COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bimatoprost Idifarma 0.3 mg/ml, eye drops, solution

(bimatoprost)

NL/H/3769/001/DC

Date: 29 January 2020

This module reflects the scientific discussion for the approval of Bimatoprost Idifarma 0.3 mg/ml, eye drops, solution. The procedure was finalised on 3 May 2018. 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

I. INTRODUCTION

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

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 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 were Germany, 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 for locally acting medicinal products such as eye drops bioequivalence cannot be demonstrated through bioavailability studies.

II. QUALITY ASPECTS

II.1 Introduction

Bimatoprost Idifarma 0.3 mg/ml is a clear, colourless solution with pH of about 7.3 and osmolality of approximately 300 mOsmol/kg.

One ml of solution contains 0.3 mg bimatoprost.

The solution is packed in white LDPE bottles closed with a white nozzle and cap subassembly (HDPE and silicone). Silicone also comes into contact with the solution as part of the components. Each bottle has a fill volume of 3 ml.

The excipients are: citric acid monohydrate, disodium phosphate heptahydrate, sodium chloride, sodium hydroxide or hydrochloric acid (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 almost white crystalline powder, which is slightly soluble in water. Bimatoprost shows no polymorphism. The drug substance is optically active due to the presence of five chiral centres and shows cis-trans isomerism. This cis-isomer has been selected for the active product.

The Active Substance Master File (ASMF) procedure is used for both 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 manufacturing process of the first supplier consists of eleven steps that can be divided into two parts. The second supplier prepares the active substance in a seven-stage synthesis. Sufficient data have been provided.

Quality control of drug substance

The drug substance specification is acceptable and includes tests for appearance, solubility, identification, water content, specific optical rotation, assay, related substance and microbiological quality. The MAH has sufficiently described and validated the analytical procedures. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches per manufacturer of the drug substance. Additionally, the batch analysis results for the same batches issued by the suppliers have been provided. The results comply with the proposed specification.

Stability of drug substance

The MAH applies the retest period and storage conditions as stated for the bimatoprost manufacturers.

Stability data on the active substance from the first manufacturer have been provided for three batches stored at -15 to -20°C and 2-8°C. The proposed retest period of 3 years when stored in a freezer in tight, light resistant containers, under nitrogen atmosphere is justified.

Stability data on the active substance from the second manufacturer have been provided. Based on the available stability data in the ASMF, the claimed retest period of 60 months for the drug substance when stored at -20°C in a tight, light resistant container, under nitrogen atmosphere is justified. The stability testing at an elevated temperature (i.e. 2-8°C) sufficiently confirms the stability of the drug substance in case of short term excursions outside the proposed label storage condition.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. A waiver of the need to provide equivalence data can be considered in accordance with the *Guideline on the Investigation of Bioequivalence*, as the test product is the same type of aqueous solution and contains the same active substance. However, the excipients are not the same as the reference medicinal product as the product at issue does not contain the preservative benzalkonium chloride.

The MAH provided sufficient evidence that the test product (without benzalkonium chloride) and the reference product (with benzalkonium chloride) are similar. The results from a previously published clinical trial showed that eye drops with bimatoprost 0.03% without benzalkonium chloride is non-inferior and equivalent to bimatoprost 0.03% with low dosage of benzalkonium chloride of 50 ppm. It is regarded unlikely that the differences in drop size and surface tension between test product and reference product are clinically relevant.

The other physico-chemical parameters of the test and reference product, such as pH, density (g/cm3), osmolality (mOsm/kg) and dynamic viscosity (cP) were found to be similar. The proposed method of sterilisation and the selected packaging materials/container closure system are adequately justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The process 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 benzalkonium chloride content of 50% was demonstrated therefore it is acceptable to establish a lower limit of 60% of declaration for the preservative benzalkonium chloride for shelf life and in use.

Quality control of drug product

The product specification includes tests for appearance, identity, deliverable volume, filling volume, weight loss, clarity of solution, degree of colouration, visual particulate matter, osmolality, pH, bimatoprost assay, degradation products, and subvisible particles. The product specifications cover appropriate parameters for this dosage form and all limits are

deemed acceptable. The MAH has studied extractable and leachables of the container closure system and found compounds well below their permitted daily exposure. Hence no test for this dosage form and all limits are deemed acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three batches of drug product, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three batches. The batches were stored at 25°C/40% RH (24 months), 30°C/65% RH (24 months) and 40°C/NMT 25% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The photostability data show that the drug product is sensitive to light. The proposed shelf-life of 24 months with storage condition 'the product should also be stored in the original bottle (in the outer carton) in order to protect from light' is justified.
Stability data has been provided demonstrating that the product remains stable for 28 days following first opening of the container.

Specific measures for 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 Idifarma 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.

No post-approval commitment were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Bimatoprost Idifarma 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.

IV.2 Pharmacokinetics

Biowaiver
The request for a biowaiver has been made with a reference to the *NfG on Investigation of Bioequivalence, Appendix II, Locally acting, locally applied products*. According to the guideline, in case of solutions, such as eye drops, a biowaiver may be acceptable, 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 MAH has adequately discussed the qualitative and quantitative differences between the test product and reference product (Lumigan 0.3 mg/mL eye drops with preservatives, EU/1/02/205/001-002). The main difference between the products is the presence of the preservative benzalkonium chloride (BAK) in the reference product, while the proposed product is preservative free. It is noted that Lumigan 0.3 mg/mL eye drops, solution, in single-dose container, (EU/1/02/205/005-007) neither contains BAK. There is clinical evidence from one double-blind randomised controlled study available, showing that eye drops with bimatoprost 0.03% without benzalkonium chloride is non-inferior and equivalent to bimatoprost 0.03% with low dosage of benzalkonium chloride of 50 ppm (Lumigan), on

lowering IOP over 12 weeks in patients with ocular hypertension or glaucoma (Day et al., 2013[1]). The two formulations used in the trail only differed regarding the presence of BAK.

Except for containing benzalkonium chloride, two other notable differences between the test product and reference product are drop volume and surface tension.
The slight difference in drop volume is probably due to the different nozzle/dropper used in the different containers. In addition, the drop volumes for the different containers are close to 30 µl. Because of the maximum volume of the conjunctival sac, also about 30 µl, the drop-sizes from test product and reference product can be considered to be similar, and no significant differences are expected from a clinical perspective.
The difference in surface tension is due to the absence/presence of BAK. This was based on comparisons of surface tension of commercially available eye drop solutions with and without BAK (Grgurevic MH et al.[2]) and by comparing the surface tension of both Lumigan 0.3 mg/mL eye drops, with (EU/1/02/205/001-002) and without (EU/1/02/205/005-007) BAK. The surface tension of the test product falls between the surface tensions of these two registered Lumigan 0.3 mg/mL eye drops. As a remark, the surface tension of the test product is relatively close to the normal range (40-46 mN/m) of surface tension at the air/tear fluid interface.

The MAH provided sufficient evidence that the test product (without benzalkonium chloride) and the reference product (with benzalkonium chloride) are similar. The results from a previously published clinical trial showed that eye drops with bimatoprost 0.03% without benzalkonium chloride is non-inferior and equivalent to bimatoprost 0.03% with benzalkonium chloride. It is regarded unlikely that the differences in drop size and surface tension between test product and reference product are clinically relevant.

Based on the above, the two formulations are considered equivalent with regard to efficacy and safety. A waiver for clinical studies is considered justified.

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 Idifarma 0.3 mg/ml.

1 Day DG, Walters TR, Schwartz GF, et al. Bimatoprost 0.03% preservative-free ophthalmic solution versus bimatoprost 0.03% ophthalmic solution (Lumigan) for glaucoma or ocular hypertension: a 12-week, randomised, double-masked trial.*Br J Ophthalmol:* June 2013 (DOI: 10.1136/bjophthalmol-2012-303040).
2 Martina Hotujac Grgurević, Marina Juretić, Anita Hafner, Jasmina Lovrić & Ivan Pepić (2017) Tear fluid-eye drops compatibility assessment using surface tension, Drug Development and Industrial Pharmacy, 43:2, 275-282, DOI: 10.1080/03639045.2016.1238924

- Summary table of safety concerns as approved in RMP:

Important identified risks	• Iris hyperpigmentation • Punctate keratitis • Acute asthma and asthmatic symptoms
Important potential risks	• Reactivation of previous infective ocular disease • Cardiovascular events (angina pectoris, bradycardia, hypotension) • Choroidal effusion • Increase in intraocular pressure • Off-label use (cosmetic use for the purpose of stimulating eyelashes growth)
Missing information	• Treatment of paediatric population • Treatment of pregnant and breastfeeding women

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 eye drops, solution. It is accepted that no new clinical and bioequivalence studies were conducted; a biowaiver was granted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet 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 questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question met the criterion of 100% correct answers. The results show that the package leaflet 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

Bimatoprost Idifarma 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, solution. Lumigan eye drops is a well-known medicinal product with an established favourable efficacy and safety profile.

Bimatoprost Idifarma is a product for ocular use (eye drops) intended to act without systemic absorption. 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 discussion in the CMD(h) regarding the provided justification by the MAH that appropriate microbiological quality of the product was maintained throughout the in-use-shelf life. The MAH provided additional studies regarding sterility of product to ensure the device is capable of delivering an acceptable drug product during the in-use period. Bases on these data, agreement between member states was reached.

The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bimatoprost Idifarma 0.3 mg/ml eye drops with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 May 2018.

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