COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dorzolamide Mylan 20 mg/ml, eye drops, solution

(dorzolamide)

NL/H/4581/001/DC

Date: 1 March 2023

This module reflects the scientific discussion for the approval of Dorzolamide Mylan 20 mg/ml, eye drops, solution. The procedure was finalised in the United Kingdom (UK/H/1757/001/DC). After a transfer in 2018, the current RMS is the Netherlands. The report presented below reflects the original procedure at the time of finalisation in the UK and has not been changed or updated since.

Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

DORZOLAMIDE 20MG/ML EYE DROPS, SOLUTION

Procedure No: UK/H/1757/001/DC

UK Licence No: PL 04569/0911

GENERICS (UK) LIMITED

Medicines and Healthcare products Regulatory Agency

LAY SUMMARY

On 13 July 2010, Belgium, Czech Republic, Germany, Denmark, Greece, Finland, France, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Sweden, Slovakia and the UK agreed to grant a Marketing Authorisation to Generics (UK) Limited for the medicinal product Dorzolamide 20mg/ml eye drops, solution (PL 04569/0911; UK/H/1757/001/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, a Marketing Authorisation was granted in the UK on 12 August 2010. This is a prescription-only medicine (POM) used to reduce high pressure in the eye.

Dorzolamide 20mg/ml eye drops, solution is a sterile eye drop solution which contains a sulphonamide-related compound called dorzolamide as the active ingredient.

Dorzolamide belongs to a group of medicines called ophthalmic carbonic anhydrase inhibitors and reduces high pressure in the eye.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Dorzolamide 20mg/ml eye drops, solution, outweigh the risks, hence a Marketing Authorisation has been granted.

TABLE OF CONTENTS

Module 1

Product Name	Dorzolamide 20mg/ml eye drops, solution
Type of Application	Hybrid, Article 10.3
Active Substances	Dorzolamide
Form	Eye drops, solution
Strength	20mg/ml
MA Holder	Generics [UK] Limited, Station Close, Potters Bar Hertfordshire EN6 1TL.
Reference Member State (RMS)	UK
CMS	Belgium, Czech Republic, Germany, Denmark, Greece, Finland, France, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Sweden, and Slovakia.
Procedure Number	UK/H/1757/001/DC
Timetable	Day 210 – 13 July 2010

Module 2
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: 0.075 mg benzalkonium chloride/ml eye drops, solution

For a 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 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
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.

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 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.

Paediatric use:
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).

4.3 Contraindications

Hypersensitivity to dorzolamide or to any of the excipients.

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 is a sulphonamide and although administered topically, is absorbed systemically. Therefore the same types of adverse reactions that are attributable to sulphonamides may occur with topical administration. 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 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 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.

Paediatric patients:

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.

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 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 20 mg/ml eye drops solution.

4.6 Pregnancy and lactation

Pregnancy: No studies were performed on pregnant women. In rabbits given maternotoxic doses associated with metabolic acidosis, malformations of the vertebral bodies were observed. The potential risk for humans is unknown. Dorzolamide should not be used during pregnancy unless clearly necessary.

Lactation: 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 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		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
Respiratory, thoracic, and mediastinal disorders				Epistaxis
Gastrointestinal disorders		Nausea, Bitter taste		Throat irritation Dry mouth
Skin and subcutaneous tissue disorders				Contact dermatitis
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

System Organ Class	Very Common	Common	Uncommon	Rare
				including angioedema, urticaria and pruritus, rash, shortness of breath, rarely bronchospasm

Laboratory findings: dorzolamide was not associated with clinically meaningful electrolyte disturbances.

Paediatric Patients
See 5.1

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 Inhibitor.
ATC code: S 01 EC 03

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 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 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 Patients
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 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.

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 disadvantage 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, dorzolamide and metabolite concentrations in 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 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%). 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 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 (Natrosol HX 250)
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

Medium density polyethylene bottle with a sealed dropper tip and a 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

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/0911

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/08/2010

10 DATE OF REVISION OF THE TEXT

12/08/2010

Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

DORZOLAMIDE 20 mg/ml EYE DROPS, SOLUTION

(dorzolamide)

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT DORZOLAMIDE IS AND WHAT IT IS USED FOR

Dorzolamide is a sterile eye drop solution. Dorzolamide contains dorzolamide, a sulphonamide-related compound, as the active ingredient.
Dorzolamide is an ophthalmic carbonic anhydrase inhibitor which reduces high pressure in the eye.

It is indicated in the treatment of elevated intra-ocular pressure in conditions such as ocular hypertension and glaucoma (open-angle glaucoma, pseudo-exfoliative glaucoma). Dorzolamide can be used alone or in addition to other medicines which lower the pressure in the eye (so-called beta-blockers).

2. BEFORE YOU USE DORZOLAMIDE

Do not use Dorzolamide:
- if you are allergic (hypersensitive) to dorzolamide or any of the other ingredients of this solution.
- if you have severe kidney problems.
- if you have a disturbance in the pH (acid/alkali balance) of your blood.

Take special care with Dorzolamide
Before treatment with Dorzolamide tell your doctor
- if you have or have had liver problems in the past
- if you have been told you have a corneal defect
- if you have had any allergies to any medicines
- if you have had, or are about to have eye surgery
- if you have suffered an eye injury or have an eye infection
- if you have a prior history of kidney stones
- if you are taking another carbonic anhydrase inhibitor
- if you wear contact lenses (see the section 'Important information about some of the ingredients of Dorzolamide').

You should contact your doctor immediately if you develop any eye irritation or any new eye problems such as redness of the eye or swelling of the surface layer of the eye or eyelids. Stop using Dorzolamide and contact your doctor immediately if you suspect that Dorzolamide is causing an allergic reaction (for example, skin rash or itching, inflammation of the eye).

Use in children
Dorzolamide should only be used in children if the benefits outweigh the risks. Your doctor will be able to advise you.

Using other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular you should tell your doctor if you are taking another carbonic anhydrase inhibitor such as acetazolamide. You may be taking this type of medicine by mouth, as eye drops, or by some other method.

Pregnancy and breast-feeding - Ask your doctor or pharmacist for advice before taking any medicine. Tell your doctor if you are pregnant or planning to become pregnant. Dorzolamide should not be used during pregnancy unless your doctor still recommends it.
Dorzolamide should not be used while breast-feeding.

Driving and using machines - Dorzolamide may cause dizziness and visual disturbances in some patients. Do not drive or use any tools or machines until the symptoms have cleared.

Important information about some of the ingredients of Dorzolamide - Dorzolamide contains the preservative benzalkonium chloride.
- Benzalkonium chloride may cause eye irritation
- Benzalkonium chloride is known to discolour soft contact lenses
- Avoid contact with soft contact lenses
- Remove contact lenses prior to application and wait until 15 minutes before reinsertion

3. HOW TO USE DORZOLAMIDE

Always use Dorzolamide exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The appropriate dosage and duration of treatment will be established by your doctor.

When Dorzolamide is used alone, the usual dose is one drop in the affected eye(s) three times a day, for example in the morning, in the afternoon and in the evening.

If your doctor has recommended you use Dorzolamide with a beta-blocker eye drop (medicines which lower the pressure of the eye), then the usual dose is one drop of Dorzolamide in the affected eye(s) two times a day, for example in the morning and in the evening.

If you use Dorzolamide with another eye drop, leave at least 10 minutes between putting in Dorzolamide and the other medicine. Alternatively if you are going to use Dorzolamide to replace another eye drop medicine, used to lower eye pressure, you should stop using the other medicine after taking the proper dosing on one day, and start Dorzolamide on the next day.

Do not change the dosage of the drug without consulting your doctor. If you must stop treatment, contact your doctor immediately.

Do not allow the tip of the container to touch your eye or areas around your eye. It may become contaminated with bacteria that can cause eye infections leading to serious damage of the eye, even loss of vision. To avoid possible contamination of the container, keep the tip of the container away from contact with any surface.

Instructions for use:
It is recommended that you wash your hands before putting in your eye drops.

It may be easier to apply your eye drops in front of a mirror.

1. Before using the medication for the first time, be sure that the tamper-proof seal on the bottle neck is unbroken. A gap between the bottle and the cap is normal for an unopened bottle.
2. Take off the cap of the bottle.
3. Tilt your head back and gently pull your lower eyelid down to form a small pocket between your eyelid and your eye.
4. Invert the bottle, and squeeze it until a single drop is dispensed into the eye as directed by your doctor.
   DO NOT TOUCH YOUR EYE OR EYELID WITH THE DROPPER TIP.
5. Repeat steps 3 & 4 with the other eye if instructed to do so by your doctor.
6. Put the cap back on and close the bottle straight after you have used it.

If you use more Dorzolamide than you should - If you put too many drops in your eye or swallow any of the contents, you should contact your doctor immediately.

If you forget to use Dorzolamide - It is important to use Dorzolamide as prescribed by your doctor.

If you miss a dose, use it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to your regular dosing schedule.

Do not use a double dose to make up for forgotten individual doses.

If you stop using Dorzolamide - Dorzolamide should be used every day to work properly. If you must stop treatment, contact your doctor immediately.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Dorzolamide can cause side effects, although not everybody gets them.

The chance of having a side effect is described by the following categories:

Very common - Occurs in more than 1 out of 10 patients
Common - Occurs in between 1 and 10 out of every 100 patients
Uncommon -Occurs in between 1 and 10 out of every 1,000 patients
Rare - Occurs in between 1 and 10 out of every 10,000 patients

The following side effects may be seen with Dorzolamide:

Eye disorders:

Very common: burning and stinging

Common: inflammation or swelling of the surface layer of the eye(s) and possible inflammation of the eyelid(s) and/or skin around the eye(s), watering or itching of the eye(s), blurred vision, effects on the surface of the eye

Uncommon: inflammation of the middle layer of the eye

Rare: swelling of the surface layer of the eye(s), choroidal detachment which may be accompanied by visual changes/disturbances (following eye surgery), ocular hypotony, redness of the eye(s), eye pain, crusting of the eyelid(s), temporary shortsightedness (which stops when the medicine is discontinued)

Gastrointestinal disorders:

Common: nausea, bitter taste

Rare: throat irritation, dry mouth

General disorders and administration site conditions:

Common: asthenia/fatigue

Rare: Hypersensitivity: signs and symptoms of local reactions (palpebral reactions) and systemic allergic reactions including swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, hives and itching, rash, shortness of breath and more rarely bronchospasm (contraction of the smooth muscle in the bronchi).

Nervous system disorders:

Common: headache

Rare: dizziness, numbness/tingling sensation.

Renal and urinary disorders:

Rare: formation of urinary calculi.

Respiratory, thoracic, and mediastinal disorders:

Rare: bleeding from the nose.

Skin and subcutaneous tissue disorders:

Rare: skin inflammation.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DORZOLAMIDE

Keep out of the reach and sight of children.

Do not use Dorzolamide after the expiry date which is stated on the bottle label and the carton after 'EXP': The expiry date refers to the last day of that month.

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

Dorzolamide should be used within 28 days after the bottle is first opened. Therefore, you must throw away the bottle 4 weeks after you first opened it, even if some solution is left. To help you remember, write down the date that you opened it in the space on the carton.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Dorzolamide contains:

- The active substance is dorzolamide. Each ml contains 20 mg dorzolamide (as dorzolamide hydrochloride).
- The other ingredients are Mannitol, Hydroxy Ethyl Cellulose, Benzalkonium Chloride (as a preservative), Sodium Citrate, Sodium Hydroxide for pH adjustment and Water for injection.

What Dorzolamide looks like and contents of the pack - Dorzolamide is a sterile, isotonic, buffered, colourless, slightly viscous solution in a white opaque medium density polyethylene bottle with a sealed dropper tip and a two-piece cap assembly. Each bottle contains 5 ml of the eye drop solution.

Dorzolamide is available in packs containing 1 bottle, 3 bottles or 6 bottles. Not all pack sizes may be marketed.

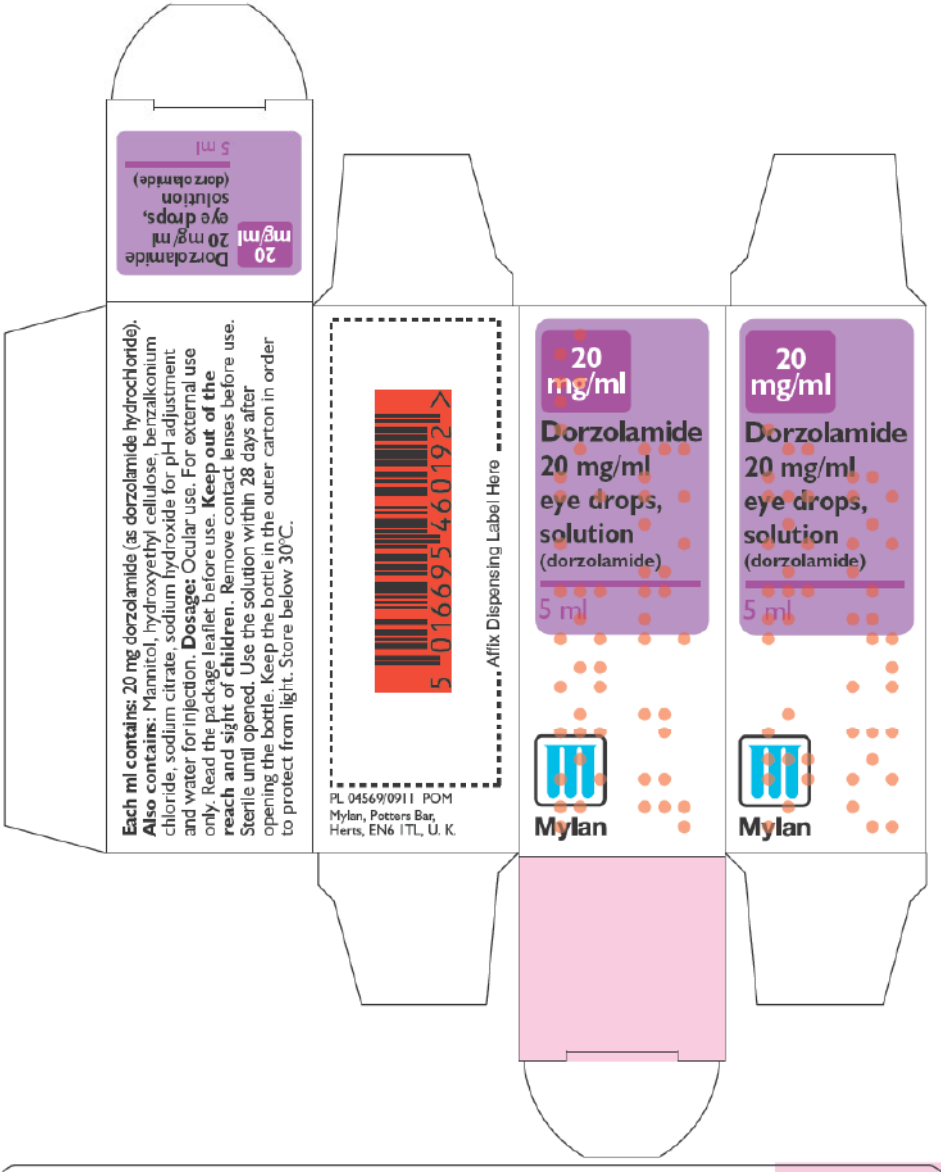
Marketing Authorisation Holder and Manufacturer

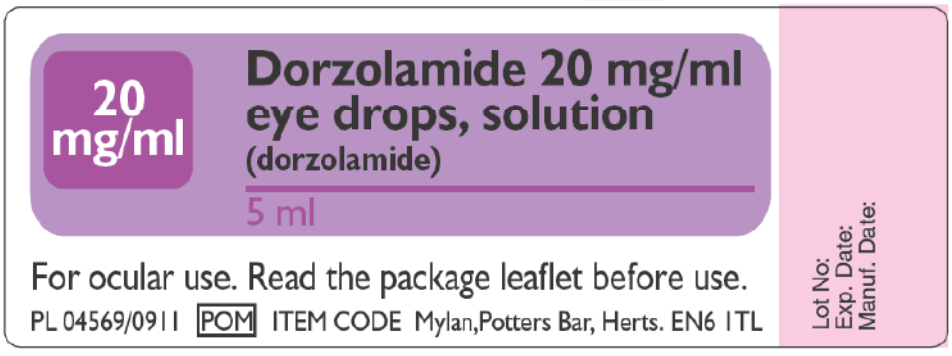
Marketing Authorisation Holder: Generics [UK] Limited t/a Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom.

Manufacturer: Mylan SAS, 112 alle des parcs, 69800 Saint Priest, France.

Date of leaflet preparation: July 2010 ITEM CODE

Module 4
Labelling





Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Dorzolamide 20mg/ml eye drops, solution (PL 04569/0911; UK/H/1757/001/DC) could be approved. This application was submitted by the decentralised procedure, with the UK as Reference Member State (RMS), and Belgium, Czech Republic, Germany, Denmark, Greece, Finland, France, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Sweden, Slovakia as Concerned Member States (CMS).

The product is a prescription-only medicine 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 and pseudo-exfoliative glaucoma.

This application is made via the Decentralised Procedure (DCP), according to Article 10.3 of 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is Truspot 2% Eye Drops which was originally granted a licence in 1995 to Merck Sharp & Dohme Limited.

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. 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).

No new non-clinical or clinical studies were conducted, which is acceptable given that this is a hybrid application with an originator product that has been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 13 July 2010. After a subsequent national phase, the licence was granted in the UK on 12 August 2010.

II. ABOUT THE PRODUCT

Name of the product in the Reference Member State	Dorzolamide 20mg/ml eye drops,solution
Name(s) of the active substance(s) (INN)	Dorzolamide hydrochloride
Pharmacotherapeutic classification (ATC code)	Antiglaucoma preparations and miotics, carbonic anhydrase inhibitor (S01EC03)
Pharmaceutical form and strength(s)	Eye drops, solution
Reference numbers for the Mutual Recognition Procedure	UK/H/1757001DC
Reference Member State	United Kingdom
Member States concerned	Belgium, Czech Republic, Germany, Denmark, Greece, Finland, France, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Sweden, Slovakia
Marketing Authorisation Number(s)	PL 04569/0911
Name and address of the authorisation holder	Generics [UK] Limited, Station Close, Potters Bar, Hertfordshire EN6 1TL.

III SCIENTIFIC OVERVIEW AND DISCUSSION

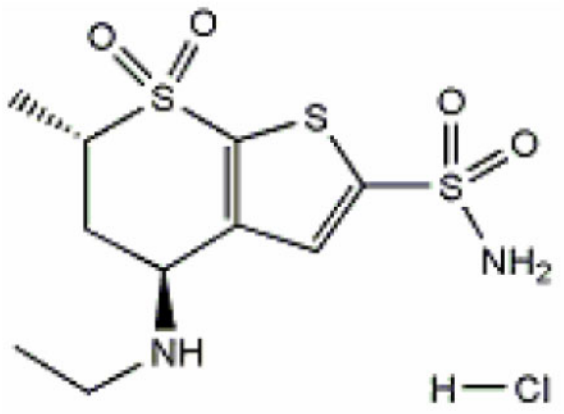
III.1 QUALITY ASPECTS

S. Active substance

INN: Dorzolamide hydrochloride

Chemical name: (4S-trans) – 4 – (Ethylamino) – 5,6 – dihydro – (6S) – methyl – 4H – thieno – [2,3 –b]thiopyran – 2 – sulphonamide – 7,7 – dioxide, monohydrochloride salt.
It is a 4S Trans, 6S stereoisomer.

Structure:



Molecular formula: $C_{10}H_{16}N_2O_4S_3 \cdot HCl$

Molecular weight: Base:324.44 Salt (HCl):360.90

Appearance: Dorzolamide hydrochloride is a white to off white, odourless crystalline powder. Dorzolamide hydrochloride presents two different polymorphic forms (Form A and Form B).

Dorzolamide hydrochloride is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients mannitol, hydroxyethyl cellulose, (Natrosol HX 250), sodium citrate, sodium hydroxide for pH adjustment, benzalkonium chloride solution 50 % and water for injection.

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with their respective monograph.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate a stable ophthalmic preparation that is comparable in performance to the reference product Truspot 2% Eye drops, solution (Merck Sharp & Dohme Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Container-Closure System

The finished product is packaged in medium density polyethylene bottles with a sealed dropper tip and a two-piece cap assembly in a cardboard box in pack sizes of 1 x 5ml bottle, 3 x 5ml bottle and 6 x 5ml bottle.

It has been stated that not all pack sizes may be marketed, however, the marketing authorisation holder has committed to submitting the mock-ups for any pack size to the relevant regulatory authorities for approval before marketing.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product

Stability studies were performed in accordance with current guidelines on batches of the finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years (unopened) which reduces to 28 days once opened. The storage conditions are ‘Keep the bottle in the outer carton in order to protect from light. Store below 30°C’

Bioequivalence/bioavailability
Bioequivalence studies are not necessary to support this application.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA forms
The MAA form is satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of dorzolamide hydrochloride are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products' pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS

Pharmacokinetics
No new data have been submitted and none are required.

Biowaiver
No clinical studies have been conducted to support the application. Essential similarity with the originator product is based on the comparative quality attributes of the product. The applicant refers to clarification provided from the Co-ordination Group for Mutual Recognition and Decentralised Procedures - human (CMD(h)) [CMD (h) minutes from meeting held on 20 and 21 April 2009], this application is being made under Article 10.3 of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption - in this case – after ocular administration. As bioavailability studies are not required (per Article 10.3 of the directive) and do not form part of the development strategy for this product (due to the biowaiver), the product is not designated a generic, but is rather a hybrid version of the reference product.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for this application.

Efficacy
No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical overview. The efficacy of dorzolamide hydrochloride is well-established from its extensive use in clinical practise.

Safety
No new safety data were submitted and none were required for this application.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A suitable justification has been provided for not submitting a Risk Management Plan for this product.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in-line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a clinical viewpoint.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Dorzolamide20mg/ml eye drops, solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY AND SAFETY
No clinical studies have been conducted to support the application. Essential similarity with the originator product is based on the comparative quality attributes of the product. The applicant refers to clarification provided from the Co-ordination Group for Mutual Recognition and Decentralised Procedures - human (CMD(h)) [CMD (h) minutes from meeting held on 20 and 21 April 2009], this application is being made under Article 10.3 of Directive 2001/83/EC, which states that bioequivalence cannot be demonstrated through bioavailability studies for products for local use intended to act without systemic absorption -

in this case – after ocular administration. As bioavailability studies are not required (per Article 10.3 of the directive) and do not form part of the development strategy for this product (due to the biowaiver), the product is not designated a generic, but is rather a hybrid version of the reference product.

No new or unexpected safety concerns arise from this application.

The SmPC, PIL and labelling are satisfactory

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with dorzolamide hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome