COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

NL/H/5325/001/DC

27 May 2022

This module reflects the scientific discussion for the approval of Bimeox. The procedure was finalised at 19 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 Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bimeox 0.3 mg/ml eye drops, solution, in single-dose container, from Laboratorios Salvat S.A.

The product is indicated for the 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 solution, in single-dose container (EU/1/02/205), which has been registered through the centralized procedure since 8 March 2002. A hybrid application was chosen the two products have the same qualitative and quantitative composition regarding Drug substance and excipients, the same pharmaceutical form but the bioequivalence cannot be demonstrated through bioavailability studies. This is considered to be acceptable.

The concerned member states (CMS) involved in this procedure were Portugal and Spain.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Bimeox is a clear and colourless aqueous solution.

1 ml of solution contains 0.3 mg bimatoprost.

The solution is packed in low density polyethylene (LDPE) containers in pouches and cartons.

The excipients are sodium chloride, sodium phosphate dibasic heptahydrate (E339), citric acid monohydrate (E330), hydrochloric acid or sodium hydroxide (to adjust pH) and water for injection

II.2 Drug Substance

The active substance is bimatoprost, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). Bimatoprost is a white powder and is slightly soluble in

water. Bimatoprost has five chiral centres and therefore exhibits optical isomerism. Bimatoprost exhibits polymorphism, the crystal form I is consistently produced. However, as the active substance is dissolved in the final product, this is not considered to be relevant.

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 chemical synthesis of bimatoprost consists of nine transformation steps and one purification step. Extensive information about the manufacturing process, control of materials and of impurities is provided in the Restricted part of the ASMF.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and is in line with the drug substance specification as proposed in the ASMF. Since the finished product is a solution of the active substance, additional physical parameters as particle size distribution or polymorphic form are not considered critical and not included in the drug substance specification. The drug substance specification is acceptable. Batch analytical data demonstrating compliance with this specification have been provided for two full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for six batches at long term conditions (-20°C± 5°C) for 60 months and for three batches at accelerated conditions (5°C±3°C) for six months in accordance with applicable European guidelines demonstrating the stability of the active substance for 60 months/years. Based on the data submitted, a retest period could be granted of 60 months when stored in containers similar to those used for commercial production.

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 pharmaceutical development is based on reference product Lumigan 0.3 mg/ml eye drops, solution, in single-dose container by Allergan, which has been adequately characterized. No formulation development study has been provided, as the quali-quantitative composition is based on the composition of Lumigan according to a public patent. This is acceptable.

Essential similarity of the drug product with the reference product Lumigan has been determined by comparing three batches of each product for the parameters appearance, pH, osmolality, density, surface tension, viscosity, drop size, buffering capacity, assay and related substances. All results are comparable between test and reference product, therefore the essential physico-chemical similarity of the two products can be endorsed. The manufacturing process is a common one for this pharmaceutical form. An acceptable justification has been given for the choice of sterilisation process. The chosen packaging system is a common one for eye drops and the same as used for the reference product. Usability and suitability for the target population has been acceptably discussed. Microbial quality is adequately controlled in the process.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. In-process controls are described at different stages of the process. The manufacturing process description includes sufficient details about the compounding, filtration steps and the vial-filling process. Holding times have been justified based on media fills and are clearly stated in the manufacturing process description in the dossier. The in-process controls of all process steps are adequately described and justified. Filter validation studies have been performed and confirm suitability of the selected filters for the proposed process in presence of the drug product. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients

All excipients used in the Drug product are reported in a Ph. Eur. monograph, except for sodium phosphate dibasic heptahydrate, for which a United States Pharmacopoeia USP monograph is available. For specification, analytical methods, their validation and justification of specification, reference is made to the Ph. Eur./USP monographs. 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, pH, osmolality, identity, assay, related substances, sterility and water loss (only applicable in stability studies). Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The risk assessment on elemental impurities is adequately performed. The risk assessment on nitrosamines is adequately performed, all relevant possible sources of contamination have been discussed and all background documentation is provided. No risk is identified, which is endorsed.

Satisfactory validation data for the analytical methods have been provided.

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

Stability of drug product

Stability data on the product have been provided for three batches stored at 5°C, at 25°C/40%RH, at 30°C/65%RH and at 40°C/25%RH (up to 12, 12, 12 and six months respectively) in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. Photostability studies according to Guideline ICH Q1B have been performed and show that the product is not sensitive to light. Freeze-thaw study is performed and show no change in product characteristics. On basis of the data submitted, a shelf life was granted of 24 months with no special storage conditions. An in-use study has been performed to investigate stability of the product after first opening of the pouch, in normal long-term storage condition and in low humidity conditions. All results comply to the limits up to 30 days, therefore the proposed in-use shelf-life of 30 days after first opening of the pouch is considered acceptable.

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

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Bimeox 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 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.

For this hybrid application, the MAH has not submitted any bioequivalence studies.

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. According to the Guideline on Bioequivalence and bioavailability this may be acceptable since the qualitative and quantitative composition of the product is similar to that of the reference product Lumigan eye drops, solution in single dose container. Pharmaceutical properties (i.e. appearance, pH, osmolality, density, surface tension, viscosity, assay and related substances) are comparable to that of the reference product as well. Furthermore, comparative data on drop size and buffering capacity have been provided and are considered acceptable. The omission of bioequivalence studies is acceptable.

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 Bimeox.

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

Important identified risks	- Iris pigmentation - Punctate keratitis - Acute asthma and asthmatic symptoms (asthma, exacerbation of asthma and dyspnoea)
Important potential risks	- Reactivation of previous infective ocular disease - Choroidal effusion - Increase in intraocular pressure - Cardiovascular events (bradycardia, angina pectoris and hypotension) - Off-label use (cosmetic use for the purpose of stimulating eyelash growth)

Missing information	- Exposure in paediatric patients - Exposure in pregnancy and lactation

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 Lumigan. 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

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English. The test consisted of a pilot test with three participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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

Bimeox 0.3 mg/ml eye drops, solution, in single-dose container has a proven chemical-pharmaceutical quality and is a hybrid form of Lumigan. Lumigan is a well-known medicinal product with an established favourable efficacy and safety profile.

Essential similarity with the originator product is based on comparative qualitative attributes of the product.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bimeox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 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