LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Bimaprez
# (bimatoprost)

# SE/H/2447/01/DC

**This module reflects the scientific discussion for the approval of Bimaprez. The procedure was finalised on 2025-05-05. For information on changes after this date please refer to the module 'Update'.**

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Bimaprez, 0,1 mg/ml, Eye drops, solution.

The active substance is bimatoprost. 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 Bimaprez, 0,1 mg/ml, Eye drops, solution, 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 NO as the sole concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Lumigan 0,1 mg/ml, Eye drops, solution, authorised in the European Union since 2022, with AbbVie Deutschland GmbH & Co as marketing authorisation holder.

**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**
Pharmacodynamic, pharmacokinetic and toxicological properties of bimatoprost are well known. As bimatoprost is a 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)**
An environmental risk assessment has been submitted including a justification that approval of Bimaprez will not lead to an increased exposure to the environment. The justification is considered acceptable.

In conclusion, the are no objections to approval of Bimaprez from the non-clinical perspective.

# IV. CLINICAL ASPECTS

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

Absorption
Bimatoprost penetrates the human cornea and sclera well in vitro. After ocular administration in adults, the systemic exposure of bimatoprost is very low with no accumulation over time. After once daily ocular administration of one drop of 0.3 mg/ml 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 bimatoprost 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 l/kg. In human blood, bimatoprost resides mainly in the plasma. The plasma protein binding of bimatoprost is approximately 88 %.

Biotransformation
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.

Elimination
Bimatoprost is eliminated primarily by renal excretion, up to 67 % of an intravenous dose administered to healthy adult 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 l/hr/kg.

Characteristics in elderly patients
After twice daily dosing with bimatoprost 0.3 mg/ml eye drops, solution, the mean AUC0-24hr value of 0.0634 ng•hr/ml bimatoprost in the elderly (subjects 65 years or older) were significantly higher than 0.0218 ng•hr/ml in young healthy adults. However, this finding is not clinically relevant as systemic exposure for both elderly and young subjects remained very low from ocular dosing. There was no accumulation of bimatoprost in the blood over time and the safety profile was similar in elderly and young patients.

**Pharmacokinetic conclusion**
Bimatoprost 0.1 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, Lumigan 0.1 mg/ml, eye drops, solution (Guideline on the Investigation of the Bioequivalence, CPMP/ EWP/ QWP/ 1401/ 98 Rev. 1/ Corr **). From a chemical pharmaceutical point of view the criteria for a biowaiver are met, see Quality AR for details. The biowaiver is therefore acceptable.

**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.

**Pharmacovigilance system**
*Proposed MAH: Blumont Ofta Trading Ltd*

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

**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 Bimaprez. All relevant sections of the RMP were provided.

Part II Safety specification
Summary table of proposed safety concerns (RMP Part II: Module SVIII).

Table SVIII.1: Summary of safety concerns

| **Summary of safety concerns** | |
|---|---|
| Important identified risks | Iris hyperpigmentation |
| | Punctate keratitis |
| | Acute asthma and asthmatic symptoms |
| | BAK-related corneal toxicity |
| Important potential risks | Increase in intraocular pressure |
| | Reactivation of previous infective ocular disease |
| | Choroidal effusion |
| | Cardiovascular events (bradycardia, angina and hypotension) |
| | Off-label use (cosmetic use for the purpose of stimulating eyelash growth) |
| Missing information | Exposure in paediatric patients |
| | Exposure in pregnancy and lactation |

The initial proposed summary of safety concerns was not entirely in line with the safety concerns of the innovator product Lumigan or the safety concerns published on the CMDh website for

bimatoprost, as the applicant listeded “Long term toxicity” as Missing information. As bimatoprost has been on the market in the EU since 2002 and its safety profile is considered well characterized, the RMS requested that “Long term toxicity” be deleted from the Summary of safety concerns. The applicant updated the summary of safety concerns accordingly.

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 MAH has satisfactorily responded to the questions raised in their Day 106 response and updated the RMP accordingly, by deleting Long term toxicity as Missing information in the Summary of Safety concerns.
**Issue is resolved.**

The submitted Risk Management Plan, version 1 signed 19-April-2024 is considered acceptable.

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

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 language used for the purpose of user testing the PL was English.
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

The benefit/risk ratio is considered positive and <product name, strength, pharmaceutical form> is 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 Bimaprez, 0,1 mg/ml, Eye drops, solution was positively finalised on 2025-05-05.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# 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)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se