COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bimatoprost/Timolol Brown & Burk 0,3 mg/ml + 5 mg/ml eye drops, solution in single dose container (bimatoprost/timolol maleate)

NL/H/5182/001/DC

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This module reflects the scientific discussion for the approval of Bimatoprost/Timolol Brown & Burk 0,3 mg/ml + 5 mg/ml eye drops, solution in single dose container. The procedure was finalised on 3 February 2022. 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
USP	United States Pharmacopeia (USP)

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bimatoprost/Timolol Brown & Burk 0,3 mg/ml + 5 mg/ml eye drops, solution in single dose container, from Brown & Burk IR Limited.

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 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container (NL RVG 72923) which has been registered in the European Economic Area (EEA) by Allergan Pharmaceuticals Ireland since 19 May 2006 by the centralised procedure EMEA/H/C/000668.

The concerned member states (CMS) involved in this procedure were Sweden and the United Kingdom (Northern Ireland).

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 Brown & Burk are eye drops in single-dose containers. The solution is a clear colourless to slightly yellow solution, with a pH between 6.80 and 7.50 and osmolality between 260 and 330 mOsmol/kg. One ml of solution contains 0.3 mg of bimatoprost and timolol maleate equivalent to 5 mg of timolol.

The solution is packed in natural translucent low density polyethylene (LDPE) single-dose containers. Each single-dose container contains 0.4 ml solution, and 5 single-dose containers are packaged in a sealed Aluminium pouch.

The excipients are: sodium chloride, disodium phosphate heptahydrate E339, citric acid monohydrate E330, hydrochloric acid E507 or sodium hydroxide E524 (to adjust pH) and water for injection.

II.2 Drug Substances

II.2.1 Bimatoprost

The active substance bimatoprost is an established active substance not described in any pharmacopoeia. The active substance is slightly soluble in water. Bimatoprost shows no polymorphism, nor it is 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 the active substance bimatoprost. 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 consists of seven steps. No heavy metal catalysts are used in the manufacture. Class 1 solvents are used, but spiking studies show that the class 1 solvents are adequately removed from the synthesis process. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of bimatoprost

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 three full scale batches. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of bimatoprost

Stability data on the active substance bimatoprost have been provided for four batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 60 months when preserved in well-closed containers to protect from moisture, at 20°C ± 5°C.

II.2.2 Timolol maleate

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

The CEP procedure is used for 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 timolol maleate

The drug substance specification has been established in-house by the applicant based on the specification of the Ph.Eur., additional tests of the CEP-holder, and a test for microbiological purity. 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 three full scale batches.

Stability of timolol maleate

The active substance is stable for five years when stored in a polyethylene bag in an aluminium/polyethylene bag placed in a fibre drum. 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 are explained. The main development studies concerned the characterisation of the reference product and comparative characteristics studies. The comparative studies included the following parameters: appearance, pH, specific gravity, surface tension, buffer capacity, tonicity, osmolality, viscosity, impurities, assay and drop size. The results are considered sufficient to confirm physico-chemical similarity of the test and reference product. A waiver to provide bioequivalence data was requested, which is discussed in section IV on the clinical aspects.

Manufacturing process

The manufacturing process consists of preparing a bulk solution, followed by aseptic filtration of the bulk solution and aseptic filling. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches.

Control of excipients

The excipients comply with Ph.Eur. or the United States Pharmacopeia (USP) requirements. Their specifications are acceptable.

Microbiological attributes

In general, adequate information on the microbiological attributes of the drug product has been provided. Microbiological attributes like bioburden and sterility testing, which are critical attributes for an ophthalmic product, would be monitored as relevant as part of in-process, product release and stability parameters. The methods used to monitor microbial attributes are based on general chapters of Ph.Eur and are validated as applicable. The bioburden and endotoxin of the bulk solution are controlled by controlling the microbial load on each of the input ingredients and manufacturing the drug product solution in a controlled environment.

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, pH, osmolality, viscosity, extractable volume, colour, assay, particulate contamination, sterility, related substances water loss. The release and shelf-life limits are identical, except for pH, osmolality, assay and related substances. 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. Further, an adequate risk assessment on possible contamination from N-nitrosamines has been provided.

Batch analytical data from three full scaled 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 on three full scaled batches stored at 25°C/40% RH (18 months) and 40°C/25% RH (six months), in accordance with applicable European guidelines. The batches were stored in low density polyethylene single- dose containers in an opened or unopened aluminium sachet. No clear trends have been observed in the available stability results.

Photostability studies were performed in accordance with ICH recommendations and showed that the product is photostable when exposed to light in the marketed pack. The drug product in the immediate package was sensitive to light and therefore storage in an aluminium pouch is warranted to protect from light. Freeze-thaw studies were performed and showed that the product is stable to temperature excursions outside the labelled storage temperature.

On basis of the data submitted, a shelf life was granted of 24 months for the unopened aluminium pouch, without special temperature storage conditions requirements.

The in-use stability data demonstrate that the product remains stable for seven days following the first opening of the aluminium sachet when stored at 25°C/40% RH.

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/Timolol Brown & Burk 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/Timolol Brown & Burk is intended for substitution of a similar product, 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

The request for a biowaiver has been made with reference to the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), which states that "a waiver of the need to provide equivalence data may be acceptable in the case of solutions, e.g. eye drops, nasal sprays or cutaneous solutions, 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 method and means of administration should also be the same as the medicinal product currently approved, unless otherwise justified."

The drug product is an ophthalmic solution and contains the same active and inactive ingredients in the same concentration as the reference product Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container. The MAH has performed physico-chemical characterisation of the test product against the reference product, which confirmed physico-chemical similarity.

Based on the submitted data, a waiver for the need to provide equivalence data can be considered in accordance with the *Guideline on the Investigation of Bioequivalence*.

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/Timolol Brown & Burk.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Iris hyperpigmentation • Punctate keratitis • Acute asthma and asthmatic symptoms • Bradycardia • Cystoid macular oedema
Important potential risks	• Cardiovascular events (angina, hypotension, congestive heart failure) • Choroidal detachment
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. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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 Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bimatoprost/Timolol Brown & Burk 0,3 mg/ml + 5 mg/ml eye drops, solution in single dose container has a proven chemical-pharmaceutical quality and is a hybrid form of Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution, in single-dose container. Ganfort is a well-known medicinal product with an established favourable efficacy and safety profile.

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 Bimatoprost/Timolol Brown & Burk with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 February 2022.

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