# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Dorzolamide Mylan 20 mg/ml Eye Drops Solution

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect:
Each ml of solution contains 0.075 mg benzalkonium chloride.

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 Mylan 20 mg/ml eye drops solution 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 intra-ocular 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 another ophthalmic anti-glaucoma agent is substituted by dorzolamide, the agent must be discontinued after proper dosing on one day, and dorzolamide must be started on the next day.

If more than one topical ophthalmic medicinal product is being used, the products should be administered at least ten minutes apart.

Patients should be instructed to avoid allowing the tip of the dispensing container to contact 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.

*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
For ocular use.

Patients should be instructed to wash their hands before use.

Patients should be informed of the correct handling of the ophthalmic dispensers.

*Usage instructions:*
1. The tamper-proof seal on the bottle neck must be intact and then broken before the product is 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 sulfonamido group, which also occurs in sulfonamides and although administered topically, is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration, including severe reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. If signs of serious reactions of 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 (eg. 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 intra-ocular surgery while using Dorzolamide Mylan 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.

Paediatric population:
Dorzolamide has not been studied in patients less than 36 weeks gestational age and less than one 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.

Dorzolamide Mylan 20 mg/ml eye drops solution contains the preservative benzalkonium chloride, which may cause eye irritation. Benzalkonium chloride is known to discolour soft contact lenses. Contact with soft contact lenses should be avoided. Contact lenses should be removed prior to application and reinserted at least 15 minutes after application.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

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

Dorzolamide is a carbonic anhydrase inhibitor and despite locally applied it is absorbed systemically. In clinical research no acid-base disturbances have been reported with this medicine. However therapy with oral carbonic anhydrase inhibitors has been associated with such disturbances and have, in some cases, resulted in drug interactions (e.g., toxicity associated with high-dose salicylate therapy). Therefore, the potential risk should be taken into account for patients also using Dorzolamide Mylan 20 mg/ml eye drops solution.

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*: No studies were performed on pregnant women. The potential risk for humans is unknown. Dorzolamide should not be used during pregnancy unless clearly necessary.

Breast-feeding: There are no data showing whether the active substance is excreted in human milk. Dorzolamide should not be used during lactation. In lactating rats, decreases in the body weight gain of offspring were observed.

## 4.7 Effects on ability to drive and use machines

Dorzolamide Mylan has minor or moderate influence on the ability to drive and use machines. Possible side effects such as dizziness and visual disturbances may occur (see also section 4.8).

## 4.8 Undesirable effects

Dorzolamide was evaluated in more than 1400 individuals in controlled and uncontrolled clinical studies. In long term studies of 1108 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.

Adverse reactions reported either during clinical trials or during post-marketing experience as more than an isolated case are listed below, by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000).

| System Organ Class | Very Common | Common | Uncommon | Rare |
|---|---|---|---|---|
| **Nervous system disorders** | | Headache | | Dizziness<br>Paraesthesia |
| **Eye disorders** | Burning and stinging | Superficial punctate keratitis<br>Tearing<br>Conjunctivitis Eyelid inflammation Eye itching Eyelid irritation Blurred vision | Iridocyclitis | Irritation including redness<br>Pain<br>Eyelid crusting<br>Transient myopia (which resolved upon discontinuation of therapy)<br>Corneal oedema<br>Ocular hypotony<br>Choroidal detachment following filtration surgery |
| **Respiratory, thoracic, and mediastinal disorders** | | | | Epistaxis |
| **Gastrointestinal disorders** | | Nausea,<br>Bitter taste | | Throat irritation<br>Dry mouth |
| **Skin and subcutaneous tissue disorders** | | | | Contact dermatitis<br>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 |

Laboratory findings: 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

## 4.9 Overdose

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

Treatment should be symptomatic and supportive. Electrolyte imbalance, development of an acidotic state, and possible central nervous system reactions 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 intra-ocular pressure (IOP).

Dorzolamide Mylan 20 mg/ml eye drops solution contains dorzolamide hydrochloride, a potent inhibitor of human carbonic anhydrase II. Following topical ocular administration, dorzolamide reduces elevated intra-ocular pressure, whether or not associated with glaucoma. Elevated intra-ocular 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 intra-ocular 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 efficacy and safety
Adult Patients
In patients with glaucoma or ocular hypertension, the efficacy of dorzolamide given three times daily.. as monotherapy (baseline IOP ≥23 mmHg) or giventwice daily.. 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%four times daily.

Paediatric population
A three month, double-masked, active-treatment controlled, multicentre study was undertaken in 184 (122 for dorzolamide) paediatric patients from one week of age to < 6 years of age with glaucoma or elevated intraocular pressure (baseline IOP > 22 mmHg) to assess the safety of dorzolamide eye drops solution when administered topically three timesdaily. 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<br>Age range: 1 to 23 months | Timolol GS 0.25% n=27<br>Age range: 0.25 to 22 months |
| Age cohort ≥ 2 - < 6 years | n=66<br>Age range: 2 to 6 years | Timolol 0.5% n=35<br>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.

Overall, this study did not reveal additional safety concerns in paediatric patients: approximately 20% of patients while on dorzolamide monotherapy were observed to experience adverse affects related to the active substance, the majority of which were local, non-serious ocular effects such as ocular burning and stinging, injection and eye pain. A small percentage < 4% were 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.

Absorption
When topically applied, dorzolamide reaches the systemic circulation. To assess the potential for systemic carbonic anhydrase inhibition following topical administration, dorzolamide and metabolite concentrations in RBCs and plasma and carbonic anhydrase inhibition in RBCs were measured.

Distribution
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.

Biotransformation
The parent substance forms a single N-desethyl metabolite that inhibits CA-II less potently than the parent 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%).

Elimination
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 dorzolamide 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 side effects 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 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

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 (unopened)

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

Medium density polyethylene white bottle with a sealed dropper tip and a tamper-proof two-piece cap assembly in a cardboard box.

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

No special requirements.

# 7 MARKETING AUTHORISATION HOLDER

Generics (UK) Limited
Station Close
Potters Bar
Hertfordshire EN6 1TL
United Kingdom

# 8 MARKETING AUTHORISATION NUMBER

PA 0405/052/001

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10th September 2010

Date of last renewal: 12th July 2015

# 10 DATE OF REVISION OF THE TEXT

July 2018