CBG MEB

Public Assessment Report

Scientific discussion

Bimagan Plus 0.3 mg/ml + 5 mg/ml eye drops, solution

(bimatoprost/timolol maleate)

NL/H/3804/001/DC

Date: 25 September 2017

This module reflects the scientific discussion for the approval of Bimagan Plus 0.3 mg/ml + 5 mg/ml eye drops, solution. The procedure was finalised on 8 June 2017. 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 Member States have granted a marketing authorisation for Bimagan Plus 0.3 mg/ml + 5 mg/ml eye drops, solution from S.C. Rompharm Company S.R.L.

The product is indicated for reduction of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to topical beta-blockers or prostaglandin analogues.

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 Ganfort which has been registered in the EEA by Allergan Pharmaceuticals Ireland through a centralised procedure (EU/1/06/340/001-002) since 23 May 2006.

The concerned member states (CMS) involved in this procedure were Bulgaria and Romania.

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/Timolol is a colourless to slightly yellow eye drops, solution. The pH of the solution is 6.5 to 7.8, the osmolality is 260 to 320 mOsmol/kg.

One ml of solution contains 0.3 mg of bimatoprost and 5 mg of timolol as 6.8 mg of timolol maleate.

The solution is packed in white LDPE bottles with a dark blue HDPE screw cap and a white LDPE dropper insert. Each bottle has a fill volume of 3 ml.

The excipients are benzalkonium chloride, sodium chloride, disodium phosphate heptahydrate, citric acid monohydrate, concentrated hydrochloric acid or sodium hydroxide (for pH adjustment), and purified water.

II.2 Drug Substance

Bimatoprost
The active substance is bimatoprost, an established active substance, not described in any pharmacopoeia. The active substance is slightly soluble in water. Bimatoprost shows no polymorphism, nor is it relevant as the intended drug product is 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 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

Manufacturer-I

The manufacturing process consists of eleven steps. The last stage of the synthesis consists of several crystallisation and washing steps for purification. No heavy metal catalysts or class 1 organic solvents are used in the process.

Manufacturer-II

Bimatoprost is prepared in a four-step synthesis from two key intermediates. The synthesis of both intermediates consists of a five step synthesis. The two intermediates are then combined to Bimatoprost. Purification in the last step of the synthesis is performed. No heavy metal catalysts or class 1 organic solvents are used in the process.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches (one of each manufacturer).

Stability of drug substance

Manufacturer-I

Stability data on the active substance have been provided for three full scaled batches for each of the two manufacturing sites stored at -20°C (24-60 months) and 2-8°C (six months). The long-term stability data show no changes or trends in any of the tested parameters. At accelerated conditions (2-8°C) an increase in water content was seen. The proposed retest period of three years when stored in a freezer (-20°C) in tight, light resistant containers, under nitrogen atmosphere is justified.

Manufacturer-II

Stability data on the active substance have been provided for three full scaled batches stored at -20°C (36 months), 2-8°C (36 months) and 25°C/60% RH (six 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.

Timolol maleate

The active substance is timolol maleate, an established active substance, described in the European Pharmacopoeia (Ph.Eur.). The active substance is soluble in water. The substance contains an asymmetric carbon centre. Since the drug substance is fully solubilised in the drug product, polymorphism is not a matter of concern.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two full scale batches (one of each manufacturer).

Stability of drug substance

The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 main development studies concerned the characterisation of the reference product and comparative characteristics studies. The comparative studies included parameters appearance, colour, pH, density, osmolality, assay, surface tensions and drop size. The volume of generated drops is a robust parameter and in consequence, the drop size is not susceptible to any changes may be caused by temperature during handling (storage) of the drug product. The MAH has also provided sufficient data on opalescence and buffer capacity. The excipients used are well known and are similar to those present in the reference product. The choice of concentration of benzalkonium chloride as preservative has been fully justified. In order to compensate for losses during the manufacture of the preservative an overage is used. The choices of the packaging and manufacturing process are also justified. The pharmaceutical development of the product has been adequately performed.

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 smallest production scale batches. It is regarded as a standard process. Process validation for full-scale batches will be performed post authorisation.

Microbial attributes
The MAH provided a thorough justification for the selection of sterile filtration followed by aseptic filling. The choice is justified.

Control of excipients
The excipients comply with pharmacopoeial requirements. 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, colour, pH, relative density, osmolality, filling volume, closure integrity, identity of bimatoprost, timolol, maleate and benzalkonium chloride, assay of bimatoprost, timolol maleate and benzalkonium chloride, related substances and sterility. Except for colour, pH, volume, benzalkonium chloride 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 three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for three batches with fill volume of 2.5 ml (one batch) and 3 ml (two batches) stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. At both storage conditions except for a decrease in benzalkonium chloride no clear trends or changes were seen. The proposed shelf-life of 36 months with storage condition ‘This medicinal product does not require any special storage conditions’ is justified. The drug product is not sensitive to light.

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.

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 Bimagan Plus 0.3 mg/ml + 5 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 commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Bimagan Plus 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 Ganfort 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 and timolol maleate are well-known active substances 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/239/95) 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 Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution and the pharmaceutical properties (i.e. osmolality, pH, relative density, surface tension and droplet volume) are comparable to that of the reference product as well, a biowaiver can be granted. Bimagan Plus 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 Bimagan Plus.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Iris hyperpigmentation • Punctate keratitis • Acute asthma and asthmatic symptoms • Bradycardia
Important potential risks	• Cardiovascular events (angina, hypotension, atrial fibrillation/arrhythmias, congestive heart failure) • Choroidal detachment • Cystoid macular edema • Drug interaction with calcium channel blockers, guanethidine, beta-adrenergic blocking agents, para-sympathomimetics, anti-arrhythmics, digitalis glycosides, mydriatic agents and CYP2D6 inhibitors.
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 Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution. No new clinical studies were conducted. The product can be considered essentially similar to the reference product based on chemical-pharmaceutical properties. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has (PL) 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 test consisted of 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bimagan Plus 0.3 mg/ml + 5 mg/ml eye drops, solution has a proven chemical-pharmaceutical quality and is a hybrid form of Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution. Ganfort is a well-known medicinal product with an established favourable efficacy and safety profile.

Bimagan Plus 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 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 Bimagan Plus 0.3 mg/ml + 5 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 8 June 2017.

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)