COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bimatoprost 0.3 mg/ml, preservative-free, eye drops, solution in single dose container (bimatoprost)

NL/H/5183/001/DC

Date: 8 March 2022

This module reflects the scientific discussion for the approval of Bimatoprost 0.3 mg/ml preservative-free, eye drops, solution in single dose container. The procedure was finalised on 12 January 2022. 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
USP	United States Pharmacopeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bimatoprost 0.3 mg/ml preservative-free, eye drops, solution in single dose container, from Brown & Burk IR Limited.

The product is indicated for reduction of elevated intraocular pressure in chronic open-angle glaucoma and ocular hypertension in adults (as monotherapy or as adjunctive therapy to beta-blockers).

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 Lumigan 0,3 mg/ml, eye drops (NL RVG 71252) which has been registered by Allergan Pharmaceuticals Ireland since 8 March 2002 via centralised procedure EMEA/H/C/000391.

The concerned member states (CMS) involved in this procedure were Sweden and the United Kingdom (Northern Ireland).

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

Bimatoprost is a clear colourless to pale yellow solution having a pH range between 6.80 to 8.00 and osmolality between 270 to 330 mOsmol/kg. One mL of solution contains 0.3 mg bimatoprost. One drop contains approximately 0.00966 mg bimatoprost.

The solution is packed in natural translucent low density polyethylene (LDPE) single-dose containers. Each single-dose container contains 0.4 mL solution, and five single-dose containers are packaged in a sealed aluminium pouch.

The excipients are sodium chloride, disodium phosphate heptahydrate (E339), citric acid monohydrate (E330), hydrochloric acid (E507) (for pH adjustment), sodium hydroxide (E524) (for pH adjustment) and water for injection.

II.2 Drug Substance

The active substance is bimatoprost, a substance that is not described in the European Pharmacopoeia (Ph.Eur.), the United States Pharmacopeia (USP), the British Pharmacopoeia or the Pharmacopoeia of a member state. The active substance is a white to off-white crystalline powder, soluble in methanol and alcohol, slightly soluble in water and in 0.1 N HCL.

The active substance bimatoprost contains five asymmetric carbons; consequently it exhibits optical isomerism. The manufacturer of the drug substance produces the (R,R,R,S,S)-isomer, which is the crystalline Form I. Bimatoprost has been found to be very hygroscopic.

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 consists of seven steps. No heavy metal catalysts are used in the manufacture. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The drug substance specification has been established in-house by the applicant based on the specifications of the supplier, with tests for appearance, solubility, identification, water content, specific optical rotation, related substances, assay, residual solvents and microbial contamination. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for four batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months. Based on the data submitted, a retest period could be granted of 60 months when stored at -20°C ± 5°C.

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 choice of excipients is justified and their functions are explained. The excipients used are well known and are the same as those present in the reference product. The main development studies concerned the characterisation of the reference product and comparative characteristics studies. The comparative studies included the following parameters: appearance, osmolality, density, tonicity, pH, specific gravity, viscosity, surface tension, buffer capacity, assay of bimatoprost, related substances and drop size. The results are considered sufficient to confirm physico-chemical similarity of the test and reference product. A waiver to provide bioequivalence data was requested, which is discussed in section IV on the clinical aspects.

Compatibility of the product with equipment and primary packaging materials has been demonstrated by leachables studies. Usability and suitable dose delivery (e.g. drop size studies) have been adequately discussed.

Manufacturing process

The manufacturing process consists of preparing a bulk solution, followed by aseptic filtration of the bulk solution and aseptic filling. The manufacturing process has been validated according to relevant European guidelines. The description of the manufacturing process and critical process parameters are provided with sufficient details. Adequate in-process controls are included. Process validation data on the product has been presented for three batches.

Control of excipients

The excipients comply with Ph.Eur. or USP requirements. Their specifications are acceptable.

Microbiological attributes

In general, adequate information on the microbiological attributes of the drug product has been provided. Microbiological attributes like bioburden and sterility testing, which are critical attributes for an ophthalmic product, would be monitored as relevant as part of in-process, product release and stability parameters. The methods used to monitor microbial attributes are based on general chapters of Ph.Eur and are validated as applicable. The bioburden and endotoxin of the bulk solution are controlled by controlling the microbial load on each of the input ingredients and manufacturing the drug product solution in a controlled environment.

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, identification, colour and clarity of solution, pH, osmolality, viscosity, extractable volume, assay of bimatoprost, particulate contamination, related substances, sterility and water loss. The release and shelf-life limits are identical, except for pH and related substances. 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. A risk assessment on possible contamination from N-nitrosamines has been provided and is adequately performed. No risk is identified.

Batch analytical data from the proposed production site have been provided on three commercial batches demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided for three commercial batches stored at 25°C/40% RH (up to 18 months) and 40°C/25% RH (six months). The conditions used in the stability studies are according to the EMA stability guideline for semipermeable containers. No trends or out of specification results are observed in the available stability results. On basis of the data submitted, a shelf life was granted of 24 months for the unopened aluminium pouch, without any special temperature storage conditions.

In-use stability data have been provided demonstrating that the product remains stable for 30 days following the first opening of the aluminium sachet when stored at 25°C/40% RH and 40°C/25% RH.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is photostable when exposed to light in the marketed pack. Freeze-thaw studies were performed and showed that the product is stable to temperature excursions outside the labelled storage temperature.

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 Bimatoprost 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 Bimatoprost is intended for substitution of a similar medicinal product, 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 Lumigan 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

Bimatoprost 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

Biowaiver

The request for a biowaiver has been made with reference to the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), which states that “a waiver of the need to provide equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, if the test product is of the same type of solution (aqueous or oily), and contains the same concentration of the same active substance as the medicinal product currently approved. Minor differences in the excipient composition may be acceptable if the relevant pharmaceutical properties of the test product and reference product are identical or essentially similar. Any qualitative or quantitative differences in excipients must be satisfactorily justified in relation to their influence on therapeutic equivalence. The method and means of administration should also be the same as the medicinal product currently approved, unless otherwise justified.”

The drug product is an ophthalmic solution and contains the same active and inactive ingredients in the same concentration as the reference product Lumigan 0.3 mg/mL eye drops, solution, in single-dose container. The MAH has performed physico-chemical characterisation of the test product against the reference product, which confirmed physico-chemical similarity.

Based on the submitted data, a waiver for the need to provide equivalence data can be considered in accordance with the *Guideline on the Investigation of Bioequivalence*.

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 Bimatoprost.

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

Important identified risks	• Iris pigmentation • Punctate keratitis • Acute asthma and asthmatic symptoms
Important potential risks	• Choroidal effusion • Increase in intraocular pressure • Reactivation of previous infective ocular disease • Cardiovascular events (angina, bradycardia and hypotension) • Off label use (cosmetic use for eyelash growth)
Missing information	• Exposure in pregnancy and lactation • Exposure in paediatric patients

The member states agreed that here are no other routine pharmacovigilance activities proposed beyond adverse reactions reporting and signal detection for bimatoprost. In line with the innovator medicinal product Lumigan and published information for bimatoprost containing eye drops on the CMDh website, there are no additional risk minimisation measures in place for bimatoprost. Alignment of the safety information in the proposed product information with the reference medicinal product is acceptable.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lumigan. No new clinical studies were conducted. A biowaiver has been granted in accordance with the *Guideline on the Investigation of Bioequivalence*. 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 Lumigan 0,3 mg/ml, eye drops (NL RVG 71252). 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

Bimatoprost 0.3 mg/ml preservative-free, eye drops, solution in single dose container has a proven chemical-pharmaceutical quality and is a hybrid form of Lumigan 0,3 mg/ml, eye drops. Lumigan 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. 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 Bimatoprost with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 January 2022.

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