**Approved Professional Information for Medicines for Human Use:**

**DORZOPRES FORTE**

## SCHEDULING STATUS

S3

## 1. NAME OF THE MEDICINE

DORZOPRES FORTE (2,0 + 0,5) % *w/v* Eye drops Solution

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains:

22,26 mg dorzolamide hydrochloride equivalent to 20 mg dorzolamide and

6,83 mg timolol maleate equivalent to 5,0 mg timolol.

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

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Eye drops solution

Slightly opalescent, nearly colourless, slightly viscous solution.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

DORZOPRES FORTE 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 DORZOPRES FORTE in the affected eye(s) two times daily.

**Paediatric population**

Safety and efficacy in paediatric patients below the age of 2 years have not been established. Although DORZOPRES FORTE 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.

**Method of administration**

DORZOPRES FORTE is for ocular use only.

When substituting DORZOPRES FORTE for another ophthalmic antiglaucoma medicine, discontinue the other medicine after proper dosing on one day, and start DORZOPRES FORTE on the next day.

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

**4.3 Contraindications**

- Hypersensitivity to dorzolamide and/or timolol or to any of the excipients listed in section 6.1.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block not controlled with pacemaker, overt cardiac failure, cardiogenic shock
- Severe renal impairment (CrCl < 30 mL/min) or hyperchloraemic acidosis

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

DORZOPRES FORTE contains the preservative benzalkonium chloride, which may be deposited in soft contact lenses; therefore, DORZOPRES FORTE 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.

**4.4 Special warnings and precautions for use**

***Cardiovascular/Respiratory Reactions***

Topically applied ophthalmic medicine timolol is absorbed systemically. Due to beta-adrenergic component, timolol, cardiovascular, pulmonary and other adverse reactions may occur. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration. To reduce the systemic absorption, see section 4.2.

**Cardiac Disorders**

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. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

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

**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.

**Respiratory Disorders**

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers.

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

***Hepatic Impairment***

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

***Immunology and Hypersensitivity***

Topically applied ophthalmic medicines may be absorbed systemically. Dorzolamide contains a sulfonamido group, which also occurs in sulfonamides. Therefore, the same types of adverse reactions found with systemic administration of sulfonamides may occur with topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions or hypersensitivity occur, discontinue use of DORZOPRES FORTE.

Local ocular adverse effects, similar to those observed with dorzolamide hydrochloride eye drops, have been seen with DORZOPRES FORTE. If such reactions occur, discontinuation of DORZOPRES FORTE should be considered.

While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and may be unresponsive to the usual dose of adrenaline used to treat anaphylactic reactions.

***Concomitant Therapy***

The effect on intra-ocular pressure or the known effects of systemic beta-blockade may be potentiated when timolol as contained in DORZOPRES FORTE is given to the patients already receiving a systemic beta-blocking medicine. The response of these patients should be closely observed. The use of two topical beta-adrenergic blocking medicines is not recommended (see section 4.5).

The use of dorzolamide as contained in DORZOPRES FORTE and oral carbonic anhydrase inhibitors is not recommended.

***Withdrawal of Therapy***

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. 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. The anaesthesiologist should be informed when the patient is receiving timolol.

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 DORZOPRES FORTE 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 DORZOPRES FORTE.

***Other***

The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive medicines. This medicine 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 intraocular 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 DORZOPRES FORTE to these groups of patients.

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

Diminished responsiveness to ophthalmic timolol maleate after prolonged therapy has been reported in some patients. However, in clinical studies in which 164 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilisation.

**Paediatric population**

See section 5.1.

**Excipients: Benzalkonium chloride**

DORZOPRES FORTE contains 0,075 mg benzalkonium chloride (a preservative) in each mL of eye drop solution which is equivalent to 0,0075 % *(m/v).*

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.

**Contact Lens Use**

DORZOPRES FORTE contains the preservative benzalkonium chloride, which may cause eye irritation. Remove contact lenses prior to application and wait at least 15 minutes before reinsertion. Benzalkonium chloride is known to discoloursoft contact lenses.

**4.5 Interaction with other medicines and other forms of interaction**

Specific medicine interaction studies have not been performed with DORZOPRES FORTE.

In clinical studies, dorzolamide and timolol was used concomitantly with the following systemic medications without evidence of adverse interactions: ACE-inhibitors, calcium channel blockers, diuretics, non-steroidal anti-inflammatory medicines including aspirin, and hormones (e.g. oestrogen, insulin, thyroxine).

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when ophthalmic beta-blockers solution is administered concomitantly 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 CYP2D6 inhibitors (e.g. quinidine, selective serotonin uptake inhibitors such as fluoxetine, paroxetine) and timolol.

Although DORZOPRES FORTE 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**

DORZOPRES FORTE should not be used during pregnancy.

The safety of DORZOPRES FORTE in pregnant women has not been established (see section 4.3).

*Dorzolamide*

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

*Timolol*

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

**Breastfeeding**

It is not known whether dorzolamide is excreted in human 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 DORZOPRES FORTE.

**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, dizziness and syncope which may affect some patients' ability to drive and/or operate machinery.

**4.8 Undesirable effects**

In clinical studies, the observed adverse reactions have been consistent with those that were reported previously with dorzolamide hydrochloride and/or timolol maleate.

During clinical studies, 1035 patients were treated with dorzolamide hydrochloride and/or timolol maleate. Approximately 2,4 % of all patients discontinued therapy with this medicine 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 adverse drug reactions (ADRs) after topical ophthalmic administration is lower than for systemic administration.

The table below shows all ADRs observed during clinical trials and postmarket spontaneous reports.

| **System Organ Class** | **Formulation** | **Frequency** | | |
|---|---|---|---|---|
| | | **Frequent** | **Less Frequent** | **Not known** |
| Immune system disorders | DORZOPRES FORTE | | Signs and symptoms of systemic allergic | |

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|---|---|---|---|---|
| | | | reactions, including angioedema, urticaria, pruritus, rash, anaphylaxis | |
| | Timolol maleate eye drops, solution | | Signs and symptoms of allergic reactions including angioedema, urticaria, localised and generalised rash, anaphylaxis | Pruritus |
| Metabolism and nutrition disorders | Timolol maleate eye drops, solution | | | Hypoglycaemia |
| Psychiatric disorders | Timolol maleate eye drops, solution | | Depression* insomnia*, nightmares*, memory loss | Hallucination |
| Nervous system disorders | Dorzolamide hydrochloride eye drops, solution | Headache* | Dizziness*, paraesthesia* | |

| | | | | |
|---|---|---|---|---|
| | Timolol maleate eye drops, solution | Headache* | Dizziness*, syncope* paraesthesia*, increase in signs and symptoms of myasthenia gravis, decreased libido*, cerebrovascular accident*, cerebral ischaemia | |
| Eye disorders | DORZOPRES FORTE | Burning and stinging conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing | | |
| | Dorzolamide hydrochloride eye drops, solution | Eyelid inflammation*, eyelid irritation* | Iridocyclitis* irritation including redness*, pain*, eyelid | Foreign body sensation in eye |

| | | | | |
|---|---|---|---|---|
| | | Superficial punctuate keratitis | crusting*, transient myopia (which resolved upon discontinuation of therapy), corneal oedema*, ocular hypotony*, choroidal detachment (following filtration surgery)* | |
| | Timolol maleate eye drops, solution | Signs and symptoms of ocular irritation including blepharitis*, keratitis*, decreased corneal sensitivity, and dry eyes* Conjunctivitis | Visual disturbances including refractive changes (due to withdrawal of miotic therapy in some cases)* ptosis, diplopia, choroidal detachment following filtration surgery* (see Special warning and precautions for use 4.4) | Itching, tearing, redness, blurred vision, corneal erosion |

| | | | | |
|---|---|---|---|---|
| Ear and labyrinth disorders | Timolol maleate eye drops, solution | | Tinnitus* | |
| Cardiac disorders | Timolol maleate eye drops, solution | | Bradycardia*<br>chest pain*, palpitation*, oedema*, dysrhythmia*, congestive heart failure*, cardiac arrest*, heart block | Atrioventricular block, cardiac failure |
| | Dorzolamide hydrochloride eye drops, solution | | | Palpitations |
| Vascular disorders | Timolol maleate eye drops, solution | | Hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet* | |
| Respiratory, thoracic, and mediastinal disorders | DORZOPRES FORTE | Sinusitis | ~~s~~Shortness of breath, respiratory failure, rhinitis, rarely bronchospasm | |

| | | | | |
|---|---|---|---|---|
| | Dorzolamide hydrochloride eye drops, solution | | Epistaxis* | Dyspnoea |
| | Timolol maleate eye drops, solution | | Dyspnoea*<br>Bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, respiratory failure, cough* | |
| Gastrointestinal disorders | DORZOPRES FORTE | Dysgeusia | | |
| | Dorzolamide hydrochloride eye drops, solution | Nausea* | Throat irritation, dry mouth* | |
| | Timolol maleate eye drops, solution | | Nausea*, dyspepsia* diarrhoea, dry mouth* | Dysgeusia, abdominal pain, vomiting |

| | | | | |
|---|---|---|---|---|
| Skin and subcutaneous tissue disorders | DORZOPRES FORTE | | Contact dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis | |
| | Dorzolamide hydrochloride eye drops, solution | | Rash* | |
| | Timolol maleate eye drops, solution | | Alopecia*, psoriasiform rash or exacerbation of psoriasis* | Skin rash |
| Musculoskeletal and connective tissue disorders | Timolol maleate eye drops, solution | | Systemic lupus erythematosus | Myalgia |
| Renal and urinary disorders | DORZOPRES FORTE | | Urolithiasis | |
| Reproductive system and breast disorders | Timolol maleate eye drops, solution | | Peyronie's disease*, decreased libido | Sexual dysfunction |

| | | | | |
|---|---|---|---|---|
| General disorders and administration Site conditions | Dorzolamide hydrochloride eye drops, solution | Asthenia/fatigue* | | |
| | Timolol maleate eye drops, solution | | Asthenia/fatigue* | |

*These adverse reactions were also observed during post-marketing experience.

**Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with DORZOPRES FORTE.

**Reporting of suspected adverse reactions**

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

## 4.9 Overdose

No data are available in humans in regard to overdose by accidental or deliberate ingestion of DORZOPRES FORTE.

### Signs and symptoms

There have been reports of inadvertent overdoses 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 overdoses of dorzolamide are electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects.

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

Category and Class: A.15.4 Ophthalmic preparations, other.

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Beta blocking medicines, Timolol, combinations
ATC Code: S01ED51

**Mechanism of action**

DORZOPRES FORTE is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intra-ocular pressure by reducing aqueous humor 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 humor 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.

**Paediatric population**

An ophthalmic solution containing 2 % dorzolamide hydrochloride and 0,5 % timolol has been used in children 2 to 6 years of age whose intraocular 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.

## 5.2 Pharmacokinetic properties

***Dorzolamide Hydrochloride***

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, agent and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in red blood cells (RBCs) were measured. Dorzolamide accumulates in RBCs during chronic dosing as a result of selective binding to CA-II while low concentrations of free dorzolamide in plasma are maintained. The parent agent 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–dorzolamide concentration initially, followed by a slower elimination phase with a half-life of about four months.

***Timolol Maleate***

In a study of plasma timolol concentration 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 and following afternoon dosing was 0,35 ng/mL.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Benzalkonium chloride

Hydroxyethyl Cellulose

Mannitol

Sodium Citrate Dihydrate

Sodium Hydroxide solution 1N

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 months

**After first use**: 28 days (4 weeks)

### 6.4 Special precautions for storage

Store at or below 30 °C.

Do not use this medicine after the month and year following EXP on the bottle.

Do not use this medicine more than 28 days after opening.

### 6.5 Nature and contents of container

DORZOPRES FORTE is available in a 10 mL LDPE bottle with dropper and seal and packed into a cardboard carton.

Each bottle contains 5 mL of DORZOPRES FORTE.

The following pack sizes are available: cartons containing 1 or 3's.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

No special requirements for disposal.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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## 8. REGISTRATION NUMBER

DORZOPRES FORTE: 54/15.4/0258.257

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 September 2023

## 10. DATE OF REVISION OF THE TEXT