CBG MEB

Public Assessment Report

Scientific discussion

Leachim 40 microgram/ml eye drops, solution

(travoprost)

NL/H/3290/001/DC

Date: 24 June 2016

This module reflects the scientific discussion for the approval of Leachim 40 microgram/ml eye drops, solution. The procedure was finalised on 21 October 2015. 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
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Leachim 40 microgram/ml eye drops, solution from Alfred E. Tiefenbacher (GmbH & Co. KG).

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 Spain, 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

Leachim 40 microgram/ml is a clear, colourless solution with pH 6.3-7.3 and osmolality 265-320 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 LDPE bottles with transparent LDPE droppers and light blue, tamper proof HDPE screw cap.

The excipients are: boric acid (E284), sodium chloride, mannitol (E421), macrogolglycerol hydroxystearate 40, polyquaternium-1, propylene glycol (E1520), sodium hydroxide (E524) and/or hydrochloric acid (E507) (for pH adjustment), and 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. Travoprost does not possess polymorphism nor is it relevant as the drug substance is used in solution only. The drug substance is optically active due to the presence of multiple chiral centres.

Two active substance manufacturers are used. For both manufacturers, the Active Substance Master File (ASMF) procedure is used. 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 two manufacturers 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
Travoprost is prepared via a three steps or two stages (including nine steps) synthesis and subsequent purification. Both suppliers apply purification by preparative HPLC. Appropriate starting materials are defined for both ASMFs. The drug substance was adequately characterised.

Quality control of drug substance
In-house specifications were developed for the drug substance. The specifications are acceptable in view of the route of synthesis and the various ICH guidelines. Batch analysis data have been presented of each manufacturer, showing compliance with the proposed specification.

Stability of drug substance
Stability studies were performed in line with ICH guidance. For travoprost a retest period of 36 months at -20±5°C was claimed, when manufactured by one manufacturer. For travoprost manufactured by the other manufacturer, a retest period of 36 months stored below -15°C and protected from light was claimed. Sufficient stability data have been provided to justify the retest periods.

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 excipients used are common in the manufacture of eye drops and are also present in the innovator product. The packaging is usual and suitable for the product at issue. In line with the innovator product, a benzalkonium chloride free preparation has been developed. The pharmaceutical similarity of the test product with the reference product has been demonstrated. The MAH made a comparison with respect to pH, relative density, osmolality, assay of the active substance, assay of the preservative, related substances, surface tension, and drop size under various conditions. Similarity has been sufficiently demonstrated. As the solution and the container closure system can not withstand autoclaving or moist heat, the sterilisation process of aseptic filtration and processing is justified.

Manufacturing process
The eye drops are prepared by preparation of a stock and bulk solution. As the primary packaging material cannot be terminally sterilised, the solution is filtered through two sterilizing filters and aseptically filled into containers that have been sterilised by ionization radiation. Process validation data on the product have been presented for six batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the requirements of the European Pharmacopoeia (Ph.Eur.), except for the preservative polyquaternium-1. However, the quaternary ammonium polymer polyquaternium-1 is a well-accepted antimicrobial agent. A detailed safety justification on polyquaternium-1 was provided, including a comparison of its use in other products. This is acceptable.

Quality control of drug product
The product specification includes tests for appearance, colour, pH, relative density, osmolality, filling volume, closure integrity, identity and assay of drug substance and preservatives, impurities, and sterility. Different shelf life requirements are applied for filling volume and total impurities. . The analytical methods have been adequately described and validated. Batch analysis product data were presented on the three validation batches. Compliance with the proposed release requirements was demonstrated.

Microbiological attributes
The widely established and approved preservative polyquaternium-1 guarantees sufficient preservation of eye drops (provided in multi-dose containers) as per Ph.Eur. 5.1.3, criterion A. The results of testing show that for the product at issue will be effective as low as 90% of the preservative content. This is satisfactory.

Stability of drug product
Stability data on the product have been provided on six production-scale batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are

according to the ICH stability guideline. The batches stored at accelerated conditions show some variability in some of the tested parameters, but no out of specification results were observed. All batches comply with the criteria of the shelf-life specification. The 24 months long term stability data confirm the drug product remains stable. Results of photostability testing showed that the product both without packaging (i.e. in glass vial) as in the proposed primary packaging, is sensitive to light exposure, as the travoprost assay decreased and related substances increased. However, all results comply with the drug product specification if the bottles are kept in the secondary packaging. In-use stability data has been provided demonstrating that the product remains stable for 28 days following opening of the container.
Based on the available stability data the granted shelf-life of 2 years and storage conditions 'Discard 4 weeks after first opening. This medicinal product does not require any special temperature storage conditions. Keep the bottle in the outer carton in order to protect from light.' are justified.

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 Leachim eye drops solution has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH committed to perform additional compatibility studies with PE bottles prior to marketing the product in this bottle type.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Leachim eye drops solution 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 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

No comparative bioavailability studies have been conducted to support the application. A biowaiver was applied for. 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 reference product Travatan. Sufficient comparative data have been provided regarding pharmaceutical properties such as osmolality, pH, relative density and droplet volume. The differences in the mannitol content and osmolality between the test and the reference product are considered significant. The MAH submitted results of testing to confirm that neither the difference in mannitol content, nor the resulting differences in osmolality have any detectable impact on travoprost's permeation behaviour. The results sufficiently demonstrate that the test and reference product are essentially similar, and the biowaiver is considered acceptable. 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 Leachim 40 microgram/ml eye drops.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Macular oedema • Hyperpigmentation • Hypertrichoses • 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	• Long term safety in the paediatric population • 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 40 microgram/ml eye drops, solution. 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 the centrally authorised PL of Travatan (EMEA/H/C/000390). The content of the two PLs is identical. Furthermore, a tested layout is used. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

Both Leachim and Travatan are solutions intended for local use with the same concentration of the active substance and similar physico-chemical properties. Therefore Leachim 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 Leachim 40 microgram/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 21 October 2015.

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