COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Travoprost Mylan 40 micrograms/ml, eye drops, solution

(travoprost)

NL/H/4928/001/DC

Date: 9 February 2021

This module reflects the scientific discussion for the approval of Travoprost Mylan. The procedure was finalised on 12 November 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
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 Travoprost Mylan 40 micrograms/ml, eye drops, solution from Mylan B.V.

The product is indicated for:

- decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle glaucoma.
- decrease of elevated intraocular pressure in paediatric patients aged 2 months to < 18 years with ocular hypertension or paediatric 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 Travatan 40 micrograms/ml eye drops, solution, which has been registered in the EEA by Alcon Laboratories (UK) Ltd since 2001 through centralised procedure EU/1/01/199/001.

The concerned member states (CMS) involved in this procedure were France, Italy and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Travoprost Mylan 40 micrograms/ml is a clear, colourless solution with pH 5.5-7.0 and osmolality 266-294 mOsmol/kg.

One ml of solution contains 40 micrograms travoprost. One drop contains approximately 1.2 micrograms travoprost.

The solution is packed in 2.5 ml transparent, polypropylene bottle with a sealed LDPE dropper tip and a white HDPE/LDPE screw cap with tamper proof seal, placed inside a PET/ALU/PE sachet.

The excipients are: benzalkonium chloride, macrogolglycerol hydroxystearate 40, trometamol, disodium edetate, boric acid [E284], mannitol, sodium hydroxide (for pH adjustment) [E524], water for injection or purified water.

II.2 Drug Substance

The active substance is travoprost, an established active substance described in the Pharmacopoeia of the United States (USP). The active substance is a colourless to yellowish oil which is practically insoluble in water. Polymorphism is not applicable. The drug substance is optically active due to the presence of multiple chiral centres.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Manufacturer I

The manufacturing process has been described and validated. No class 1 organic solvents are used. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, reagents and solvents.

Manufacturer II

The manufacturing process has been described and validated. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The specification of the MAH is presented as a combined specification including material from both sources. This is acceptable. The specification includes tests for appearance, identification, water content, specific rotation, residue on ignition, heavy metals, assay, related substances and residual solvents.

The batch results show compliance with the specification of the active substance. The information on the reference materials has been provided.

Stability of drug substance

Manufacturer I

Stability data on the active substance have been provided for thirteen batches stored at 2-8°C (up to 24 months) and 25°C/60% RH (6 months). At all storage conditions, accelerated

(25°C/60% RH) and long term (2-8°C), no changes or trends are seen. The proposed retest period of 2 years when protected from light and stored refrigerated (2-8°C) is justified.

Manufacturer II
Stability data on the active substance have been provided for eight production scale batches stored at -20°C (0-36 months) three batches at 5°C (3 months). A re-test period of 3 years is accepted when stored at -20°C.

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 main development studies regarded the characterisation of the reference product and the development of the manufacturing process.
From the provided data it can be concluded that results for the proposed product with respect to the critical parameters specific gravity, pH, osmolality and surface tension fall within the range of the innovator product (Travatan). pH and osmolality are both within the physiological ranges as well.
Data on the usability and dose delivery performance of the plastic container has been provided. Drop volume measurements demonstrate that drop volume is comparable between Travoprost Mylan and originator Travatan samples, demonstrating that the administered dose is equivalent. Therapeutic equivalence can therefore also be concluded.

Manufacturing process
The manufacturing process consists of the preparation of the solution, aseptic filtering (with pre-filtration) and filling aseptically into containers. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three production-scale batches at each manufacturing site.

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

Quality control of drug product
The product specification includes tests for appearance, average volume per vial, pH, specific gravity, osmolality, identification (active substance and preservatives), assay of actives, assay of preservatives, related substances active substance, sterility, water loss and tightness of vials. The test and limits at release and shelf-life are identical except for assay of API and preservatives and related substances. The specification is acceptable.
A risk evaluation on nitrosamine presence has been provided. No risks have been identified.
The analytical methods have been adequately described. Validation reports have been provided showing suitability of these methods. The methods for assay and related substances are stability indicating.

Batch analytical data from the two proposed production sites have been provided on three production-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided on three production-scale batches stored at 25°C/60% RH (36 months), 40°C/75% RH (6 months), 30°C/65% RH (36 months) and 30°C/75% RH (36 months) for one manufacturing site. For the other manufacturing site, stability data at 25°C/60% RH (36 months), 40°C/75% RH (6 months) and 30 °C/75% RH (24 months) has been provided for two commercial-scale batches. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored upright and inverted in the marketed containers.

No significant changes are seen and all parameters remain within the specified limits. A shelf-life of 36 months has been granted. The proposed storage condition is acceptable and set in line with the guideline on the declaration of storage conditions for medicinal products: 'Keep the bottle in the sealed sachet in order to protect from moisture until after first opening of the bottle. This medicinal product does not require any special temperature storage conditions.'. Photostability studies as well as freeze and thaw studies have been performed. The product is not sensitive to light and freezing.

In-use stability data has been provided demonstrating that the product remains stable for 28 days following opening of the container.

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 Travoprost Mylan 40 micrograms/ml 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 Travoprost Mylan 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 Travatan 40 micrograms/ml eye drops, solution 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

Travoprost 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

Travoprost Mylan 40 micrograms/ml is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The qualitative composition of the test product is the same as the innovator/reference product Travatan before changes were made to the composition of the innovator product in 2010. This is accepted, since the current and previous formulation of Travatan are considered therapeutically equivalent.
Therefore, Travoprost Mylan may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference 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 Travoprost Mylan.

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

Important identified risks	• Macular oedema

	• Hyperpigmentation • Hypertrichosis • Iris and uveal inflammations • Cardiac and vascular disorders • Respiratory disorders • Hypersensitivity reactions
Important potential risks	• Melanoma • Corneal damage due to use of preserved eye drops • Use during pregnancy and lactation
Missing information	• Use in children below the age of 2 months • Potential interactions

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 Travatan. No new clinical studies were conducted. The MAH demonstrated that the qualitative and quantitative composition of the product is similar to the qualitative and quantitative composition of this reference product. 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 PL of Brinzolamide 10 mg/ml eye drops, suspension to bridge with regard to the key safe messages for safe use and design and layout. 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

Travoprost Mylan 40 micrograms/ml, eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Travatan 40 micrograms/ml eye drops, solution. Travatan is a well-known medicinal product with an established favourable efficacy and safety profile.

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.

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 Travoprost Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 November 2020.

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