Public Assessment Report

UKPAR

Dorzolamide / Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution

(Dorzolamide hydrochloride and timolol maleate)

UK Licence No: PL 18956/0019

Medicom Healthcare Ltd.
LAY SUMMARY

Dorzolamide / Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution
(Dorzolamide hydrochloride 20 mg/ml, timolol maleate 5 mg/ml, eye drops, solution)

This is a summary of the Public Assessment Report (PAR) for Dorzolamide / Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution (PL 18956/0019). It explains how Dorzolamide / Timolol 20 mg/ml + 5 mg/ml 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 20 mg/ml + 5 mg/ml Eye Drops, Solution.

The product will be referred to as Dorzolamide/Timolol throughout the remainder of this PAR.

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

What is Dorzolamide/Timolol and what is it used for?
Dorzolamide/Timolol 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.

This medicine is the same as Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution (PL 17918/0016) which is already authorised.

The company (Tubilux Pharma S.p.A) that makes Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution (PL 17918/0016) has agreed that its scientific data can be used as a basis for the grant of an identical licence for Dorzolamide/Timolol (informed consent).

How does Dorzolamide/Timolol work?
Dorzolamide/Timolol contains two medicines: dorzolamide and timolol.
- Dorzolamide belongs to a group of medicines called “carbonic anhydrase inhibitors”.
- 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 used?
The pharmaceutical form of this medicine is an eye drops, solution and the route of administration is for use in the eye (ocular use).

The patient should always use this medicine exactly as their doctor has told them. They should check with their doctor or pharmacist if they are 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 with another eye drop, the drops should be instilled at least 10 minutes apart.

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

Do not allow the tip of the container to touch the eye or areas around the 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, the patient should wash their hands before using this medicine and keep the tip of the container away from contact with any surface. If the patient thinks their medication may be contaminated, or if they develop an eye infection, the patient should contact their doctor immediately concerning continued use of this bottle.

Please refer to section 3 of the package leaflet for information on how to use and apply this medicine.

This medicine can only be obtained with a prescription.

For further information on how Dorzolamide/Timolol is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

**What benefits of Dorzolamide/Timolol have been shown in studies?**
The application for Dorzolamide/Timolol is considered to be identical to the previously authorised application for Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution (PL 17918/0016), with the same benefits and risks, so, no new studies have been provided for Dorzolamide/Timolol but reference is made to the studies for Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution (PL 17918/0016).

**What are the possible side effects from Dorzolamide/Timolol?**
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Dorzolamide/Timolol is considered to be identical to the previously authorised application for Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution (PL 17918/0016) with the same benefits and risks.

For a full list of all the side effects reported with Dorzolamide/Timolol see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

**Why is Dorzolamide/Timolol approved?**
The MHRA decided that the benefits of Dorzolamide/Timolol are greater than their risks and recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Dorzolamide/Timolol?**
A Risk Management Plan has been developed to ensure that Dorzolamide/Timolol 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 including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Dorzolamide/Timolol**
A Marketing Authorisation was granted in the UK on 19 December 2016.

The full PAR for Dorzolamide/Timolol follows this summary.
For more information about treatment with Dorzolamide/Timolol read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2017.
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I INTRODUCTION
The Medicines and Healthcare products Regulatory Agency (MHRA) granted Medicom Healthcare Ltd a Marketing Authorisation for the medicinal product Dorzolamide/Timolol (PL 18956/0019) on 19 December 2016. The product is a Prescription Only Medicine (POM) 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.

This application was submitted as a simple abridged (informed consent) application according to Article 10c of Directive 2001/83/EC, as amended.

The application cross-refers to the reference product Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution, which was first authorised to the marketing authorisation holder Tubilux Pharma S.p.A (PL 17918/0016) on 07 March 2013 via the Decentralised procedure with Italy as reference member state (RMS) and Germany and the UK as concerned member states (CMSs).

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

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase II. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humor secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

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

No new data were submitted nor were necessary to be submitted for this application, as the data are identical to the data for the previously granted cross-referenced product.
II QUALITY ASPECTS

II.1 Introduction
This is an abridged application for Dorzolamide/Timolol (PL 18956/0019) submitted under Article 10c of Directive 2001/83/EC, as amended.

The application cross-refers to the reference product Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution, which was first authorised to the marketing authorisation holder Tubilux Pharma S.p.A (PL 17918/0016) on 07 March 2013 via the Decentralised procedure with Italy as reference member state (RMS) and Germany and the UK as concerned member states (CMSs). The application is considered valid.

II.2 Drug Substance

Drug substance specifications
The proposed drug substance specifications are consistent with the details registered for the cross-reference product.

II.3 Medicinal Product

Name
The proposed product name for this application is Dorzolamide / Timolol 20 mg/ml + 5 mg/ml Eye Drops, Solution. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes
Each ml of eye drops solution contains 22.3 mg of dorzolamide hydrochloride corresponding to 20 mg dorzolamide and 6.84 mg of timolol maleate corresponding to 5 mg timolol.

The finished product is packed into low density polyethylene bottles with a low density polyethylene tip and a polypropylene tamper-evident cap. Each bottle contains 5 ml of eye drops solution and is available in a pack size of 1 single bottle.

The proposed shelf life of the unopened product is 3 years with the storage conditions ‘This medicinal product does not require any special temperature storage conditions. Keep the bottle in the outer carton in order to protect from light.’

Once opened, the in-use shelf life of the product is 28 days after first opening.

The proposed packaging, shelf-life and storage conditions are consistent with the details registered for the cross-reference product.

Legal status
Prescription only medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Medicom Healthcare Ltd, 235 Hunts Pond Road, Titchfield Common, PO14 4PJ, UK.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.
Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process
The proposed manufacturing processes are consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

TSE Compliance
None of the excipients contain materials of animal or human origin. This is consistent with the cross-reference product.

Bioequivalence
No bioequivalence data are required to support this simple abridged application because the proposed product is manufactured to the same formula utilising the same processes as the cross-reference product, Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution (PL 17918/0016).

Expert Report
The applicant cross-refers to the data for Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution (PL 17918/0016) to which this application is claimed to be identical. This is acceptable.

Product Name and Appearance
See Section II.3 ‘Medicinal Product; Name’ for details of the proposed product name. The appearance of the product is identical to that of the cross-reference product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.
III  NON-CLINICAL ASPECTS

Introduction
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV  CLINICAL ASPECTS

Introduction
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

<table>
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<tr>
<th>Important identified risks</th>
<th>Reactive airway disease, bronchial asthma or severe COPD</th>
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<tbody>
<tr>
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<td>Sinus bradycardia, sino-atrial block, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock</td>
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<td>Hypersensitivity</td>
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<td>Use in severe renal impairment</td>
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<td>Important potential risks</td>
<td>Vascular disorders</td>
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<td>Masking of hypoglycaemic symptoms in patients with diabetes mellitus</td>
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<td></td>
<td>Masking of thyrotoxicosis</td>
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<td></td>
<td>Surgical anaesthesia</td>
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<td>Concomitant use with other oral or topical carbonic anhydrase inhibitors or beta-blockers</td>
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<td></td>
<td>Choroidal detachment</td>
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<td>Corneal oedema in patients with low endothelial cell counts</td>
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<td>Missing information</td>
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<td>Use in lactation</td>
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<td></td>
<td>Use in children younger than 2 years of age</td>
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Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.
Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended.

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 the product for Dorzolamide / Timolol 20 mg/ml + 5 mg/ml eye drops, solution (PL 17918/0016). The bridging report submitted by the applicant is acceptable.

VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with dorzolamide and timolol is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.
**Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels**

The Summary of Product Characteristics and Patient Information Leaflet (PIL) are consistent with the details registered for the cross-reference product.

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

The approved labelling for this medicine is presented below:
Annex 1

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

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<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
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