Public Assessment Report

Scientific discussion

Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml eye drops, solution

(travoprost/timolol maleate)

NL/H/3748/001/DC

Date: 14 May 2018

This module reflects the scientific discussion for the approval of Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml eye drops, solution. The procedure was finalised on 18 May 2017. 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 Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml eye drops, solution, from Teva Nederland B.V.

The product is indicated in adults for the decrease of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

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 DuoTrav 40 microgram/ml + 5 mg/ml eye drops, solution which has been registered in the EEA by Novartis Europharm Limited since 24 April 2006 trough a centralised procedure (EU/1/06/338).

The concerned member states (CMS) involved in this procedure were Germany, Spain, France, Italy, Luxembourg and Portugal.

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

Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml is a clear and colourless solution. Each ml of solution contains 40 micrograms of travoprost and 5 mg of timolol (as timolol maleate). The solution has a pH between 5.5 and 7.0 and an osmolality of 252-308 mOsmol/kg.

The solution is packed in polypropylene bottles with colourless LDPE nozzle and a white opaque HDPE/LDPE cap with tamper proof seal. Each bottle has a fill volume of 5 ml and contains 2.5 ml of solution.

The excipients are: benzalkonium chloride, macrogolglycerol hydroxystearate, trometamol, edetate disodium, boric acid (E284), mannitol (E421), Sodium hydroxide (E524) for pH adjustment and water for injections.

II.2 Drug Substances

Travoprost
One of the two active substances is travoprost, an established active substance described in the United States Pharmacopoeia (USP). It is a colourless to yellowish oil, which is practically insoluble in hexane and water (at different temperatures), soluble in methanol and isopropyl alcohol and freely soluble in acetonitrile, toluene and ethyl acetate. Travoprost is a single enantiomer. As the substance is an oil, polymorphism is not applicable.

The Active Substance Master File (ASMF) procedure is used for this 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. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is established in-house and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 2 batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 production scaled batches stored at -20°C (24 months) and 5°C (3 months) in accordance with applicable European guidelines. All results remained within the proposed limits, no changes or trends were seen. Based on the data submitted, a retest period could be granted of 36 months when stored under the stated conditions.

Timolol maleate
The second active substance is timolol, an established active substance described in the European Pharmacopoeia (Ph. Eur.). It is a white or almost white crystalline powder or colourless crystals and soluble in water and in alcohol, practically insoluble in ether. As the active substance is a solution, particle size and polymorphism are not considered relevant.

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 European Pharmacopoeia.

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 meets the requirements of the monograph in the Ph.Eur. including a test on microbial contamination. Batch analytical data demonstrating compliance with this specification have been provided for 2 batches.

Stability of drug substance
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.

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. The selection of the sterilisation process of the drug product is adequately justified. The validation of the sterilisation process for the container closure system is sufficient and in line with applicable guidelines. A bioburden limit before sterilisation of the packaging is included.
Sufficient information is provided on the suitability of the container to deliver the required dose (drop). Studies are performed as per administration required (in-use), under different angles and also on a full, half full and nearly empty bottle. All results were found within the acceptance criteria. Considering that different batches of the nozzles were used and that no issues occurred after storage of the product, it is considered that the omission of a test for droplet size can be accepted.

Manufacturing process
The manufacturing process consists of the preparation of the solution, aseptical filtering (with pre-filtration) and filling aseptically containers. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for 3 production scaled batches in accordance with the relevant European guidelines. An acceptable limit for bioburden is included.

Control of excipients
The excipients comply with the requirements of the Ph. Eur. 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, extractable volume, pH, osmolality, water loss, identification, assay of actives, assay of preservatives, related substances, sterility and tightness of vials. The test and limits at release and shelf-life are identical, with the exception of water loss, extractable volume, identification, enantiomeric purity of timolol and tightness of vial. 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 of 3 production scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

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. The efficacy of the preservative was evaluated as per Ph.Eur recommendations and criteria. In conclusion, adequate preservative properties in the concentrations are used.

Stability of drug product
Stability data on the product have been provided from 3 production scaled batches stored at 25°C/60% RH (24 months), 40°C/75% RH (6 months) and 30°C/75% RH (12 months). The conditions used in the stability studies are in accordance with applicable ICH guidelines. No significant changes are seen and all parameters remain with the specified limits. The proposed shelf-life of 3 years is justified. The proposed storage condition is acceptable, the product does not require a temperature restriction, and needs protection from water and light. The MAH has discussed the difference in storage conditions with the innovator product. Data provided supported that the difference in storage conditions does not lead to changes in product quality for the period of use. Photostability studies, as well as freeze and thaw studies are performed. 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 microgram/ml + Timolol 5 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 Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml eye drops, solution 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 DuoTrav 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 and timolol are well-known active substances 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/239/05) 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 products is similar to that of the reference product DuoTrav 40 microgram/ml + 5 mg/ml eye drops, solution, and the pharmaceutical properties are comparable to that of the reference product as well, a biowaiver can be granted. Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml eye drops, solution eye drops, solution may be considered therapeutic equivalent with 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 Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml eye drops, solution

- Summary table of safety concerns as approved in RMP

Important identified risks	• Macular oedema • Hyperpigmentation • Hypertrichosis • Iris and uveal inflammation • Cardiac and vascular disorders • Respiratory disorders
Important potential risks	• Use during pregnancy and lactation • Long term use of preserved eye drops • Ocular and skin melanoma

Missing information	• 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 DuoTrav. 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

The package leaflet 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. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of DuoTrav 40 microgram/ml + 5 mg/ml eye drops, solution. Duotrav is a well-known medicinal product with an established favourable efficacy and safety profile

Travoprost Teva is a product for ocular use. 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 Travoprost Teva 40 microgram/ml + Timolol 5 mg/ml eye drops, solution with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 May 2017.

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