COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ganmono 0.3 mg/ml eye drops solution

(bimatoprost)

NL License RVG: 123465

Date: 13 February 2020

This module reflects the scientific discussion for the approval of Ganmono 0.3 mg/ml eye drops solution. The procedure was finalised on 1 August 2019. 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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Ganmono 0.3 mg/ml eye drops solution, from Rockmed Pharma 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 national 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 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

Ganmono 0.3 mg/ml is a clear, colourless solution with pH between 6.8 and 7.6 and osmolality between 270 and 310 mOsmol/kg.

One ml of solution contains 0.3 mg bimatoprost.

The solution is packed in white LDPE bottles closed with a screw cap (HDPE and silicone). Each bottle has a fill volume of 3 ml.

The excipients are: citric acid monohydrate (E330), disodium phosphate heptahydrate, sodium chloride, sodium hydroxide (E524) or hydrochloric acid (E507) for pH-adjustment), purified water.

II.2 Drug Substance

The active substance is bimatoprost, an established active substance but not described in any pharmacopoeia. The drug substance is a white crystalline powder and slightly soluble in water. Stereoisomerism and polymorphism have been described (form I is used).

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 manufacture of the drug substance is based on a conjugated addition route, which consists of four steps. The drug substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is established in-house by the MAH with tests for appearance, identification, specific optical rotation, heavy metals, sulphated ash, water content, related substances, assay, residual solvents and microbial limits. The limits are acceptable. An acceptable risk assessment on elemental impurities in line with ICH Q3D is included. Batch analytical data demonstrating compliance with this specification have been provided for three full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three full-scale batches stored at -20 °C (36 months), 5 °C (36 months) and 25 °C/60% RH (6 months). The retest period is 36 months in a freezer with a temperature lower than -15 °C in the original packaging.

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 explained. The test and reference products have been compared with regards to several physicochemical properties. All relevant aspects, like design verification and microbial stress testing, for multi-dose containers for preservative-free eye drops have been adequately addressed. In addition, a toxicological evaluation of the substances from the extractable study is provided. Overall, the pharmaceutical development of the product is acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant guidelines. A solution is prepared from the drug substance and excipients. After pH adjustment, the solution is filtered and filled in the container closure system. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with either the Ph. Eur. or the USP, which is acceptable. As relevant, the bioburden of the excipients is included. These specifications are acceptable.

Microbiological attributes

Extensive microbiological challenge tests have been performed on the container closure system. It has been demonstrated that the test product remains sterile in and on the container closure system during storage and use. The microbiological attributes of the container closure system are considered to be 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, identification, extractable volume, water loss, pH, osmolality, assay, related substances, sterility and tightness of the container. 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 three full-scale 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 full-scale batches stored at 25°C/60% RH (36 months), 30°/65% RH (12 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 the proposed commercial packaging. No significant changes were observed during the stability studies. The proposed shelf-life of 36 months without any special storage requirements is acceptable. Stability data has been provided demonstrating that the product remains stable for four weeks at room temperature following first opening of the container. Sterility was maintained throughout the in-use 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 MEB considers that Ganmono 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 Ganmono 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 MEB agrees 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 MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The MAH request a waiver for an *in vivo* study, as the hybrid and reference formulations are solutions containing the same concentration of the same active substance and having a minor difference in the excipient composition. The reference formulation is Lumigan 0.3 mg/ml, eye drops, solution (Allergan Pharmaceuticals Ireland).

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.

According to the SmPC of Lumigan, the solution contains sodium chloride, sodium phosphate dibasic heptahydrate, citric acid monohydrate, sodium hydroxide and/or hydrochloric acid for pH adjustment, water for injection and benzalkonium chloride (0.05 mg/ml). The main difference between the products is the presence of the preservative benzalkonium chloride 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 benzalkonium chloride.

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 trial only differed regarding the presence of benzalkonium chloride. So the absence of benzalkonium chloride is considered not clinically relevant.

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 Ganmono.

- 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

[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).

	• 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 MEB agrees 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

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 a comparable bimatoprost eye drops solution. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ganmono 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.

Ganmono 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.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Ganmono was authorised in the Netherlands on 1 August 2019.

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