CBG MEB

Public Assessment Report

Scientific discussion

Bimatoprost Farmaprojects 0.3 mg/ml, eye drops, solution

(bimatoprost)

NL/H/2774/001/DC

Date: 21 March 2016

This module reflects the scientific discussion for the approval of Bimatoprost Farmaprojects 0.3 mg/ml, eye drops, solution. The procedure was finalised on 8 September 2013. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bimatoprost Farmaprojects 0.3 mg/ml, eye drops, solution from Farmaprojects, S.A.U.

The product is indicated for in 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 which has been registered in the EEA by Allergan Pharmaceuticals Ireland since 2002 through centralised procedure EU/1/02/205/002.

The concerned member states (CMS) involved in this procedure was Germany.

The marketing authorisation is granted based on article 10(3) of Directive 2001/83/EC, 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 Farmaprojects 0.3 mg/ml is a clear, colourless solution, practically free from particles with pH 6.5-7.5 and osmolality of 280-340 mOsmol/kg.

One ml of solution contains 0.3 mg bimatoprost. One drop contains approximately 9.0 micrograms bimatoprost.

The solution is packed in white opaque LDPE bottles with white opaque LDPE dropper insert, and closed with a white opaque, tamper-proof HDPE screw cap. The bottles have a fill volume of 3 ml.

The excipients are: disodium phosphate 12-hydrate, citric acid monohydrate, sodium chloride, benzalkonium chloride, hydrochloric acid and/or sodium hydroxide (for pH adjustment), purified water.

II.2 Drug Substance

The active substance is bimatoprost, an established active substance however not described in any pharmacopoeia. It is a white to slightly off-white crystalline powder, which is slightly soluble in water. Bimatoprost shows no polymorphism. The drug substance is optically active due to the presence of several chiral centres.

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
Bimatoprost is prepared in a four-step synthesis from the key intermediates. The synthesis of the key intermediates from the starting material consists of 5 steps. No heavy metal catalysts or class 1 organic solvents are used in the process.

Quality control of drug substance
The drug substance specification has been established in-house by the MAH. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full-scale batches of drug substance.

Stability of drug substance
Stability data on the active substance have been provided for three pilot-scale and three full-scale batches stored at -20°C (24-36 months), 2-8°C (6-18 months) and 25°C/60% RH (6 months). No changes or trends are seen at refrigerated or frozen conditions. At 25°C/60% RH a slight increase in impurities is seen. The claimed retest period of 36 months, when stored in a freezer at below -15°C and protected from light is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product is satisfactorily performed and explained. The excipients used are well known and are also present in the reference product. The choices of the packaging and manufacturing process are justified. No overage or overfill is applied. The similarity of droplet volume of the test product with the reference product was demonstrated and although a statistical difference was noted, this was considered clinically irrelevant.

Manufacturing process
The eye drops are prepared by dissolving the excipients and drug substance in water. As the primary packaging material cannot be terminally sterilized, the manufacturing process consists of preparing the bulk solution, filtration through two bacterial retentive filters, directly followed by aseptically filling into bottles which were previously sterilized by gamma irradiation. The manufacturing process has been adequately validated according to relevant European guidelines.

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

Microbiological attributes
Benzalkonium chloride is added as an antimicrobial preservative to prevent proliferation or to limit microbial contamination during normal conditions of use, since the packaging material is a multidose container. The results of testing in accordance with Ph.Eur. 5.1.3. “Efficacy of antimicrobial preservation” demonstrate that the product remains sterile.

Quality control of drug product
The product specification includes tests for appearance, colour, clarity, identity, assay of drug substance and preservative, related substances, pH, osmolality and sterility. Different shelf life requirements are applied for assay (active substance and preservative) and related substances. The specification is considered acceptable. 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 stored at 25ºC/40% RH (12 months), 30ºC/65% RH (12 months) and 40ºC/25% RH (6 months) in accordance with applicable European guidelines. The batches were stored in LDPE bottles with LDPE dropper insert and HDPE cap.
The long-term stability data indicate a slight increase in assay and water loss, and a slight decrease in impurities. For the other parameters, no trends could be observed. The intermediate and accelerated stability data demonstrate an increase in assay and water loss and a clear decrease for preservative assay. The results remain within limits. For the other parameters, no trends could be observed.

The in-use stability study has been performed in line with daily practice and the data demonstrates the bottle can be used safely for at least 4 weeks. The photostability data show that the drug product is not sensitive to light. The proposed shelf-life of 24 months with storage condition 'This medicinal product does not require any special storage conditions' is 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 Bimatoprost Farmaprojects 0.3 mg/ml, 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 commitments were made:
- The MAH committed to perform the osmolality test at the end of the formal stability studies for 25ºC ± 2ºC/40% ± 5% RH conditions.
- The MAH committed to review these limits at the end of shelf-life and when more stability data will be available.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since this medicinal product 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 tot 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 the product is similar to that of the reference product 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 Farmaprojects 0.3 mg/ml may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. 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 Bimatoprost Farmaprojects.

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Iris Pigmentation, Punctate Keratitis, BAK-related corneal toxicity.
Important potential risks	Asthma; Choroidal Effusion; Increase in IOP; Reactivation of Corneal infiltrates; Reactivation of previous infective ocular disease; Cardiovascular events (angina, bradycardia and hypotension); Off-label use (cosmetic use for the purpose of stimulating eyelash growth).
Important missing information	Exposure in Paediatric patients; Exposure in Pregnancy & Lactation.

**The risk of BAK-related corneal toxicity 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

The package leaflet has not been evaluated via a user consultation study. A bridging statement has been provided in which it is stated that, since the wording of the package leaflet submitted with the present application was taken literally from the currently approved package leaflet of Lumigan 0.3 mg/ml, eye drops, solution, no user testing was considered necessary. This justification is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bimatoprost Farmaprojects 0.3 mg/ml, eye drops, solution 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.

As Bimatoprost Farmaprojects 0.3 mg/ml 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 similarity has been demonstrated for Bimatoprost Farmaprojects 0.3 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 September 2013.

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
Introduction of, or changes to, the summary of pharmacovigilance system, only in Germany.	NL/H/2774/ 001/IA/001	IA	1-6-2015	1-7-2015	Approval	No
Change of the product name in Germany.	NL/H/2774/ 001/IB/002	IB	21-10-2015	20-11-2015	Approval	No