Public Assessment Report

Scientific discussion

Travoprost Teva 40 micrograms/ml, eye drops, solution

(travoprost)

NL/H/2577/001/DC

Date: 22 September 2014

This module reflects the scientific discussion for the approval of Travoprost Teva 40 microgram/ml, eye drops, solution. The procedure was finalised on 23 March 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Travoprost Teva 40 micrograms/ml, eye drops, solution from Teva Nederland B.V.

The product is indicated for decrease of elevated intraocular pressure in adult patients with ocular hypertension or open-angle 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 Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Poland, Romania, Spain 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 Teva 40 micrograms/ml is a clear, colourless solution with pH 5.5-7.0 and osmolality 280 mOsmol/kg.

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

The solution is packed in 5 ml translucent polypropylene bottles with transparent LDPE dropper tip and white HDPE screw cap, with tamper-proof seal, presented in a PET/Al/PE overwrap pouch. Each bottle contains 2.5 ml solution.

The excipients are: benzalkonium chloride solution, macrogol glycerol hydroxy stearate (Cremophor RH40), trometamol, disodium edetate, boric acid (E284), mannitol (E421), sodium hydroxide (to adjust pH) and water for injections.

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 pale yellow to yellowish viscous oil, which is practically insoluble in water. The active substance is a single enantiomer.

The Active Substance Master File (ASMF) procedure is used for 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

The manufacturing process is divided into seven steps. No class 1 organic solvents are used. 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 drug substance specification has been established in-house. Specifications are adequate. All analytical methods applied for testing of the active substance have been satisfactorily validated. Sufficient batch analysis data have been provided.

Stability of drug substance
Stability data on the active substance have been provided for three batches stored at 2-8°C (24 months) and 25°C/60% RH (6 months). At both storage conditions 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.

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 selection of the excipients was based on the composition of the reference product The main development studies regarded the characterisation of the reference product and the development of the manufacturing process. The choices of the packaging and manufacturing process are justified.
The Board noted, however, that in 2010 changes were made to the preservative system of the innovator product (change from benzylalcohol, BAC, to Polyquaternium-1), which is presented on the EMA website. The travoprost formulation applied for is based on the old formulation of the innovator. The MAH has provided sufficient comparative data for showing essential similarity with the BAC-preserved the innovator product Travatan.
The MAH argued that in the centralised variation to change the composition of the innovator product, therapeutic equivalence was accepted based on pharmacokinetic, efficacy and safety data. As the old and new formulation of the innovator product are therapeutically equivalent, it is acceptable that the old formulation is used to demonstrate equivalence with the hybrid product applied for. Most of the efficacy and safety data obtained for the innovator product are based on the original formulation.
An overage is applied in the manufacturing process, which is considered acceptable based on the data provided. The use of aseptic filtration plus aseptic processing is justified for the sterilization of travoprost eye drops, as the active substance cannot be sterilised by methods that employ high temperatures.

Manufacturing process
The manufacturing process consists of the preparation of the solution (clean room), aseptic filtering and aseptic filling of the 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, particulate mater, pH, density, average volume, drop volume, osmolality, identification, related substances, assay of the active substance, assay of benzalkonium chloride, assay of edetate disodium, assay of boric acid, sterility, tightness of vials and leak test. Except for assay of active and related substances, the release and shelf-life requirements/limits are identical. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches, demonstrating compliance with the release specification.

Microbiological attributes
The efficacy of antimicrobial preservation has been tested according to Ph. Eur. 5.1.3. The results were satisfactory.

Stability of drug product
Stability data on the product have been provided on three production-scale batches stored at 25°C/60% RH (12 months), 40°C/75% RH (6 months) and 30°C/75% RH (12 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored upright and inverted in the marketing containers.

No significant changes are seen and all parameters remain with the specified limits. The proposed shelf-life of 2 years and storage conditions ‘No special storage conditions' and 'Storage before the first use: Keep bottle in the overwrap pouch, in order to protect from moisture' are justified. Results of photostability testing showed that the product, stored in upright or inverted vials with or without the outer carton, is photostable.
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 Teva 40 micrograms/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 Travoprost Teva 40 micrograms/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 Travatan, which is available on the European market. Reference is made tot 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

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/239/05) states that in order to demonstrate therapeutic equivalence clinical trials are in principal necessary, but other models may be used or developed. The MAH claims physiochemical essential similarity to the BAC-preserved reference product Travatan. Sufficient comparative data have been provided regarding pharmaceutical properties such as osmolarity, pH, relative density and droplet volume.

However, the reference product has undergone a formulation change in particular with respect to the preservative agent which was changed from benzalkonium chloride (BAC) to polyquaternium-1, and the MAH has compared their product with the older BAC formulation. The MAH addressed the differences in the formulations and comment on any potential impurity differences between test and reference products.
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 Teva 40 micrograms/ml eye drops.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Macular oedema - Hyperpigmentation - Hypertrichoses - Iris and uveal inflammation - Cardiac and vascular disorders - Respiratory disorders - Hypersensitivity
Important potential risks	- Corneal damage due to use of preserved eye drops - Ocular and skin melanomas - Use during pregnancy and lactation
Missing information	- Potential interactions - Use in paediatric population

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. There are however some questions remaining with regard to the risk management plan. The MAH will address these issues by submission of an updated RMP after closure of the procedure.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Travatan 40 micrograms/ml eye drops, solution. No new clinical studies were conducted. 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 information leaflet (PL) has not been performed. The MAH submitted a bridging report. The MAH stated that the proposed PL is identical to the centrally authorised package leaflet of Travatan (EMEA/H/C/000390). Furthermore, a tested layout is used. Bridging is considered justified.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

Both the reference and current product are solutions intended for local use with the same concentration of the active substance and with the same physico-chemical properties. Therefore it is

exempted for bioequivalence study (Guideline CPMP/239/95 on locally applied, locally acting products, containing known constituents).

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 Teva 40 micrograms/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 March 2014.

The following post-approval commitment has been made during the procedure:
- The MAH committed to submit an updated RMP.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Extension of the shelf life from 2 to 3 years.	NL/H/2577/ 001/IB/001	IB	21-5-2014	20-6-2014	Approval	N