CBG MEB

Public Assessment Report

Scientific discussion

Bimatoprost CF 0.1 mg/ml and 0.3 mg/ml eye drops, solution

(bimatoprost)

NL/H/3057/001-002/DC

Date: 25 April 2016

This module reflects the scientific discussion for the approval of Bimatoprost CF 0.1 mg/ml and 0.3 mg/ml, eye drops, solution. The procedure was finalised on 19 March 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
BAK	Benzalkonium chloride
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 Bimatoprost CF 0.1 & 0.3 mg/ml, eye drops, solution from Centrafarm B.V.

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 0.1 mg/ml and 0.3 mg/ml eye drops, solution, which has been registered in the EEA by Allergen Pharmaceuticals Ireland in 2002 through centralised procedure EU/1/02/205/001-004.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Germany, Denmark, Spain, France, Italy, Luxembourg, Sweden and Slovenia.

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 CF is a clear, colourless solution, practically free from particles and with a pH between 6.8 and 7.8 and an osmolality of 260-330 mOsmol/kg.

Bimatoprost CF 0.1 mg/ml contains 0.1 mg bimatoprost per ml and one drop contains approximately 2.5 micrograms bimatoprost. Bimatoprost CF 0.3 mg/ml contains 0.3 mg bimatoprost per ml and one drop approximately 7.5 mg micrograms bimatoprost.

The solution is packed into multi-dose white LDPE bottles with a white LDPE dropper insert and a bluish green (0.1 mg/ml) / white (0.3 mg/ml) HDPE screw cap. Each bottle has a fill volume of 2.5 ml or 3 ml.

The excipients are: benzalkonium chloride (BAK), citric acid monohydrate, disodium phosphate heptahydrate, sodium chloride, sodium hydroxide or hydrochloric acid (to adjust pH) and purified water.

II.2 Drug Substance

The active substance is bimatoprost, an established active substance not described in any pharmacopoeia. The active substance is slightly soluble in water. Particle size and polymorphism of the drug substance are not considered relevant for the final drug product as the product is manufactured as a solution. The drug substance is optically active due to the presence of several chiral centres.

The Active Substance Master File (ASMF) procedure is used for all three manufacturers of 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 drug substance is supplied by three different companies. These manufacturers all have a different approach in the synthesis of bimatoprost from the starting material. No heavy metal catalysts or class 1 organic solvents are used in any of the processes. Sufficient data have been provided.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH based on the specifications of the suppliers, with no additional requirements. 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 one batch of drug substance from each supplier.

Stability of drug substance
Stability data on the active substance have been provided for 3 batches from each supplier in accordance with applicable European guidelines.

For the first manufacturer, stability data on the active substance have been provided for three full scaled batches for each manufacturing site stored at -20°C (24-48 months) and 2-8°C (6 months). The long-term stability data show no changes or trends in any of the tested parameters. At accelerated conditions (i.e. 2-8°C) an increase in water content was seen. The proposed retest period of 2 years when stored in a freezer (-20°C) in tight, light resistant containers, under nitrogen atmosphere is justified.

Stability data on the active substance from the second manufacturer have been provided for three full scaled batches stored at -20°C (36 months), 2-8°C (36 months) and 25°C/60% RH (6 months). No changes or trends are seen at refrigerated or frozen conditions. At 25°C/60% RH an slight increase in impurities is seen. The claimed retest period of 36 months, when stored in a freezer below -15°C and protected from light is justified.

For the third manufacturer, stability data on the active substance have been provided for three full scaled batches stored at -20°C (24 months), and 2-8°C (6 months). No changes or trends are seen at refrigerated or frozen conditions. The claimed retest period of 36 months, when stored in a freezer below -15°C and protected from light is justified. The proposed retest period of 2 years when stored in a freezer (-20°C), under inert atmosphere (argon or nitrogen) is justified. The drug substance appears not to be light-sensitive.

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 main development studies concerned the characterization of the reference product and comparative drop volume studies. The excipients used are well known and are similar to those present in the reference product. The choices of the packaging and manufacturing process are justified.
The results of a comparison of drop size with the reference product for both strengths show that the selected dropper ensures delivery of drops similar in size and volume with the reference product. The MAH has sufficiently demonstrated that the pharmaceutical properties (i.e. osmolarity, pH, relative density) are comparable to that of the reference product. Viscosity is not considered a relevant parameter in this respect as the product does not include any viscosity enhancers.
For ophthalmic preparations sterility is an essential parameter. The choice of the sterilisation method (i.e. aseptic filtration / processing) was selected in accordance with the decision tree for sterilisation choices for aqueous product (Annex to the Note for Guidance on Development Pharmaceutics) because terminal sterilisation by autoclaving or moist heat might negatively influence the product quality.

Manufacturing process
The manufacturing process mainly consists of preparing the bulk solution, pre-filtration through a bacterial retentive filter and second filtration through a bacterial retentive filter directly followed by filling into bottles. 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.

Control of excipients
The excipients comply with pharmacopoeial requirements. These specifications are acceptable.

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. Preservative efficacy down to a BAK content of 65% of the product specification was demonstrated.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. It includes tests for appearance, colour, pH, relative density, osmolality, filling volume, closure integrity, identity of bimatoprost and BAK, assay of bimatoprost and BAK, related substances and sterility. Except for colour, BAK assay and related substances the release and shelf-life specifications are the same. 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 from the proposed production site have been provided on three full scale batches of drug product, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three batches for each product strength with fill volume of 3 ml in accordance with applicable European guidelines demonstrating the stability of the product for 18-24 months (when stored at 25°C/60% RH) and 6 months (when stored at 40°C/75% RH). In addition, stability data have been provided for one batch with fill volume of 2.5 ml that was stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in LDPE bottles with LDPE dropper insert and HDPE cap. At both storage conditions except for a decrease in BAK no clear trends or changes were seen. A photostability study has been performed in accordance with the Note for Guidance on Photostability Testing, demonstrating that the product is not sensitive to light. The proposed shelf-life of 30 months for the 0.1 mg/ml product and 36 months for the 0.3 mg/ml product, with storage condition 'This medicinal product does not require any special storage conditions' is justified.

Stability data has been provided demonstrating that the product remains stable for 28 days following first opening of the container, when stored at ambient conditions. The bottles were opened once daily and the administration of the product was simulated (*i.e.* two drops per day). In-use studies were conducted at the beginning of the shelf-life period and towards the end of the shelf-life.

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 CF 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 Bimatoprost CF 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 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
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 both products is similar to that of the reference products Lumigan 0.1 mg/ml eye drops and Lumigan 0.3 mg/ml eye drops, and the pharmaceutical properties (*i.e*. osmolarity, pH, relative density and droplet volume) are comparable to that of the reference product as well, a biowaiver can be granted. Bimatoprost CF eye drops, solution may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of 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 Bimatoprost CF 0.1 mg/ml and 0.3 mg/ml eye drops, solution.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Iris pigmentation • Punctate keratitis • BAK–related corneal toxicity*
Important potential risks	• Reactivation of previous infective ocular disease • Reactivation of corneal infiltrates • Choroidal effusion • Increase in intraocular pressure

	• Angina • Bradycardia and hypotension • Asthma • Off-label use (eyelash growth)
Missing information	• Paediatric use • Use in pregnancy and lactation.

**This risk is applicable for preserved formulations only*

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

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 EU/1/02/205/002. The bridging report submitted by the MAH has been found acceptable. The bridging study shows that the PLs of Bimatoprost CF 0.1 mg/ml and 0.3 mg/ml eye drops, solution with the approved product, Lumigan eye drops, solution are strongly similar. No separate user testing is required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bimatoprost CF 0.1 mg/ml and 0.3 mg/ml, eye drops, solution have a proven chemical-pharmaceutical quality and are hybrid forms of Lumigan 0.1 and 0.3 mg/ml, eye drops, solution. Lumigan eye drops is a well-known medicinal product with an established favourable efficacy and safety profile.

As Bimatoprost CF is a product for ocular use (eye drops) intended to act without systemic absorption, with a comparable composition to the reference product, it is exempted for biostudy.

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 CF 0.1 mg/ml and 0.3 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 19 March 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