Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Dorzolamide/Timolol 20 mg/ml + 5 mg/ml eye drops, solution in single-dose container

(dorzolamide hydrochloride and timolol maleate)

UK Licence No: PL 35533/0086

Aspire Pharma Limited

LAY SUMMARY

Dorzolamide/Timolol 20 mg/ml + 5 mg/ml eye drops, solution in a single-dose container

(dorzolamide hydrochloride and timolol maleate)

This is a summary of the Public Assessment Report (PAR) for Dorzolamide/Timolol 20 mg/ml + 5 mg/ml eye drops, solution in single-dose container (PL 35533/0086). For ease of reading, this medicinal product will be called 'Dorzolamide/Timolol eye drops, solution' in the remainder of this lay summary. It explains how Dorzolamide/Timolol eye drops, solution was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Dorzolamide/Timolol eye drops, solution.

For practical information about using Dorzolamide/Timolol eye drops, solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Dorzolamide/Timolol eye drops, solution and what is it used for?
Dorzolamide/Timolol eye drops, solution is a 'hybrid medicine'. This means that it is similar to a reference medicine, COSOPT Preservative-Free 20 mg/ml + 5 mg/ml, eye drops, solution in single-dose container (PL 16058/0015; Santen Oy, Finland) containing the same active substances.

Dorzolamide/Timolol eye drops, solution is prescribed to lower raised pressure in the eye in the treatment of glaucoma when beta-blocker eye drop medicine used alone is not adequate.

How does Dorzolamide/Timolol eye drops, solution work?
Dorzolamide/Timolol eye drops, solution contains the active ingredients dorzolamide (as dorzolamide hydrochloride) and timolol (as timolol maleate). Dorzolamide belongs to a group of medicines called "carbonic anhydrase inhibitors" and timolol belongs to a group of medicines called "beta blockers". These medicines lower the pressure in the eye in different ways.

How is Dorzolamide/Timolol eye drops, solution used?
The pharmaceutical form of this medicine is an eye drop, solution in single-dose container and the route of administration is by application into the eye (ocular use).

This medicine can only be obtained with a prescription

The patient should always use this medicine exactly as the prescribing doctor has advised. The patient should check with his/her doctor or pharmacist if he/she is not sure.

The appropriate dosage and duration of treatment will be established by the patient's doctor.

The recommended dose is one drop in the affected eye(s), in the morning and in the evening.

If the patient is using Dorzolamide/Timolol eye drops, solution with another eye drop, the drops should be instilled at least 10 minutes apart.

Patients must not change the dose of the medicine without consulting their doctor.

There is limited experience with the use of this medicine in infants and children.

The patient should not allow the single-dose container to touch the eye or areas around the eye. This could cause injury to the eye(s). Also, the single-dose container 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 single-dose container, the patient should wash his/her hands before using this medicine and keep the tip of the single-dose container away from contact with any surface. A new single-dose container should be opened immediately prior to each use; there is enough solution in each container for both eyes if the prescribing doctor has advised the patient to use the drops in both eyes.

The patient should discard the opened container with any remaining contents immediately after use.

For further information on how Dorzolamide/Timolol eye drops, solution is used, please see the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Dorzolamide/Timolol eye drops, solution have been shown in studies?
Since Dorzolamide/Timolol eye drops, solution is a hybrid application, studies have been limited to tests to determine that this medicine is pharmaceutically equivalent to, and demonstrates equivalent physicochemical characteristics as, the reference medicine, COSOPT Preservative-Free 20 mg/ml + 5 mg/ml, eye drops, solution in single-dose container (PL 16058/0015; Santen Oy, Finland). On this basis, it is considered that Dorzolamide/Timolol eye drops, solution is therapeutically equivalent to the reference product. Two medicines are therapeutically equivalent when they produce the same measure of therapeutic effect in the body.

What are the possible side effects from Dorzolamide/Timolol eye drops, solution?
Like all medicines, eye drops, solution can cause side effects although not everybody gets them.

The following adverse reactions have been reported with this medicine or one of its components either during clinical trials or during post-marketing experience:

Very common (may affect more than 1 in 10 people):

Burning and stinging of the eyes, taste perversion.

Common (may affect up to 1 in 10 people):

Redness in and around the eye(s), watering or itching of the eye(s), corneal erosion (damage to the front layer of the eyeball), swelling and/or irritation in and around the eye(s), feeling of having something in the eye, decreased corneal sensitivity (not realising of getting something in the eye and not feeling pain), eye pain, dry eyes, blurred vision, headache, sinusitis (feeling of tension or fullness to the nose), nausea, weakness/tiredness and fatigue.

For the full list of all side effects reported with eye drops, solution, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for eye drops, solution.

Why is Dorzolamide/Timolol eye drops, solution approved?
It was concluded that, in accordance with EU requirements, Dorzolamide/Timolol eye drops, solution has been shown to have comparable quality attributes to COSOPT Preservative-Free 20 mg/ml + 5 mg/ml, eye drops, solution in single-dose container (PL 16058/0015; Santen Oy, Finland).Therefore, the MHRA decided that, as for COSOPT Preservative-Free 20 mg/ml + 5 mg/ml, eye drops, solution in single-dose container (PL 16058/0015; Santen Oy, Finland), the benefits outweigh the identified risks and recommended that Dorzolamide/Timolol eye drops, solution can be approved for use in the treatment of glaucoma when beta-blocker eye drop medicine used alone is not adequate.

What measures are being taken to ensure the safe and effective use of Dorzolamide/Timolol eye drops, solution?

A risk management plan has been developed to ensure that Dorzolamide/Timolol eye drops, solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Dorzolamide/Timolol eye drop solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Dorzolamide/Timolol eye drops, solution

A Marketing Authorisation was granted in the UK on 16 August 2018.

The full PAR for Dorzolamide/Timolol eye drops, solution follows this summary.

This summary was last updated in October 2018.

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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Aspire Pharma Limited, a Marketing Authorisation for the medicinal product for Dorzolamide/Timolol 20 mg/ml + 5 mg/ml eye drops, solution in single-dose container (PL 35533/0086) on 16 August 2018. This product is a Prescription Only Medicine (POM) and is 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. For ease of reading, the medicinal product will be referred to as 'Dorzolamide/Timolol eye drops, solution' in this scientific discussion.

This application was submitted as abridged national application, according to Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference product for the purpose of data exclusivity is COSOPT 20 mg/ml + 5 mg/ml, eye drops, solution (PL 16058/0016; Santen Oy, Finland), a preservative-containing, multi-dose eye drops solution formulation, which was first authorised in Denmark to Merck Sharpe & Dohme B.V. by Denmark on 06 March 1998 and subsequently in the UK (PL 00025/0373) via a Mutual Recognition Procedure (MRP) on 04 August 1998. The reference product for data alignment is COSOPT Preservative-Free 20 mg/ml + 5 mg/ml, eye drops, solution in single dose container (PL 16058/0015; Santen Oy, Finland), which was first authorised to Merck Sharpe & Dohme B.V. by Denmark on 11 August 2005 and subsequently in the UK (PL 00025/0698), via a MRP on 31 July 2006).

Dorzolamide/Timolol eye drops, solution contains two active substances called 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.

No new non-clinical or clinical studies were conducted, which is acceptable given that this application was based on being hybrid medicinal product of originator product that has been licensed for over 10 years.

Comparable physico-chemical parameters between the proposed and reference and proposed products were provided. In accordance with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, a waiver of a therapeutic equivalence study between the proposed and the reference products has been granted.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacturing and assembly of this product. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Dorzolamide/Timolol eye drops, solution outweigh the risks and a Marketing Authorisation was granted.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a clear, colourless to nearly colourless, slightly viscous solution, with a pH between 5.5 and 5.8, and an osmolarity of 270-325 mosmol/kg.

Each ml of eye drops solution contains 22.26 mg of dorzolamide hydrochloride corresponding to 20 mg dorzolamide and 6.83 mg of timolol maleate corresponding to 5 mg timolol. The product also contains pharmaceutical excipients, namely hydroxyethyl cellulose, mannitol (E421), sodium citrate (E331), sodium hydroxide (E524) for pH adjustment and water for injections.

The finished product is packaged in 0.2 ml low density polyethylene single-dose containers in an aluminium sachet containing 5 single-dose containers.

The product is available in the following pack sizes:

- 30 x 0.166 ml (6 sachets with 5 single-dose containers)
- 60 x 0.166 ml (12 sachets with 5 single-dose containers)
- 120 x 0.166 ml (24 sachets with 5 single dose containers)

Not all pack sizes may be marketed.

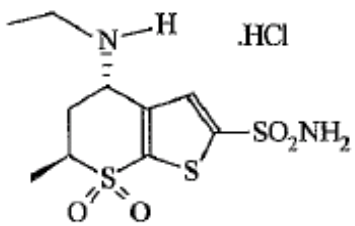
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug Substance

(1) Dorzolamide hydrochloride

INN:	Dorzolamide hydrochloride
Chemical Name:	(4S,6S)-4-(Ethylamino)-6-methyl-5,6-dihydro-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide hydrochloride

Structure:



Molecular Formula:	$C_{10}H_{16}N_2O_4S_3$-HCl
M_r:	Base: 324.44 Hydrochloride =360.90
Appearance:	White or almost white crystalline powder
Solubility	Soluble in water, slightly soluble in methanol, very slightly soluble in anhydrous ethanol
Polymorphism	Dorzolamide hydrochloride exhibits polymorphism
Isomerism	Dorzolamide hydrochloride exhibits stereoisomerism

Appearance: White or almost white, crystalline powder.
Solubility: Soluble in water, slightly soluble in methanol and very slightly soluble in anhydrous ethanol.

Dorzolamide hydrochloride is the subject of a European Pharmacopoeia monograph.

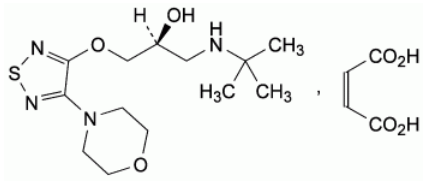
All aspects of the manufacture and control of the active substance, dorzolamide hydrochloride, are covered by European Directorate for the Quality of Medicine and Healthcare (EDQM) Certificates of Suitability.

(2) Timolol maleate

INN: **Timolol maleate**

Chemical name(s): (2S)-1-[(1,1-dimethylethyl)amino]-3-[[4-morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol (Z)-butenedionate (1:1) salt.

Structure:



Molecular formula: $C_{17}H_{28}N_4O_7S$
Molecular weight: 432.5 g/mol
Appearance: White or almost white crystalline powder or colourless crystals.
Solubility: Soluble in water and in ethanol (96%)

Timolol maleate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, timolol maleate, are covered by a European Directorate for the Quality of Medicines Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a stable eye drop solution that could be considered as a hybrid medicinal product of reference product COSOPT 20 mg/ml + 5 mg/ml Eye Drops solution in single-dose container (Merck Sharp & Dohme Limited).

The physicochemical properties of the proposed product versus the reference product have shown that the products are comparable.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used in the product contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Based on full-scale production batches, the manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 3 years for unopened bottle with special storage conditions 'Do not store above 25°C', 'Do not refrigerate or freeze' and 'Store in the original package in order to protect from light' has been approved.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended, from a quality point of view.

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of dorzolamide hydrochloride and timolol maleate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

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

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Environmental Risk Assessment (ERA)
Since Dorzolamide/Timolol eye drops, solution is intended for generic substitution, its use will not lead to an increased exposure to the environment. An environmental risk assessment is, therefore, not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of originator product that has been licensed for over 10 years.

There are no objections to the approval of this application, from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of dorzolamide hydrochloride and timolol maleate are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In accordance with the guidance on 'The clinical requirements for locally applied, locally acting products containing known constituents' (CPMP/EWP/239/95/final) and the 'Note for guidance on the investigation of bioavailability and bioequivalence', no bioavailability, pharmacodynamics, or comparative clinical studies have been performed with the test product which is a locally applied, locally acting, ophthalmic solution.

A biowaiver is considered satisfactorily justified on the basis of pharmaceutical equivalence and demonstrated equivalent physicochemical characteristics of the test and reference medicinal products.

IV.3 Pharmacodynamics

No new pharmacodynamics data are required for this application and none have been submitted.

IV.4 Clinical efficacy

No new clinical efficacy data are required for this application and none have been submitted.

IV.5 Clinical safety

No new clinical safety data are required for this application and none have been submitted.

IV.6 Risk Management Plan (RMP)

The Marketing Authorisation Holder (MAH) has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dorzolamide/Timolol eye drops, solution.

A summary of safety concerns is listed in the table below:

Table 1: Summary table of safety concerns:

Important identified risks	• Systemic beta-blockade associated side effects • Cardiac disorders • Vascular disorders • Respiratory disorders (including bronchospasm, worsening of pre-existing reactive respiratory diseases) • Ophthalmic disorders (including Corneal disorders and choroidal detachment) • Hypoglycaemia/diabetes • Interaction with surgical anaesthesia • Anaphylactic reactions • Drug interaction with other beta-blocking agents, CYP2D6 inhibitors, adrenaline
Important potential risks	• Eye infection (including bacterial keratitis) or injury • Sulphonamide-associated severe hypersensitivity reactions • Urolithiasis • Medication error
Missing information	• Use in pregnancy/ breast-feeding women • Use in patients with hepatic or severe renal impairment • Use in paediatric patients

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended, from a clinical point of view.

V USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Dorzolamide/Timolol 20mg/ml + 5mg/ml eye drops, solution (PL 17277/0052). The bridging report has been found to be acceptable.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. Extensive clinical experience with timolol maleate and dorzolamide hydrochloride is considered to have demonstrated the therapeutic value of the compounds A biowaiver on the basis of pharmaceutical equivalence and demonstrated equivalent physicochemical characteristics of the test and reference medicinal products has been accepted.

The benefit-risk assessment is, therefore, considered to be positive.

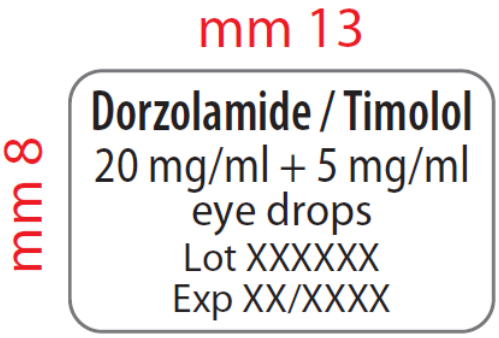
The grant of a Marketing Authorisation is recommended

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

The current approved labelling for Dorzolamide/Timolol eye drops, solution in single-dose container is provided below:


Dorzolamide/Timolol
20mg/ml + 5mg/ml eye drops, solution
in single-dose container
1ml of solution contains 20mg of dorzolamide
(as hydrochloride) and 5mg of timolol (as maleate)
Also contains: Mannitol, sodium citrate, hydroxyethyl
cellulose, sodium hydroxide, water for injections.
See the leaflet for further information.
Ocular use. Read the package leaflet before use.
Keep out of the sight and reach of children.
For single use only.
Once the sachet is opened, use the single-dose containers
within 7 days.
Do not store above 25°C.
Do not refrigerate or freeze.
Keep single-dose containers in the original package in order
to protect from light.
Discard the opened single-dose container immediately
after use.
MA Holder:
Aspire Pharma Limited
Unit 4, Rotherbrook Court, Bedford Road, Petersfield
Hampshire, GU32 3QG, UK
POM PL 35533/0086 1010425-S1.13
5 single-dose containers
Lot:
Exp:


mm 13
mm 8
Dorzolamide / Timolol
20 mg/ml + 5 mg/ml
eye drops
Lot XXXXXX
Exp XX/XXXX

Dorzolamide/Timolol 20 mg/ml + 5 mg/ml eye drops, solution in single-dose container

(dorzolamide hydrochloride and timolol maleate)

UK Licence No: PL 35533/0086

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome