SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Dorzolamide 20 mg/mL eye drops, solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 20 mg dorzolamide (as dorzolamide hydrochloride).

Excipient with known effect
0.075 mg benzalkonium chloride (as 0.15 mg benzalkonium chloride solution 50%)/mL eye drops, solution

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution.

Isotonic, buffered, slightly viscous, clear, colourless aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Dorzolamide is indicated:
• as adjunctive therapy to beta-blockers,
• as monotherapy in patients unresponsive to beta-blockers or in whom beta-blockers are contraindicated, in the treatment of elevated intraocular pressure in:
- ocular hypertension,
- open-angle glaucoma,
- pseudo-exfoliative glaucoma.

4.2 Posology and method of administration

Posology

When used as monotherapy, the dose is one drop of dorzolamide in the conjunctival sac of the affected eye(s), three times daily.

When used as adjunctive therapy with an ophthalmic beta-blocker, the dose is one drop of dorzolamide in the conjunctival sac of the affected eye(s), two times daily.

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

If more than one topical ophthalmic medicinal product is being used, the medicinal products 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 the ophthalmic dispensers.

Paediatric population
Limited clinical data in paediatric patients with administration of dorzolamide three times a day are available. (For information regarding paediatric dosing see section 5.1).

Method of administration

1. The tamper-proof seal on the bottle neck must be unbroken before the product is being used for the first time. A gap between the bottle and the cap is normal for an unopened bottle.
2. The cap of the bottle should be taken off.
3. The patient's head must be tilted back and the lower eyelid must be pulled gently down to form a small pocket between the eyelid and the eye.
4. The bottle should be inverted and squeezed until a single drop is dispensed into the eye. THE EYE OR EYELID MUST NOT BE TOUCHED WITH THE DROPPER TIP.
5. Steps 3 & 4 should be repeated with the other eye if it is necessary.
6. The cap must be put back on and the bottle must be closed straight after it has been used.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Dorzolamide has not been studied in patients with severe renal impairment (CrCl < 30 mL/min) or with hyperchloraemic acidosis. Because dorzolamide and its metabolites are excreted predominantly by the kidney, dorzolamide is therefore contraindicated in such patients.

4.4 Special warnings and precautions for use

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

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

Dorzolamide contains a sulphonamido group, which also occurs in sulphonamides and although administered topically, is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulphonamides 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 the use of this preparation.

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 dorzolamide, urolithiasis has been reported infrequently. Because dorzolamide is 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 dorzolamide.

If allergic reactions (e.g. conjunctivitis and eyelid reactions) are observed, discontinuation of treatment should be considered.

There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and dorzolamide. The concomitant administration of dorzolamide and oral carbonic anhydrase inhibitors is not recommended.

Corneal oedemas and irreversible corneal decompensations have been reported in patients with pre-existing chronic corneal defects and/or a history of intraocular surgery while using orzolamide 20 mg/mL eye drops, solution. Topical dorzolamide should be used with caution in such patients.

Choroidal detachment concomitant with ocular hypotony have been reported after filtration procedures with administration of aqueous suppressant therapies.

Dorzolamide contains the preservative benzalkonium chloride, which is known to discolour soft contact lenses. Contact lenses should be removed prior to application and wait at least 15 minutes before reinsertion.
Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. 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.

Paediatric population
Dorzolamide has not been studied in patients less than 36 weeks gestational age and less than 1 week of age. Patients with significant renal tubular immaturity should only receive dorzolamide after careful consideration of the risk benefit balance because of the possible risk of metabolic acidosis.

4.5 Interaction with other medicinal products and other forms of interaction

No specific drug interaction studies have been performed.

In clinical studies, dorzolamide was used concomitantly with the following medicinal products without evidence of adverse interactions: timolol ophthalmic solution, betaxolol ophthalmic solution and systemic medicinal products, including ACE-inhibitors, calcium-channel blockers, diuretics, non-steroidal anti-inflammatory drugs including acetylsalicylic acid, and hormones (e.g. oestrogen, insulin, thyroxine).

Association between dorzolamide and miotics and adrenergic agonists has not been fully evaluated during glaucoma therapy.

4.6 Fertility, pregnancy and lactation

Pregnancy
Dorzolamide should not be used during pregnancy. No adequate clinical data in exposed pregnancies are available. In rabbits, dorzolamide produced teratogenic effects at maternotoxic doses (see section 5.3).

Breast-feeding
It is not known whether dorzolamide is excreted in human milk. In lactating rats, decreases in the body weight gain of offspring were observed. If treatment with dorzolamide 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 adverse reactions such as dizziness and visual disturbances may affect the ability to drive and use machines.

4.8 Undesirable effects

Dorzolamide was evaluated in more than 1,400 individuals in controlled and uncontrolled clinical studies. In long-term studies of 1,108 patients treated with dorzolamide as monotherapy or as adjunctive therapy with an ophthalmic beta-blocker, the most frequent cause of discontinuation (approximately 3%) from treatment with dorzolamide was drug-related ocular adverse reactions, primarily conjunctivitis and lid reactions.

The following adverse reactions have been reported either during clinical trials or during post-marketing experience:

[Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Not known (frequency cannot be estimated from the available data).]

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Nervous system disorders		Headache		Dizziness Paraesthesia	
Eye disorders	Burning and stinging	Superficial punctate keratitis Tearing Conjunctivitis Eyelid inflammation Eye itching Eyelid irritation Blurred vision	Iridocyclitis	Irritation including redness Pain Eyelid crusting Transient myopia (which resolved upon discontinuation of therapy) Corneal oedema Ocular hypotony Choroidal detachment following filtration surgery	Foreign body sensation in eye
Cardiac disorders					Palpitations
Respiratory, thoracic and mediastinal disorders				Epistaxis	Dyspnoea
Gastrointestinal disorders		Nausea, Bitter taste		Throat irritation Dry mouth	
Skin and subcutaneous tissue disorders				Contact dermatitis Stevens-Johnson syndrome Toxic epidermal necrolysis	
Renal and urinary disorders				Urolithiasis	

General disorders and administration site conditions		Asthenia/fatigue		*Hypersensitivity:* Signs and symptoms of local reactions (palpebral reactions) and systemic allergic reactions including angioedema, urticaria and pruritus, rash, shortness of breath, rarely bronchospasm	

Investigations: dorzolamide was not associated with clinically meaningful electrolyte disturbances.

Paediatric population
See section 5.1.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Only limited information is available with regard to human overdose by accidental or deliberate ingestion of dorzolamide hydrochloride.

Symptoms
The following have been reported with oral ingestion: somnolence; topical application: nausea, dizziness, headache, fatigue, abnormal dreams and dysphagia.

Treatment
Treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and possible central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiglaucoma preparations and miotics, Carbonic Anhydrase Inhibitors, ATC code: S01EC03

Mechanism of action
Carbonic anhydrase (CA) is an enzyme found in many tissues of the body including the eye. In humans, carbonic anhydrase exists as a number of isoenzymes, the most active being carbonic anhydrase II (CA-II) found primarily in red blood cells (RBCs) but also in other tissues. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion. The result is a reduction in intraocular pressure (IOP).

Dorzolamide contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide 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 visual-field loss. Dorzolamide does not cause pupillary constriction and reduces intraocular pressure without side effects such as night blindness, accommodative spasm. Dorzolamide has minimal or no effect on pulse rate or blood pressure.

Topically applied beta-adrenergic blocking agents also reduce IOP by decreasing aqueous humor secretion but by a different mechanism of action. Studies have shown that when dorzolamide is added to a topical beta-blocker, additional reduction in IOP is observed; this finding is consistent with the reported additive effects of beta-blockers and oral carbonic anhydrase inhibitors.

Pharmacodynamic effects

Clinical effects:

Adult patients
In patients with glaucoma or ocular hypertension, the efficacy of dorzolamide given t.i.d. as monotherapy (baseline IOP ≥ 23 mmHg) or given b.i.d. as adjunctive therapy while receiving ophthalmic beta-blockers (baseline IOP ≥ 22 mmHg) was demonstrated in large-scale clinical studies of up to one-year duration. The IOP-lowering effect of dorzolamide as monotherapy and as adjunctive therapy was demonstrated throughout the day and this effect was maintained during long-term administration. Efficacy during long-term monotherapy was similar to betaxolol and slightly less than timolol. When used as adjunctive therapy to ophthalmic beta-blockers, dorzolamide demonstrated additional IOP lowering similar to pilocarpine 2% q.i.d..

Paediatric population
A 3-month, double-masked, active-treatment controlled, multicentre study was undertaken in 184 (122 for dorzolamide) paediatric patients from 1 week of age to < 6 years of age with glaucoma or elevated intraocular pressure (baseline IOP ≥ 22 mmHg) to assess the safety of dorzolamide 20 mg/mL eye drops, solution when administered topically t.i.d. (three times a day). Approximately half the patients in both treatment groups were diagnosed with congenital glaucoma; other common aetiologies were Sturge Weber syndrome, iridocorneal mesenchymal dysgenesis, aphakic patients. The distribution by age and treatments in the monotherapy phase was as follows:

	Dorzolamide 20 mg/mL	Timolol
Age cohort < 2 years	n=56 Age range: 1 to 23 months	Timolol GS 0.25% n=27 Age range: 0.25 to 22 months
Age cohort ≥ 2 - < 6 years	n=66 Age range: 2 to 6 years	Timolol 0.5% n=35 Age range: 2 to 6 years

Across both age cohorts approximately 70 patients received treatment for at least 61 days and approximately 50 patients received 81-100 days of treatment.

If IOP was inadequately controlled on dorzolamide or timolol gel-forming solution monotherapy, a change was made to open-label therapy according to the following: 30 patients < 2 years were switched to concomitant therapy with timolol gel-forming solution 0.25% daily and dorzolamide 20 mg/mL t.i.d.; 30 patients ≥ 2 years were switched to 2% dorzolamide/0.5% timolol fixed combination b.i.d. (twice a day).

Overall, this study did not reveal additional safety concerns in paediatric patients: approximately 26% (20% in dorzolamide monotherapy) of paediatric patients were observed to experience drug-related adverse reactions, the majority of which were local, non-serious ocular effects such as ocular burning and

stinging, injection and eye pain. A small percentage < 4% was observed to have corneal oedema or haze. Local reactions appeared similar in frequency to comparator. In post-marketing data, metabolic acidosis in the very young particularly with renal immaturity/impairment has been reported.

Efficacy results in paediatric patients suggest that the mean IOP decrease observed in the dorzolamide group was comparable to the mean IOP decrease observed in the timolol group even if a slight numeric advantage was observed for timolol.

Longer-term efficacy studies (> 12 weeks) are not available.

5.2 Pharmacokinetic properties

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 non linearly, 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.
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 adverse reactions were directly attributable to this finding.

5.3 Preclinical safety data

The main findings in animal studies with dorzolamide hydrochloride administered orally were related to the pharmacological effects of systemic carbonic anhydrase inhibition. Some of these findings were species-specific and/or were a result of metabolic acidosis. In rabbits given maternotoxic doses of dorzolamide associated with metabolic acidosis, malformations of the vertebral bodies were observed.

In clinical studies, patients did not develop signs of metabolic acidosis or serum electrolyte changes that are indicative of systemic CA inhibition. Therefore, it is not expected that the effects noted in animal studies would be observed in patients receiving therapeutic doses of dorzolamide.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Hydroxyethyl cellulose
Sodium citrate
Sodium hydroxide for pH adjustment
Benzalkonium chloride solution 50 %
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

After first opening: 28 days

6.4 Special precautions for storage

Keep the bottle in the outer carton in order to protect from light.
Store below 30°C.

6.5 Nature and contents of container

White opaque medium density polyethylene bottle with a sealed dropper tip and a two-piece cap assembly in a cardboard box. Each bottle contains 5 mL of solution.

Pack sizes: 1 x 5 mL bottle, 3 x 5 mL bottle, 6 x 5 mL bottle

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pharmathen International S.A.
4, Dervenakion str.,
153 51 Pallini Attiki,

Greece

8. MARKETING AUTHORISATION NUMBER(S)

PL 31225/0005

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27/03/2017

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