COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dorzolamide Brown & Burk 20 mg/ml preservative-free eye drops solution, single dose container (dorzolamide hydrochloride)

(NL/H/5104/001/DC)

Date: 16-11-2021

This module reflects the scientific discussion for the approval of Dorzolamide Brown & Burk 20 mg/ml preservative-free eye drops solution, single dose container. The procedure was finalised at 5 July 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
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 Brown & Burk 20 mg/ml preservative-free eye drops solution, single dose container, from Brown & Burk IR Ltd.

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.

This product is also indicated for the treatment of elevated intra-ocular pressure in:

- ocular hypertension,
- open-angle glaucoma,
- pseudoexfoliative 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 preservative-free 20 mg/mL eye drops solution, single dose container (FR/H/0070/002) which has been registered in France by Santen Oy (original product). A hybrid application procedure is justified as bioequivalence cannot be demonstrated through bioavailability studies. Essential similarity with the reference product is claimed on the basis of the same qualitative and quantitative composition in term of active drug substance, same pharmaceutical form and physico-chemical characterization.

The concerned member states (CMS) involved in this procedure were Sweden and the United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Dorzolamide Brown & Burk 20 mg/ml preservative-free eye drops is a colourless to nearly colourless, slightly viscous solution.

This product contains as active substance 20 mg of dorzolamide hydrochloride per ml. One drop contains approximately 0.75 mg dorzolamide hydrochloride.

The solution (0.2 ml) is packed in a low density polyethylene single dose container in an aluminium sachet.

The excipients are hydroxyethyl cellulose (E476), 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. The active substance is a white or almost white crystalline powder, is soluble in water, slightly soluble in methanol and very slightly soluble in anhydrous ethanol. Dorzolamide hydrochloride contains two chiral carbon atoms in its structure and exists as S and R isomers. The drug substance manufactured is crystalline Form II.

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 in line with the Ph.Eur., the CEP and additional test for residual solvents. The specification is acceptable in view of the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches. All results are found within the proposed specification limits.

Stability of drug substance

The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies concerned the characterization of the reference product and comparative characteristics studies (i.e. pharmaceutical equivalence). The comparative studies included the following parameters: appearance, pH, specific gravity, surface tension, buffer capacity, tonicity, osmolality, viscosity, impurities, assay and drop size. All parameters were found comparable between three batches of the reference and three batches of the test product. A waiver of the need to provide equivalence data is considered in accordance with the Guideline on the Investigation of Bioequivalence, as the test product is the same type of aqueous solution and contains the same active substance and same excipients as the medicinal product currently approved. The excipients used are well known and are the same as those present in the reference product. The pharmaceutical development of the product has been adequately performed and pharmaceutical equivalence has been shown.

Manufacturing process

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial scaled batches in accordance with the relevant European guidelines. The manufacturing process consists of preparing a bulk solution, filtration of the bulk solution and a second solution, sterilisation and aseptic transfer of the second solution, mixing of both sterile solutions and aseptic filling. The product is manufactured using conventional manufacturing techniques. In-process Controls and Control of Critical Processes have been adequately described. The in-process controls are as per EMA Q&A on the functional qualities of plastic containers for eye drops. The holding time from sterilization filtration of buffer solution to end of filling is acceptable.

Control of excipients

The excipients comply with Ph.Eur. requirements. Their specifications are acceptable. Tests and limits for relevant functionality related characteristics described in the Ph.Eur. monograph of the excipient Hydroxyethyl cellulose have been proposed. These specifications are acceptable.

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, clarity, colour, pH, osmolality, viscosity, extractable volume, assay of dorzolamide, particulate contamination, related substances, sterility and water loss. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The specification is acceptable. A risk evaluation (RE) on possible contamination from N-nitrosamines has been provided and is acceptable as per EMA/409815/2020.

The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three commercial scaled batches demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three commercial scaled batches stored at 25°C/40% RH (up to 22 months), 30°C/75% RH (12 months) and 40°C/25% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in 0.2 ml low density polyethylene single- dose containers in an opened (in-use stability) or unopened (formal stability) aluminium sachet.

Under accelerated conditions out of specification results are observed for the impurity B and total impurities. Under intermediate and long-term conditions the drug product remains stable and complies with the proposed shelf-life specification. The proposed shelf-life of 24 months for the unopened aluminium pouch with the storage condition do not store above 30°C is acceptable.

In-use stability data have been provided demonstrating that the product remains stable for 15 days following the first opening of the aluminium sachet when stored at 25ºC/40% RH. Results out of specification for Impurity B were obtained after 15 days at accelerated storage condition (40ºC/25% RH). The proposed in-use shelf life of 15 days for the opened aluminium pouch with the storage condition do not store above 30°C is acceptable.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is photostable when exposed to light in the marketed pack. Freeze-thaw studies were performed and showed that the product is stable to temperature excursions outside the labelled storage temperature.

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 Brown & Burk 20 mg/ml preservative-free eye drops 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 Brown & Burk 20 mg/ml preservative-free eye drops is intended for hybrid 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 preservative-free 20 mg/mL eye drops solution, single dose container 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. No clinical studies have been conducted to support the application. Essential similarity with the originator product is claimed to be based on comparative qualitative attributes of the product. The RMS finds this approach acceptable, as the product is an aqueous solution, the formulation is similar and the intended use and posology are identical. Overview based on literature review is, thus appropriate.

IV.2 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 Brown & Burk 20 mg/ml preservative-free eye drops.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• None
Missing information	• None

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

IV.3 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. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to TRUSOPT preservative-free 20 mg/ml eye drops, solution in single-dose container (FR/H/0070/002). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dorzolamide Brown & Burk 20 mg/ml preservative-free eye drops solution, single dose container has a proven chemical-pharmaceutical quality and is a hybrid form of TRUSOPT preservative-free 20 mg/mL eye drops solution, single dose container. TRUSOPT is a well-known medicinal product with an established favourable efficacy and safety profile.

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 Brown & Burk 20 mg/ml preservative-free eye drops with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 July 2021.

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