patients.

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

Diminished responsiveness to ophthalmic timolol maleate after prolonged therapy has been reported in some patients. However, no significant difference in mean intra-ocular pressure has been observed after initial stabilisation.

Excipient warnings:

GLAUTIDOR contains 0,075 mg benzalkonium chloride in each mL. Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Patients should remove contact lenses before using GLAUTIDOR and put them back 15 minutes afterwards. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. GLAUTIDOR should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

4.5 Interaction with other medicines and other forms of interaction

Specific interaction studies have not been performed with GLAUTIDOR.
In studies, dorzolamide/timolol eye drops were used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory drugs including aspirin, and hormones (e.g., oestrogen, insulin, thyroxine).

However, the potential exists for additive effects and production of hypotension and/or marked bradycardia when timolol maleate ophthalmic solution is administered together with oral calcium channel blockers, catecholamine-depleting medicines or beta-adrenergic blocking medicines, antidysrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, guanethidine, narcotics, and monoamine oxidase (MAO) inhibitors.

Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP206 inhibitors (e.g., quinidine, selective serotonin uptake inhibitors such as fluoxetine, paroxetine) and timolol.

The dorzolamide component of GLAUTIDOR is a carbonic anhydrase inhibitor and although administered topically, is absorbed systemically. In 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 resulted in interactions (e.g., toxicity associated with high-dose salicylate therapy).

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving oral and topical carbonic anhydrase inhibitors concomitantly. The concomitant administration of GLAUTIDOR and oral carbonic anhydrase inhibitors have not been studied and is not recommended.

Patients who are already receiving a beta-adrenergic blocking medicine systemically and who are given GLAUTIDOR should be observed for a potential additive effect either on the intra-ocular pressure or on the known systemic effects of beta-blockade. The use of two topical beta-adrenergic blocking medicines is not recommended.

Although GLAUTIDOR alone has little or no effect on pupil size, mydriasis resulting from concomitant use of ophthalmic beta-blockers and adrenaline (epinephrine) has been reported occasionally.

Beta-blockers may increase the hypoglycaemic effect of antidiabetic medicines.

Oral beta-adrenergic blocking medicines may exacerbate the rebound hypertension which can follow the withdrawal of clonidine.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of GLAUTIDOR in pregnant and lactating woman has not been established, and should not be used during pregnancy (see section 4.3).

Dorzolamide:

No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effect at maternotoxic doses (see section 5.3).

Timolol:

There are no adequate data for the use of timolol in pregnant women. Timolol should not be used during pregnancy unless clearly necessary. To reduce the systemic absorption, see section 4.2.

Studies have not revealed malformative effects but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g., bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery. If this medicinal product is administered until delivery, the neonate should be carefully monitored during the first days of life.

Breastfeeding:

The safety of GLAUTIDOR in lactating woman has not been established.
It is not known whether dorzolamide hydrochloride is excreted in human milk. In lactating rats receiving dorzolamide, decreases in the body weight gain of offspring were observed. Beta-blockers are excreted in breast milk.
Timolol maleate does appear in human milk. Because of the potential for serious adverse reactions on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the medicine. If treatment with GLAUTIDOR is required, then lactation is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Possible side effects such as blurred vision may affect some patients' ability to drive and/or operate machinery.

4.8 Undesirable effects

The observed adverse reactions have been consistent with those that were reported

previously with dorzolamide hydrochloride and/or timolol maleate.

During clinical studies approximately 2,4 % of all patients discontinued therapy with dorzolamide/timolol eye drops because of local ocular adverse reactions, approximately 1,2 % of all patients discontinued because of local adverse reactions suggestive of allergy or hypersensitivity (such as lid inflammation and conjunctivitis).

Timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking medicines. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.

Tabulated list of adverse reactions:

System Organ Class	**Formulation**	**Frequency**	**Side effects**
Metabolism and nutrition disorders	Timolol maleate	Frequency unknown	Hypoglycaemia
Psychiatric disorders	Timolol maleate	Less frequent Frequency unknown	Depression* Hallucination, insomnia*, nightmares*
Nervous system disorders	Dorzolamide hydrochloride	Frequent Less frequent	Headache* Dizziness*, paraesthesia*
	Timolol maleate	Frequent Less frequent	Headache* Dizziness*,

			paraesthesia*, memory loss, increase in signs and symptoms of myasthenia gravis, cerebrovascular accident*, cerebral ischaemia
Eye disorders	GLAUTIDOR	Frequent	Burning, stinging, conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing
	Dorzolamide hydrochloride	Frequent	Eyelid inflammation*, eyelid irritation*, superficial punctuate keratitis
		Less frequent	Iridocyclitis*, eyelid crusting*, transient myopia (which resolved upon discontinuation of therapy), choroidal detachment (following filtration surgery)*, signs and symptoms of local reactions including palpebral reaction, irritation including redness*, pain*, corneal

			oedema*, ocular hypotony* Foreign body sensation in eye
	Timolol maleate	Frequent Less frequent Frequency unknown	Signs and symptoms of ocular irritation including blepharitis*, keratitis*, decreased corneal sensitivity, dry eyes*, conjunctivitis Visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases) *, ptosis, diplopia, choroidal detachment (following filtration surgery)* Itching, tearing, redness, blurred vision, corneal erosion
Ear and labyrinth disorders	Timolol maleate	Less frequent	Tinnitus
Cardiac disorders	Timolol maleate	Less frequent	Bradycardia*, syncope*, chest pain*, palpitation*, oedema*, dysrhythmia*,

			congestive heart failure*, heart block*, cardiac arrest* Atrioventricular block, cardiac failure
	Dorzolamide hydrochloride	Frequency unknown	Palpitations
Vascular disorders	Timolol maleate	Less frequent	Hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet*
Respiratory, thoracic and mediastinal disorders	GLAUTIDOR	Frequent Less frequent	Sinusitis Respiratory failure*, shortness of breath, rhinitis, bronchospasm
	Dorzolamide hydrochloride	Less frequent Frequency unknown	Epistaxis* Dyspnoea
	Timolol maleate	Less frequent	Dyspnoea*, bronchospasm (predominantly in patients with pre-existing bronchospastic disease) *, cough*, respiratory failure
Gastrointestinal disorders	GLAUTIDOR	Frequent	Dysgeusia
	Dorzolamide hydrochloride	Frequent	Nausea*

		Less frequent	Dry mouth*, throat irritation*
	Timolol maleate	Less frequent Frequency unknown	Nausea*, dyspepsia*, diarrhoea, dry mouth* Dysgeusia, abdominal pain, vomiting
Skin and subcutaneous tissue disorders	GLAUTIDOR	Less frequent	Contact dermatitis*, Stevens-Johnson syndrome, toxic epidermal necrolysis
	Dorzolamide hydrochloride	Less frequent	Rash*
	Timolol maleate	Less frequent Frequency unknown	Alopecia*, psoriasiform rash or exacerbation of psoriasis* Pruritus, skin rash
Musculoskeletal, and connective tissue disorders	Timolol maleate	Less frequent Frequency unknown	Systemic lupus erythematosus Myalgia
Renal and urinary disorders	GLAUTIDOR	Less frequent	Urolithiasis
Reproductive system and breast disorders	Timolol maleate	Less frequent Frequency	Peyronie's disease*, decreased libido* Sexual dysfunction

		unknown	
General disorders and administration site conditions	Dorzolamide hydrochloride	Frequent Less frequent	Asthenia/fatigue* Systemic allergic reactions including angio-oedema, urticaria, bronchospasm and pruritus
	Timolol maleate	Less frequent	Asthenia/fatigue*, signs and symptoms of allergic reactions including anaphylaxis, angioedema, urticaria, localised and generalised rash

* Adverse reactions marked with an asterisk (*) were also observed with GLAUTIDOR during post-marketing experience.

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

No data is available with regard to human overdosage by accidental or deliberate ingestion of GLAUTIDOR.

Symptoms

There have been reports of inadvertent overdosage with timolol maleate ophthalmic

solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking medicines such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. The most common signs and symptoms to be expected with overdosage of dorzolamide are electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects (see section 4.8).

Only limited information is available with regard to human overdose by accidental or deliberate ingestion of dorzolamide hydrochloride. With oral ingestion, somnolence has been reported. With topical application the following have been reported: nausea, dizziness, headache, fatigue, abnormal dreams, and dysphagia.

Treatment

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

A15.4 Ophthalmic preparations, other.

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking agents, Timolol, combinations, ATC code: S01 ED51

Mechanism of action

GLAUTIDOR is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intra-ocular pressure by reducing aqueous humour secretion, but does so by a different mechanism of action.

Dorzolamide hydrochloride is an inhibitor of human carbonic anhydrase II. Inhibition

of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport. Timolol maleate is a nonselective beta-adrenergic receptor blocking medicine and reduces intra-ocular pressure. The combined effect of these two medicines results in additional intra-ocular pressure reduction compared to either component administered alone.

5.2 Pharmacokinetic Properties

Dorzolamide Hydrochloride

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, medicine and metabolite concentrations in red blood cells (RBCs) and plasma and carbonic anhydrase inhibition in RBCs were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while low concentrations of free medicine in plasma are maintained. The parent medicine forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent agent but also inhibits a less active isoenzyme (CA-I). The metabolite also accumulates in RBCs where it binds primarily to CA-I. Dorzolamide binds moderately to plasma proteins (approximately 33 %). Dorzolamide is primarily excreted unchanged in the urine; the metabolite is also excreted in urine. After dosing ends, dorzolamide washes out of RBCs nonlinearly, resulting in a rapid decline of medicine concentration initially, followed by a slower elimination phase with a half-life of about four months.

Timolol Maleate

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 and following afternoon dosing was 0,35 ng/mL.

Paediatric Use

An ophthalmic solution containing 2 % dorzolamide hydrochloride and 0,5 % timolol has been used in children 2 to 6 years of age whose intra-ocular pressure could not be controlled on monotherapy with a 2 % dorzolamide hydrochloride solution. However, safety and efficacy data with this solution are insufficient to recommend a safe and effective dose.

5.3 Preclinical safety data

The ocular and systemic safety profile of the individual components is well established.

Dorzolamide

In rabbits given maternotoxic doses of dorzolamide associated with metabolic acidosis, malformations of the vertebral bodies were observed.

Timolol

Animal studies have not shown teratogenic effect.

Furthermore, no adverse ocular effects were seen in animals treated topically with dorzolamide hydrochloride and timolol maleate ophthalmic solution or with concomitantly-administered dorzolamide hydrochloride and timolol maleate. *In vitro* and *in vivo* studies with each of the components did not reveal a mutagenic potential. Therefore, no significant risk for human safety is expected with therapeutic doses of GLAUTIDOR .

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Hydroxyethyl cellulose

Mannitol

Sodium citrate

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened container:

24 months.

Opened container:

GLAUTIDOR should not be used longer than 28 days after first opening the container.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the bottle in the outer carton in order to protect from light.

6.5 Nature and contents of container

A 5 mL translucent LDPE bottle with LDPE nozzle, containing 5 mL solution, closed with a dark blue HDPE cap, packed in an outer carton.

Pack size: 1 x 5 mL bottle.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

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Waterford Place

Century City 7441

Cape Town

South Africa

8. REGISTRATION NUMBER

51/15.4/0066

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 12 July 2022