1.3 Product information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

DORZOLAMIDE & TIMOLOL EYE DROPS BP

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Dorzolamide Hydrochloride	BP	2.226%w/v
Eq. to Dorzolamide		2.0% w/v
Timolol Maleate	USP	0.68% w/v
Eq. to Timolol		0.015% w/v
Sterile Aqueous Base		Qs.

3. PHARMACEUTICAL FORM

Ophthalmic (Eye Drop)

4. Clinical particulars

4.1 Therapeutic indications

Indicated in the treatment of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or pseudoexfoliative glaucoma when topical beta-blocker monotherapy is not sufficient.

4.2 Posology and method of administration

Method of administration

For ocular use

4.3 Contraindications

Contraindicated in patients with:

- 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
- Hypersensitivity to one or both active substances or to any of the excipients.

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

4.4 Special warnings and precautions for use

No special requirements.

4.5 Interaction with other medicinal products and other forms of interaction

Specific medicine interaction studies have not been performed with this medicine.

In a clinical study, Dorzolamide/ Timolol eye drops (preservative free) 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 agents, antiarrhythmics (including amiodarone), digitalis glycosides, parasympathomimetics, quanethidine, 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, fluoxetine, paroxetine) and timolol.

Although dorzolamide/timolol (preserved formulation) 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 agents.

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

4.6 Pregnancy and Lactation

Pregnancy

Dorzolamide/ Timolol eye drops should not be used during pregnancy.

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 unless clearly necessary. To reduce the systemic absorption.

Epidemiological 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.

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

In a clinical study for dorzolamide/timolol preservative-free the observed adverse reactions have been consistent with those that were reported previously with dorzolamide/timolol (preserved formulation), dorzolamide hydrochloride and/or timolol maleate.
During clinical studies, 1,035 patients were treated with dorzolamide/timolol (preserved formulation). Approximately 2.4 % of all patients discontinued therapy with dorzolamide/timolol (preserved formulation) 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).
Dorzolamide/timolol preservative-free has been shown to have a similar safety profile to dorzolamide/timolol (preservative containing formulation) in a repeat dose double-masked, comparative study.
Like other topically applied ophthalmic medicines, timolol is absorbed into the systemic circulation. This may cause similar undesirable effects as seen with systemic beta-blocking agents. Incidence of systemic ADRs after topical ophthalmic administration is lower than for systemic administration.
The following adverse reactions have been reported with dorzolamide/timolol preservative-free or one of its components either during clinical trials or during post-marketing experience: [Very Common: (≥ 1/10), Common: (≥ 1/100, <1/10), Uncommon: (≥ 1/1,000,_<1/100), and Rare: (≥ 1/10,000, <1/1,000), Not known (cannot be estimated from the available data)]

System Organ Class (MedDRA)	Formulation	Very Common	Common	Uncommon	Rare	Not Known**
Immune system disorders	Dorzolamide/timolol Preservative-Free				signs and symptoms of systemic allergic 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	Dorzolamide/timolol Preservative-Free	burning and stinging	conjunctival injection, blurred vision, corneal erosion, ocular itching, tearing			foreign body sensation in eye
	Dorzolamide hydrochloride eye drops, solution		eyelid inflammation*, eyelid irritation*	iridocyclitis*	irritation including redness*, pain*, eyelid crusting*, transient myopia (which resolved upon discontinuation of therapy), corneal oedema*, ocular hypotony*, choroidal detachment (following filtration	foreign body sensation in eye

					surgery)*	
	Timolol maleate eye drops, solution		signs and symptoms of ocular irritation including blepharitis*, keratitis*, decreased corneal sensitivity, and dry eyes*	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 eye drops, solution				tinnitus*	
Cardiac disorders	Dorzolamide hydrochloride eye drops, solution					palpitations
	Timolol maleate eye drops, solution			bradycardia*	chest pain*, palpitation*, oedema*, arrhythmia*, congestive heart failure*, cardiac arrest*, heart block	atrioventricular block, cardiac failure
Vascular disorders	Timolol maleate eye drops, solution				hypotension*, claudication, Raynaud's phenomenon*, cold hands and feet*	
Respiratory, thoracic, and mediastinal disorders	Dorzolamide/ timolol Preservative-Free		sinusitis		shortness of breath, respiratory failure, rhinitis, rarely bronchospasm	dyspnoea
	Dorzolamide hydrochloride eye drops, solution				epistaxis*	dyspnoea

	Timolol maleate eye drops, solution			dyspnoea*	bronchospasm (predominantly in patients with pre-existing bronchospastic disease)*, respiratory failure, cough*	
Gastrointestinal disorders	Dorzolamide/ timolol Preservative-Free	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	Dorzolamide/ timolol Preservative-Free				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	Dorzolamide/ timolol Preservative-Free			urolithiasis		
Reproductive system and breast disorders	Timolol maleate eye drops, solution				Peyronie's disease*, decreased libido	sexual dysfunction
General disorders and administrati	Dorzolamide hydrochloride eye drops, solution		asthenia/ fatigue*			

on site conditions	Timolol maleate eye drops, solution			asthenia/ fatigue*		

*These adverse reactions were also observed with dorzolamide/timolol (preserved formulation) during post-marketing experience.
**Additional adverse reactions have been seen with ophthalmic beta-blockers and may potentially occur with dorzolamide/timolol preservative-free.

4.9 Overdose

No data are available in humans in regard to overdose by accidental or deliberate ingestion of Dorzolamide/ Timolol eye drops (preserved formulation) or Dorzolamide/ Timolol eye drops (preservative free).

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 agents 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 dialyze readily.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic Group: Antiglaucoma preparations and miotics, Beta blocking agents, Timolol, combinations

ATC code: S01E D510

Mechanism of action

Dorzolamide/ Timolol eye drops is comprised of two components: dorzolamide hydrochloride and timolol maleate. Each of these two components decreases elevated intraocular pressure by reducing aqueous humor secretion, but does so by a different mechanism of action.

Dorzolamide hydrochloride is a potent 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 non-selective beta-adrenergic receptor blocking agent. The precise mechanism of action of timolol maleate in lowering intraocular pressure is not clearly established at this time, although a fluorescein study and tonography studies indicate that the predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed. The combined effect of these two agents results in additional intraocular pressure reduction (IOP) compared to either component administered alone.

Following topical administration, Dorzolamide/ Timolol eye drops reduces elevated intraocular pressure, whether or not associated with glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of optic nerve damage and glaucomatous visual field loss. This medicinal product reduces intraocular pressure without the common side effects of miotics such as night blindness, accommodative spasm and pupillary constriction.

Pharmacodynamic effects

Clinical Effects

Clinical studies of up to 15 months duration were conducted to compare the IOP-lowering effect of Dorzolamide/ Timolol eye drops (preserved formulation) b.i.d. (dosed morning and bedtime) to individually- and concomitantly-administered 0.5% timolol and 2.0% dorzolamide in patients with glaucoma or ocular hypertension for whom concomitant therapy was considered appropriate in the trials. This included both untreated patients and patients inadequately controlled with timolol monotherapy. The majority of patients were treated with topical beta-blocker monotherapy prior to study enrolment. In an analysis of the combined studies, the IOP-lowering effect of Dorzolamide/ Timolol eye drops (preserved formulation) b.i.d. was greater than that of monotherapy with either 2% dorzolamide t.i.d. or 0.5% timolol b.i.d. The IOP-lowering effect of Dorzolamide/ Timolol eye drops (preserved formulation) b.i.d. was equivalent to that of concomitant therapy with dorzolamide b.i.d. and timolol b.i.d. The IOP- lowering effect of Dorzolamide/ Timolol eye drops (preserved formulation) b.i.d. was demonstrated when measured at various time points throughout the day and this effect was maintained during long-term administration.

In an active-treatment-controlled, parallel, double-masked study in 261 patients with elevated intraocular pressure ≥ 22 mmHg in one or both eyes, Dorzolamide/ Timolol eye drops (preservative free) had an IOP-lowering effect equivalent to that of Dorzolamide/ Timolol eye drops (preserved formulation). The safety profile of Dorzolamide/ Timolol eye drops (preservative free) was similar to Dorzolamide/ Timolol eye drops (preserved formulation).

Paediatric population

A 3 month controlled study, with the primary objective of documenting the safety of 2% dorzolamide hydrochloride ophthalmic solution in children under the age of 6 years has been conducted. In this study, 30 patients under 6 and greater than or equal to 2 years of age whose IOP was not adequately controlled with monotherapy by dorzolamide or timolol received Dorzolamide/ Timolol eye drops (preserved formulation) in an open label phase. Efficacy in those patients has not been established. In this small group of patients, twice daily administration of Dorzolamide/ Timolol eye drops (preserved formulation) was generally well tolerated with 19 patients completing the treatment period and 11 patients discontinuing for surgery, a change in medication, or other reasons.

5.2 Pharmacokinetic properties

Dorzolamide Hydrochloride

Unlike oral carbonic anhydrase inhibitors, topical administration of dorzolamide hydrochloride allows for the active substance to exert its effects directly in the eye at substantially lower doses and therefore with less systemic exposure. In clinical trials, this resulted in a reduction in IOP without the acid-base disturbances or alterations in electrolytes characteristic of oral carbonic anhydrase inhibitors.

When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, active substance 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 extremely low concentrations of free active substance in plasma are maintained. The parent active substance forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent active substance 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 active substance concentration initially, followed by a slower elimination phase with a half-life of about four months.

When dorzolamide was given orally to simulate the maximum systemic exposure after long term topical ocular administration, steady state was reached within 13 weeks. At steady state, there was virtually no free active substance or metabolite in plasma; CA inhibition in RBCs was less than that anticipated to be necessary for a pharmacological effect on renal function or respiration. Similar pharmacokinetic results were observed after chronic, topical administration of dorzolamide

hydrochloride. However, some elderly patients with renal impairment (estimated CrCl 30-60 ml/min) had higher metabolite concentrations in RBCs, but no meaningful differences in carbonic anhydrase inhibition and no clinically significant systemic side effects were directly attributable to this finding.

Timolol Maleate

In a study of plasma active substance 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.

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 Dorzolamide/ Timolol eye drops.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Citric acid Anhydrous
H.P.M.C E5
Sodium Hydroxide Pellets

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Nature and contents of container<and special equipment for use, administration or implantation>

5 ml Opaque Plastic Bottle Sterile

6.5 Special precautions for disposal <and other handling>

No special requirements.

7 <APPLICANT/MANUFACTURER>

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