IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Eyzeetan 0.3 mg/ml + 5 mg/ml eye drops, solution
Bimatoprost
Timolol Maleate
PA23156/005/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/7034/001/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 19/10/2020 under procedure number IE/H/1153/001
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA23156/005/001
Marketing Authorisation Holder: European Regulatory Affairs t/a Ivowen

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Aspire Pharma Limited a Marketing Authorisation for the medicinal product Eyzeetan (PL 35533/00107) on 18 December 2017. The product is a prescription only medicine (POM), indicated for the 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.

This application was submitted as abridged national application, according to Article 10(3) of directive 2001/83/EC, as amended, as a hybrid generic application. The applicant has cross-referred to Ganfort 0.3 mg/ml + 5mg/ml eye drops, solution (EU/1/06/340/001-002) as the reference medicinal product. Ganfort 0.3 mg/ml + 5 mg/ml eye drops was authorised centrally in Europe on 19 May 2006 (Allergan Pharmaceuticals Ireland); this reference product is preserved with benzalkonium chloride. The reference medicinal product against which generic equivalence was demonstrated is Ganfort eye drops 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose container (EU/1/06/340/003-005) which was authorised on 04 October 2013 via a variation to the marketing authorisation holder Allergan Pharmaceuticals Ireland. The cited legal basis and reference medicinal product is considered valid.

Eyzeetan consists of two active substances: bimatoprost and timolol (as maleate). These two components decrease elevated intraocular pressure (IOP) by complementary mechanisms of action and the combined effect results in additional IOP reduction compared to either compound administered alone.
Eyzeetan has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance. It is a synthetic prostamide, structurally related to prostaglandin $F_{2\alpha}$ ($PGF2_{\alpha}$) that does not act through any known prostaglandin receptors.
Bimatoprost selectively mimics the effects of newly discovered biosynthesised substances called prostamides. The prostamide receptor, however, has not yet been structurally identified. The mechanism of action by which bimatoprost reduces intraocular pressure in man is by increasing aqueous humour outflow through the trabecular meshwork and enhancing uveoscleral outflow.

Timolol maleate is a $beta_1$ and $beta_2$ non-selective adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anaesthetic (membrane-stabilising) activity. Timolol maleate lowers IOP by reducing aqueous humour formation. The precise mechanism of action is not clearly established, but inhibition of the increased cyclic AMP synthesis caused by endogenous beta-adrenergic stimulation is probable.

No new non-clinical or clinical studies were conducted, which is acceptable given that this application was based on being a hybrid medicinal product of the reference product that has been licenced for over 10 years.

Comparable physicochemical parameters between the reference and proposed products were provided. As the product is a solution, no therapeutic equivalence study between the reference product Ganfort eye drops 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose container (Allergan Pharmaceuticals Ireland) and the proposed product has been conducted. The container closure system for the two products is different as the reference product is presented in a single-dose container whereas the test product is presented as multi-dose container system not requiring preservative. However, as drop volume values for the solutions from each container are similar, no differences in the safety or efficacy of the solutions are expected to result following ocular administration.

A biowaiver is considered appropriate for this application and is adequately supported by the comparative quality data provided.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the MHRA has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A Marketing Authorisation was granted in the UK on 18 December 2017.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

Each 1 ml of eye drops, solution contains 0.3 mg of the active ingredient bimatoprost and 5 mg of the active ingredient timolol (as 6.8 mg of timolol maleate). The excipients present are sodium chloride, disodium hydrogen phosphate heptahydrate, citric acid monohydrate, sodium hydroxide or hydrochloric acid (for pH adjustment) and Water for injection.

The finished product is packaged in white opaque 5 ml low density polyethylene (LDPE) bottles consisting of a high density polyethylene (HDPE), silicone, white Novelia nozzle with a blue tip which is sealed with a white high density polyethylene (HDPE) cap containing either 1 or 3 bottles of 3ml solution. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

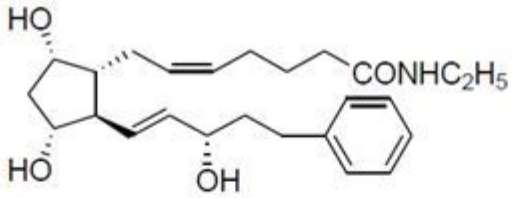
II.2 Drug Substance

Active substances

(1) Bimatoprost

INN: (Z)-7-[(1R,2R,3R,5S)-3,5-Dihydroxy-2-[1E,3S)-3-hydroxy-5-phenyl-1-pentenyl] cyclopentyl]-5-N-ethylheptenamide

Structure:



Molecular formula:	$C_{25}H_{37}NO_4$
Molecular weight:	415.57 g/mol
Appearance:	A white crystalline powder
Solubility:	Very soluble in ethyl alcohol and methyl alcohol and slightly soluble in water

Bimatoprost is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

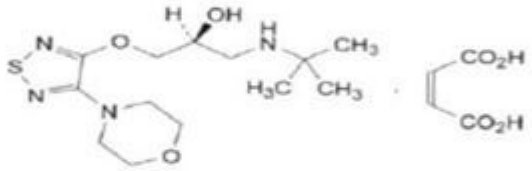
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

(2) Timolol maleate

INN: (S)-1-(tert-butylamino)-3-[(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl)oxy]-2-propanol,hydrogen maleate

Structure:



Molecular formula: $C_{17}H_{28}N_4O_7S$
Molecular weight: 432.5 g/mol
Appearance: white or almost white crystalline powder or colourless crystals
Solubility: Soluble in water and ethanol (96%)

The active substance, timolol maleate, is the subject of a European Pharmacopeia (Ph.Eur.) monograph.

All aspects of the manufacture and control of the active substance, timolol maleate are covered by the European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to develop a stable eye drop solution that could be considered as a hybrid medicinal product of the currently licensed product, Ganfort eye drops 0.3 mg/ml + 5 mg/ml eye drops, solution in single-dose container (Allergan Pharmaceuticals Ireland).

The physicochemical properties of the proposed product versus the reference product have shown that the products are comparable.

All excipients with the exception of disodium hydrogen phosphate heptahydrate, comply with their respective European Pharmacopeia monographs. Disodium hydrogen phosphate heptahydrate complies

with the United States Pharmacopeia (USP) monograph. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

None of the excipients used in this product contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial scale batches have been provided. The results are satisfactory.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

The data from these studies support a shelf-life of 3 years for unopened bottles with no special storage conditions. The in-use shelf life of the product is 4 weeks after first opening the bottle.

Suitable post approval stability commitments to continue stability testing on batches of finished product have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of bimatoprost and timolol maleate are well-known, no new non-clinical studies are required, and none have been provided. An overview bases on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment since Eyzeetan 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.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical point of view therefore grant of a Marketing Authorisation is recommended.

IV. CLINICAL ASPECTS

IV CLINICAL ASPECTS

IV.1 Introduction

The pharmacodynamic, pharmacokinetic, clinical efficacy and safety properties of bimatoprost and timolol maleate are well known. A comprehensive review of the published literature has been provided by the applicant. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

In accordance with the guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) "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", therefore no bioequivalence study was conducted or required.

The container closure system for the two products is different as the reference product is presented in a single-dose container whereas the test product is presented as multi-dose container system not requiring preservative. However, as drop volume values for the solutions from each container are similar, no differences in the safety or efficacy of the solutions are expected to result following ocular administration.

A biowaiver is considered appropriate for this application and is adequately supported by the comparative quality data provided.

IV.3 Pharmacodynamics

No new pharmacodynamics data are required for this application and none have been submitted.

IV.4 Clinical efficacy

No new clinical efficacy data are required for this application and none have been submitted.

IV.5 Clinical safety

No new clinical safety data are required for this application and none have been submitted.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 Eyzeetan.

A summary of safety concerns, as approved in the RMP, are listed below:

Summary of safety concerns	
Important identified risks	• Hyperpigmentation • Macular oedema • Respiratory disorders • Choroidal detachment • Hypoglycaemia/diabetes • Cardiac and vascular disorders • Corneal toxicity – dry eye • Co-administration with adrenaline • Hypersensitivity to any allergen • Masking hyperthyroidism signs
Important potential risks	• Increase in intraocular pressure • Off-label use (cosmetic use for stimulation of eyelash growth) • Eye infection or injury • Medication error
Missing information	• Use during pregnancy and lactation • Paediatric use

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects

The grant of Marketing Authorisation is recommended.

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 PIL 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.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant's product is identical to the cross-reference product. Extensive clinical experience with bimatoprost and timolol maleate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

VI. REVISION DATE

28/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/7034/001/DC to IE/H/1153/001			
MAH Transfer				29/01/2021