LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Bimtim
(bimatoprost, timolol)

SE/H/2496/01/DC

This module reflects the scientific discussion for the approval of Bimtim. The procedure was finalised on 2025-03-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bimtim, 0,3 mg/ml + 5 mg/ml, Eye drops, solution in single-dose container.

The active substance is bimatoprost, timolol, timolol maleate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Bimtim, 0.3 mg/ml + 5 mg/ml, Eye drops, solution in single-dose container, is a Hybrid Art. 10(3) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Ganfort, 0,3 + 5mg/ml, Eye drops, solution authorised in Union since 2006, with AbbVie Deutschland GmbH & Co. KG as marketing authorisation holder.

The applicant has submitted a risk management plan.

No clinical trials have been submitted.

For this application no Scientific Advice was given.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Bimtim, 0.3 mg/ml + 5 mg/ml, is an eye drop, a solution in single-dose container. One ml of the solution contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate). The active substances, strength, pharmaceutical form, route of administration and indication of Bintino are the same as for the reference product Ganfort.

Pharmacodynamic, pharmacokinetic and toxicological properties of the active substances bimatoprost and timolol are well known. As bimatoprost and timolol are widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Bimtim is intended for a generic substitution, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Bimtim from a non-clinical point of view.

IV. CLINICAL ASPECTS

To support the application, the applicant has submitted as report an overview of the literature data and reasoning why a clinical study is not warranted for the product (see biowaiver).

Pharmacokinetics
No clinical study has been performed. The pharmacokinetics characteristics of bimatoprost and timolol are based on literature data.

Bimatoprost-timolol
Plasma bimatoprost and timolol concentrations were determined in a crossover study comparing the monotherapy treatments to bimatoprost-timolol multi-dose formulation treatment in healthy subjects. Systemic absorption of the individual components was minimal and not affected by co-administration in a single formulation.

In two 12-month studies of bimatoprost-timolol multi-dose formulation in which systemic absorption was measured, no accumulation was observed of either of the individual components.

Bimatoprost
Absorption
Bimatoprost penetrates the human cornea and sclera well in vitro. After ocular administration, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.03% bimatoprost to both eyes for two weeks, blood concentrations peaked within 10 minutes after dosing and declined to below the lower limit of detection (0.025 ng/ml) within 1.5 hours after dosing. Mean Cmax and AUC 0-24hrs values were similar on days 7 and 14 at approximately 0.08 ng/ml and 0.09 ng·hr/ml respectively, indicating that a steady drug concentration was reached during the first week of ocular dosing.

Distribution
Bimatoprost is moderately distributed into body tissues and the systemic volume of distribution in humans at steady-state was 0.67 1/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88%.

Metabolism
Bimatoprost is the major circulating species in the blood once it reaches the systemic circulation following ocular dosing. Bimatoprost then undergoes oxidation, N-deethylation and glucuronidation to form a diverse variety of metabolites.

Excretion
Bimatoprost is eliminated primarily by renal excretion, up to 67% of an intravenous dose administered to healthy volunteers was excreted in the urine, 25% of the dose was excreted via the faeces. The elimination half-life, determined after intravenous administration, was approximately 45 minutes; the total blood clearance was 1.5 1/hr/kg.

Timolol
Absorption
After ocular administration of a 0.5% eye drops solution in humans undergoing cataract surgery, peak timolol concentration was 898 ng/ml in the aqueous humour at one hour post-dose.

Metabolism/excretion:
Part of the dose is absorbed systemically where it is extensively metabolised in the liver. The half-life of timolol in plasma is about 4 to 6 hours. Timolol is partially metabolised by the liver with timolol and its metabolites excreted by the kidney.

Distribution
Timolol is not extensively bound to plasma.

Pharmacokinetic conclusion
Bimtim (bimatoprost/timolol) 0.3 mg/ml + 5 mg/ml, eye drops, solution is a locally applied product which exerts its effect at the site of application. For local acting products abridged applications should be regarded as hybrid applications.

No bioequivalence study has been conducted to support the application. This is acceptable since this is a locally applied product provided as an aqueous solution, which is of the same type of solution and the composition is essentially similar to the reference product, Ganfort (bimatoprost/timolol) 0.3 mg/ml + 5 mg/ml, eye drops, solution (Guideline on the Investigation of the Bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98 Rev. 1/ Corr **). From a clinical point of view the criteria for a biowaiver are met.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Bimtim.

Part II Safety specification

Summary of safety concerns	
Important identified risks	• Iris hyperpigmentation • Punctate keratitis • Acute asthma and asthmatic symptoms • Bradycardia • Cystoid macular edema
Important potential risks	• Cardiovascular events (angina, hypotension, congestive heart failure) • Choroidal detachment
Missing information	• Exposure in pediatric patients • Exposure in pregnancy and lactation

The updated Summary of safety concerns is in line with the reference product.
Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
The applicant has satisfactorily responded to the questions raised in the first round of assessment and updated the RMP accordingly.
The submitted Risk Management Plan, version 0.2 signed 14 Aug 2024 is considered acceptable.
Issue resolved.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Ganfort, EU/1/06/340, Bimatoprost +

Timolol Ratiopharm, NL/H/3810/001/DC and Acetazolamid EQL Pharma 250 mg tablets, 5.4.1-2017-52728.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bimatoprost/Timolol, 0.3 mg/ml + 5 mg/ml eye drops, solution (in single dose container) is a locally applied product which exerts its effect at the site of application.
No bioequivalence study has been conducted to support the application. This is acceptable since this is a locally applied product provided as an aqueous solution, which is of the same type of solution and the composition is essentially similar to the reference product.

The quality of the generic product, Bimtim, is found adequate. There are no objections to approval of Bimtim, from a non-clinical and clinical point of view.

The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Bimtim, 0,3 mg/ml + 5 mg/ml, Eye drops, solution in single-dose container was positively finalised on 2025-03-13.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

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

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