CBG MEB

Public Assessment Report

Scientific discussion

Dorzolamide Warren 20 mg/ml eye drops, solution

(dorzolamide hydrochloride)

NL/H/3236/001/DC

Date: 2 November 2017

This module reflects the scientific discussion for the approval of Dorzolamide Warren 20 mg/ml eye drops, solution. The procedure was finalised on 5 April 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Dorzolamide Warren 20 mg/ml eye drops, solution from Warren Generics s.r.o.

The product 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

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product TRUSOPT 20 mg/ml, eye drops, solution (NL License RVG 17618) which has been registered in the Netherlands by Merck Sharp & Dohme B.V. since 17 January 1995. It is part of mutual recognition procedure FR/H/0070/001.

The concerned member states (CMS) involved in this procedure were Cyprus, Germany, Greece, Hungary and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as for locally acting medicinal products such as eye drops bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Dorzolamide Warren is a slightly opalescent, colourless to nearly colourless, slightly viscous solution, with a pH between 5.5 and 5.8 and an osmolarity of 260-310 mOsm.

Each ml contains as active substance 20 mg of dorzolamide, as 22.3 mg dorzolamide hydrochloride. One drop (33.3 µl) contains 0.667 mg dorzolamide.

The solution is packed in a gamma sterilised translucent low density poly ethylene (LDPE) bottle with translucent LDPE nozzle and white high density polyethylene (HDPE) cap with a tamper evident ring, that has to be broken upon first time use. Each bottle contains 5 ml eye drop solution.

The excipients are: benzalkonium chloride, hydroxyethyl cellulose, mannitol (E421), sodium citrate (E331), sodium hydroxide (E524) for pH adjustment and water for injections.

II.2 Drug Substance

The active substance is dorzolamide hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a white or almost white, crystalline powder. It is soluble in water, slightly soluble in methanol and very slightly soluble in anhydrous ethanol. Since the drug product is a solution the particle size and the polymorphic form of the drug substance are not critical.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological

quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and is in line with the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 5 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 commercial scale batches stored at 30°C/65% RH (60 months) and 40°C/75% RH (6 months). A small increase in one impurity is observed at 30°C/65% RH after 18 months, 24 months and 48 months, but the Ph.Eur. limit is met. Based on the available data a retest period of 36 months in the commercial packaging configurations is justified without specific storage condition.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of the excipients justified and their functions explained. The efficacy of antimicrobial preservation has been shown at both the release and the proposed end of shelf-life lower limit. The choice of the sterilisation method was justified. The composition of the drug product was based on the composition of the reference product.

The MAH demonstrated that the drug product is essentially similar to the reference product TRUSOPT. Both products are intended for topical use by application on the ocular surface. The physicochemical properties of three batches reference product are fully comparable with those of one batch of test product, as demonstrated by the results of comparative analysis (e.g. pH, osmolality, viscosity, buffering capacity, benzalkonium chloride content, impurity profile and dorzolamide content). Also it is sufficiently shown that the drop weight and drops per ml of the test and reference product are comparable.

Manufacturing process
A slurry of hydroxyethyl cellulose and mannitol is prepared and sterilised by autoclaving. The drug substance dorzolamide hydrochloride, sodium citrate and benzalkonium chloride are dissolved in water for injection, the pH is adjusted and the solution is aseptically filtered. The sterilised slurry and the drug/buffer solution are mixed to obtain the final bulk solution. After filtration, the bulk solution is filled in the primary container under nitrogen. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three consecutive commercial batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Microbiological attributes
The drug product is routinely tested for sterility. This is in line with the requirements for eye drops solutions of the general Ph.Eur. eye preparations monograph. Preservative efficacy down to a benzalkonium chloride content of 90% of the product specification was demonstrated.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, filling volume, weight loss, pH, osmolality, viscosity, sub-visible particles, container-closure integrity, clarity and degree of opalescence, degree of coloration, assay, related substances, sterility and efficacy of antimicrobial

preservation. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 4 batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data have been provided for 3 commercial scale batches packed in the proposed packaging. The drug product has been stored under reduced humidity at long-term conditions (25°C/40% RH) for 36 months and accelerated conditions (40°C/25% RH) for 6 months. In-use testing was performed according to the dose regimen in the SmPC during 28 days at 25°C/40% RH (initial and at end of shelf-life). At accelerated conditions (6 months), at long term conditions (36 months) and during 28 days in-use testing the batches remained within specification. Weight loss data adequately demonstrate that the aqueous-based eye drops stored in semi-permeable containers could withstand low relative humidity environments.
Based on the stability data provided, the shelf-life of 24 months and the proposed in-use shelf-life after first opening of 28 days is justified without additional storage conditions. The drug product packed in the primary container is not stable under the influence of light and the bottle should be kept in the outer carton.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Dorzolamide Warren has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dorzolamide Warren is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of TRUSOPT which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dorzolamide hydrochloride is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver
No comparative bioavailability studies have been conducted to support the application. Essential similarity with the originator product is based on comparative qualitative attributes of the product. The Guideline on requirements for locally applied, locally acting products, containing known constituents (CPMP/239/95) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed.
Since the qualitative and quantitative composition of the product is similar to that of the reference product TRUSOPT 20 mg/ml eye drops, solution and the pharmaceutical properties (i.e. osmolality, pH, relative density, surface tension and droplet volume) are comparable to that of the reference product as well, a biowaiver can be granted. Dorzolamide Warren may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product.

IV.3 Risk Management Plan

The 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 Warren.

Summary table of safety concerns as approved in RMP:

Important identified risks	- Use in patients with corneal decompensation
Important potential risks	- The risk of metabolic acidosis - Effects of carbonic anhydrase inhibition - Long term use of preserved eye drops
Missing information	- Hepatic impairment - Use in pregnant and breastfeeding women - Renal impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product TRUSOPT. No new clinical studies were conducted. It is accepted that no new clinical and bioequivalence studies were conducted, while essential similarity was shown. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. A total number of 16 questions was asked. 12 questions specifically addressed the key safety messages of the leaflet in a randomised order and 4 additional, solicited questions were asked to complete the questionnaire with regards to positive, negative and stylistic feedback about the readability of the PL. The technical readability, comprehensibility of the text, traceability of information and the applicability were investigated in the test.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dorzolamide Warren 20 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of TRUSOPT 20 mg/ml, eye drops, solution. TRUSOPT is a well-known medicinal product with an established favourable efficacy and safety profile.

Dorzolamide Warren is a product for ocular use (eye drops) intended to act without systemic absorption. Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of in vitro studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dorzolamide Warren with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 April 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3236/001/IB/001	Update of PI	PI	12-4-2017	Approval	