COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Trusmono 20 mg/ml eye drops, solution

(dorzolamide hydrochloride)

NL Licence RVG 123865

Date: 22 October 2020

This module reflects the scientific discussion for the approval of Trusmono 20 mg/ml eye drops, solution. The marketing authorisation was granted on 13 January 2020. 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
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Trusmono 20 mg/ml eye drops, solution from Rockmed Pharma B.V.

The product is indicated for:
- 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
- pseudoexfoliative glaucoma.

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

This national procedure concerns a hybrid application. Similarity is claimed with the innovator product Trusopt 20 mg/ml eye drops, solution (NL licence RVG 17618) which has been registered by Santen OY since per 17 January 1995. A preservative-free formulation, Trusopt Preservative-Free 20 mg/ml eye drops, solution in single-dose container (NL licence RVG 32633) has been registered by Santen Oy since 23 January 2006. Trusopt Preservative-Free is available in a single-dose container, while Trusmono is provided in a multi-dose preservative-free bottle.

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

Trusmono 20 mg/ml is a clear, colourless, slightly viscous solution with a pH of 5.0 to 6.0 and osmolality between 270 and 310 mOsm/kg.

The solution is packed in a 11 ml low density polyethylene (LDPE) white opaque plastic ophthalmic multi-dose dispenser, which is equipped with a HDPE screw-cap. The fill volume is 5 ml.

Each ml contains as active substance 22.26 mg of dorzolamide hydrochloride, equivalent to 20 mg dorzolamide.

Each drop contains 0.73 mg dorzolamide.

The excipients are: hydroxyethyl cellulose (E1525), mannitol (E421), sodium citrate (E331), sodium hydroxide (E524) for pH-adjustment, water for injections.

II.2 Drug Substance

The active substance is dorzolamide hydrochloride, an established active substance, described in the Ph.Eur. The active substance is a white to off-white, odourless crystalline powder is soluble in water and sparingly soluble in ethanol.

The CEP procedure is used for both manufacturers 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
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The specification of the MAH consists of the tests included in the Ph.Eur. monograph of dorzolamide HCl, with one additional test. Batch analysis data showing compliance to the specification is provided of at least three batches of each active substance supplier. Validation of the analytical procedures has been performed. Information on reference standards is provided.

Stability of drug substance
For one CEP-holder, the active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
For the second CEP-holder, stability data on the active substance have been provided for 6 batches, stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 5 years when stored under the stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The choice of the sterilisation method is expected sufficiently justified as per the applicable guidance. The main development studies concerned the characterization of the reference product and comparative characteristics studies. The comparative studies included parameters appearance, extractable volume, drop volume, pH, specific gravity, surface tension, osmolality, viscosity, density, buffer capacity, assay, and impurities. A waiver of the need to provide equivalence data can be 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 MAH has provided a sufficient discussion on these parameters showing (a slight) difference (as applicable) after comparison of three batches of the test and reference product. These differences are acceptable.

The excipients used are well known and are similar to those present in the reference product. The suitability of the container closure system is justified. Sufficient studies have been conducted to support the design of the anti-microbial one way valve, including in-use studies and drop size. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process mainly consists of preparing of bulk solution A (which is sterilized with moist heat), preparing of bulk solution B (which is sterilized via filtration) followed by mixing of both solutions and aseptic filling into bottles. Critical steps and in-process controls are acceptable. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale production batches.

Control of excipients

The excipients comply with Ph.Eur. requirements. Additional data on the functional related characteristics is discussed as relevant and control parameters are adopted accordingly. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, extractable volume, pH, viscosity, osmolality, water loss (stability), identification, related substances, assay, particulate matter, tightness of container closure (release) and sterility. Except for related substances limits the release and shelf-life specifications are the same. The specification is acceptable. The analytical methods have been adequately described and validated; the stability indicating ability of the for assay and related substance method is demonstrated. Batch analytical data from the proposed production site have been provided on 5 batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for 3 full-scale batches stored at 25°C/60% RH (up to 36 months), 30°C/65% RH (up to 12 months) and 40°C/75% RH (up to 6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the white LDPE bottle with a multi-dose HDPE dropper applicator equipped with a HDPE screw-cap. Photostability studies were performed in accordance with ICH recommendations and showed that the product in the primary packaging is stable when exposed to light. Under accelerated, intermediate and long-term conditions for all batches all tested parameters remain nearly stable and within the proposed acceptance limits for all time points. Except for a slight increase in impurities, no upward or downward trend in any of the tested parameters can be detected. The proposed shelf-life of 36 months without storage conditions is acceptable.

Stability data has been provided demonstrating that the product remains stable for 28 days following first opening of the container at all conditions.

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 MEB considers that Trusmono 20 mg/ml eye drops, solution 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 Trusmono 20 mg/ml 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 MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Dorzolamide 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 MEB 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. Trusmono may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substances 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 Trusmono.

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

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant and breast-feeding women

The MEB agrees 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. The product can be considered essentially similar to the reference product based on chemical-pharmaceutical properties. 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 the approved leaflet for Dorzolamide/timolol Preservative-Free 20 mg/ml + 5 mg/ml eye drops, solution, multi-dose container. 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

Trusmono 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.

Trusmono 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.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for this medicinal product with the reference product, and has therefore granted a marketing authorisation. Trusmono 20 mg/ml eye drops, solution was authorised in the Netherlands on 13 January 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse