Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

VISUBLEND 0.3 MG/ML + 5 MG/ML EYE DROPS, SOLUTION

bimatoprost and timolol maleate

PL 46130/0010

RAFARM UK LIMITED

LAY SUMMARY

Visublend 0.3 mg/ml + 5 mg/ml eye drops, solution
bimatoprost and timolol maleate

This is a summary of the Public Assessment Report (PAR) for Visublend 0.3 mg/ml + 5 mg/ml eye drops, solution. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Visublend in this lay summary for ease of reading.

For practical information about using Visublend, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Visublend and what is it used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the United Kingdom (UK) called Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution, albeit with certain differences.

Visublend is used in the treatment of high pressure in the eye in adults, including the elderly. This high pressure can lead to glaucoma. The doctor will prescribe their patient Visublend when other eye drops containing beta-blockers or prostaglandin analogues have not worked sufficiently on their own.

How does Visublend work?
Visublend contains two different active substances (bimatoprost and timolol (as timolol maleate)) that both reduce pressure in the eye. Bimatoprost belongs to a group of medicines called prostamides, which are prostaglandin analogues. Timolol belongs to a group of medicines called beta-blockers.

The eye contains a clear, watery liquid that feeds the inside of the eye. This liquid is constantly drained out of the eye and new liquid is made to replace it. If the liquid cannot drain out quickly enough, the pressure inside the eye builds up and could eventually damage the sight (an illness called glaucoma). Visublend works by reducing the production of liquid and also increasing the amount of liquid that is drained. This reduces the pressure inside the eye.

How is Visublend used?
The pharmaceutical form of this medicine is eye drops, solution and the route of administration is application into the eye(s).

The usual dose is one drop once a day, either in the morning or in the evening in each eye that needs treatment. The patient should use this medicine at the same time each day.

Instructions for use
The patient must not use the bottle if the tamper-evident ring on the bottle neck is broken before they first use it.

The patient should follow the below instructions for use:

1. Wash the hands and sit or stand comfortably.
2. Unscrew the cap.
3. Remove the tamper-evident ring from the bottle.
4. Tilt the head back and look at the ceiling.
5. Gently pull down the lower eyelid until there is a small pocket (Figure 2).
6. Turn the bottle upside down and squeeze it to release one drop into each eye that needs treatment (Figure 3).
7. Let go of the lower lid and close the eye (Figure 4).
8. Whilst keeping the eye closed, press a finger against the corner of the closed eye (the site where the eye meets the nose) and hold for 2 minutes (Figure 5). This helps to stop Visublend getting into the rest of the body.

If a drop misses the eye, try again.

To avoid contamination, do not let the tip of the bottle touch the eye or anything else.

Put the cap back on and close the bottle straight after it has been used.

If the patient uses Visublend with another eye medicine, they should leave at least 5 minutes between putting in Visublend and the other medicine. The patient should use any eye ointment or eye gel last.

For further information on how Visublend is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Visublend have been shown in studies?
No additional studies were needed as Visublend contains the same active substance as the reference medicine, and satisfactory data to justify any differences have been provided.

What are the possible side effects of Visublend?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Visublend is a hybrid medicine and is pharmaceutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

Why wase Visublend approved?
It was concluded that Visublend has been shown to be pharmaceutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Visublend?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Visublend. The RMP details the important risks of Visublend, how these risks can be minimised, any uncertainties about Visublend (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Visublend:

Summary of safety concerns	
Important identified risks	• Iris pigmentation • 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 information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Visublend are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

A RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Visublend
A Marketing Authorisation for Visublend was granted in the UK on 17 December 2021.

The full PAR for Visublend follows this summary.

This summary was last updated in February 2022.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Visublend 0.3 mg/ml + 5 mg/ml eye drops, solution (PL 46130/0010) could be approved.

The product is approved for the following indication:

- 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.

Visublend 0.3 mg/ml + 5 mg/ml eye drops, solution consists of two active substances: bimatoprost and timolol (as timolol 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. Bimatoprost +timolol has a rapid onset of action.

Bimatoprost is a potent ocular hypotensive active substance. It is a synthetic prostamide, structurally related to prostaglandin F2α (PGF2α) 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 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 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.

This application was approved under Regulation 52B of The Human Medicines Regulations 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution, that has been licensed within the United Kingdom (UK) for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a hybrid medicinal product of a suitable reference product.

A biowaiver was submitted with this application which was accepted. No bioequivalence or therapeutic equivalence studies were required and none were provided with this application.

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national Marketing Authorisation was granted in the UK on 17 December 2021.

II QUALITY ASPECTS

II.1 Introduction

This product contains 0.3 mg of bimatoprost and 5 mg of timolol (as 6.8 mg of timolol maleate) in each ml of solution.

In addition to bimatoprost and timolol, this product also contains the excipients benzalkonium chloride, disodium hydrogen phosphate, citric acid monohydrate, sodium chloride, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

The finished product is packaged in white low density polyethylene (HDPE) bottles, each with a low density polyethylene (LDPE) dropper and HDPE screw cap, with tamper evident ring. Each bottle has a fill volume of 3 ml.

The following pack sizes are available: cartons containing 1 or 3 bottles of 3 ml solution.

Not all pack sizes may be marketed.

II.2 ACTIVE SUBSTANCES

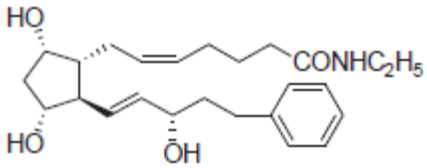
Active substance -Bimatoprost

rINN: Bimatoprost

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

Molecular Formula: $C_{25}H_{37}NO_4$

Chemical Structure:



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 not the subject of a European Pharmacopoeia monograph.

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 specifications are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

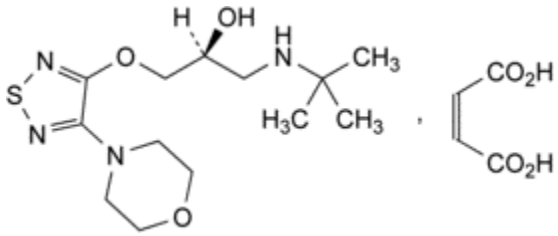
Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

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 analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all working standards.

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

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

Active Substance 2 - Timolol maleate
rINN: Timolol maleate
Chemical Name: (2*S*)-1-[(1,1-Dimethylethyl)amino]-3-[[4-(morpholin-4-yl)-1,2,5-thiadiazol-3-yl]oxy]propan-2-ol (*Z*)-butenedioate.
Molecular Formula: $C_{17}H_{28}N_4O_7S$
Chemical Structure:



Molecular Weight: 432.5 g/mol
Appearance: White or almost white, crystalline powder or colourless crystals.
Solubility: Soluble in water and in ethanol (96 per cent)

Timolol maleate is the subject of a European Pharmacopoeia monograph.

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

II.3 DRUG PRODUCT

Pharmaceutical development
A satisfactory account of the pharmaceutical development has been provided.

Comparative physicochemical data have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

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

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have 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.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and 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
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with no special storage conditions, is acceptable.

After first opening of the bottle, the product should be used within 28 days. This medicinal product does not require any special storage conditions.

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

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS

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

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction
In accordance with the regulatory requirements, the applicant has provided a suitable biowaiver. No bioequivalence or therapeutic equivalence studies have been submitted with this application.

IV. 2 Pharmacokinetics
No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical safety
No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Ganfort 0.3 mg/ml + 5 mg/ml eye drops, solution.

IV.6 Risk Management Plan (RMP)
The applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL 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 quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

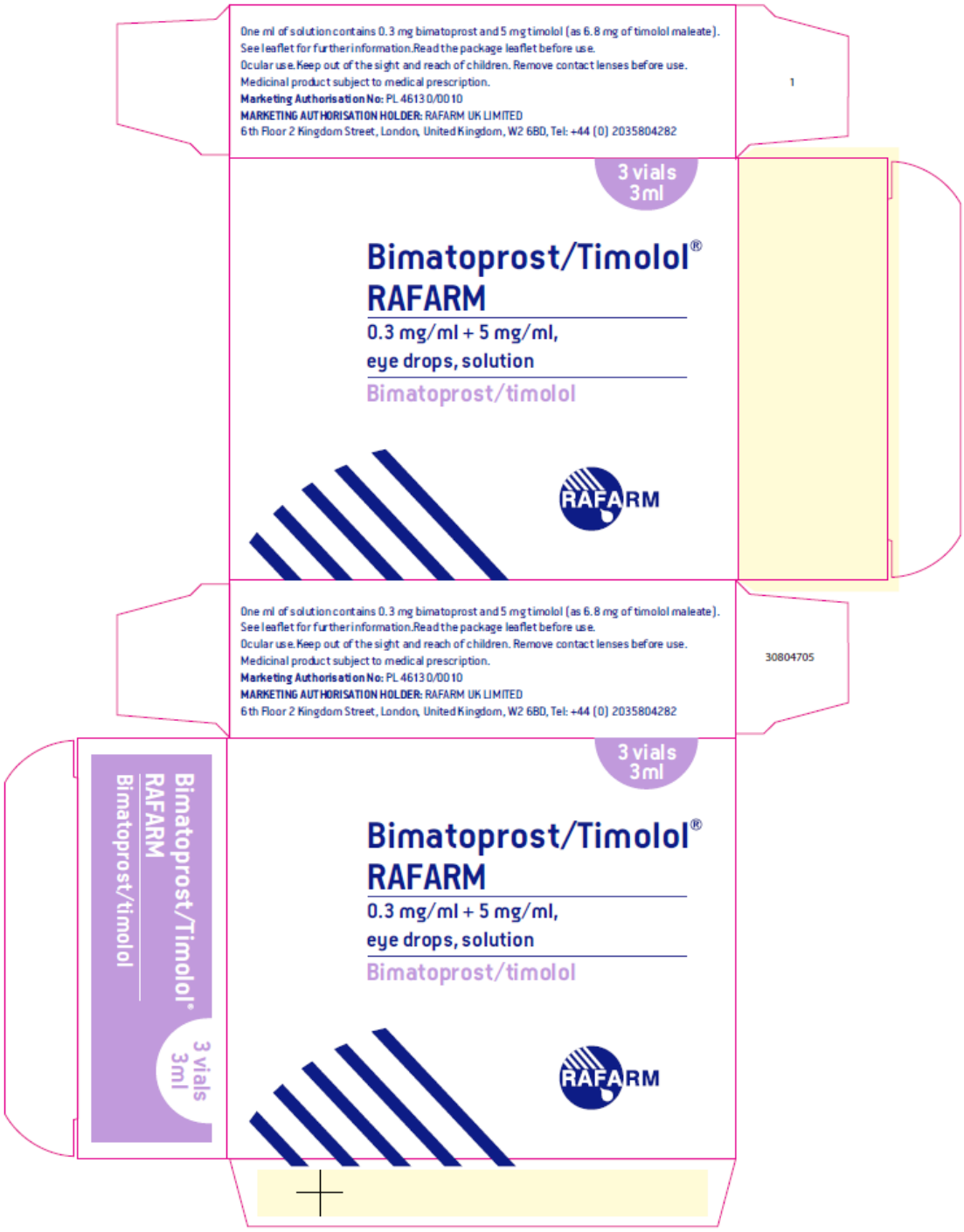
Extensive clinical experience with bimatoprost and timolol maleate is considered to have demonstrated the therapeutic value of the product.

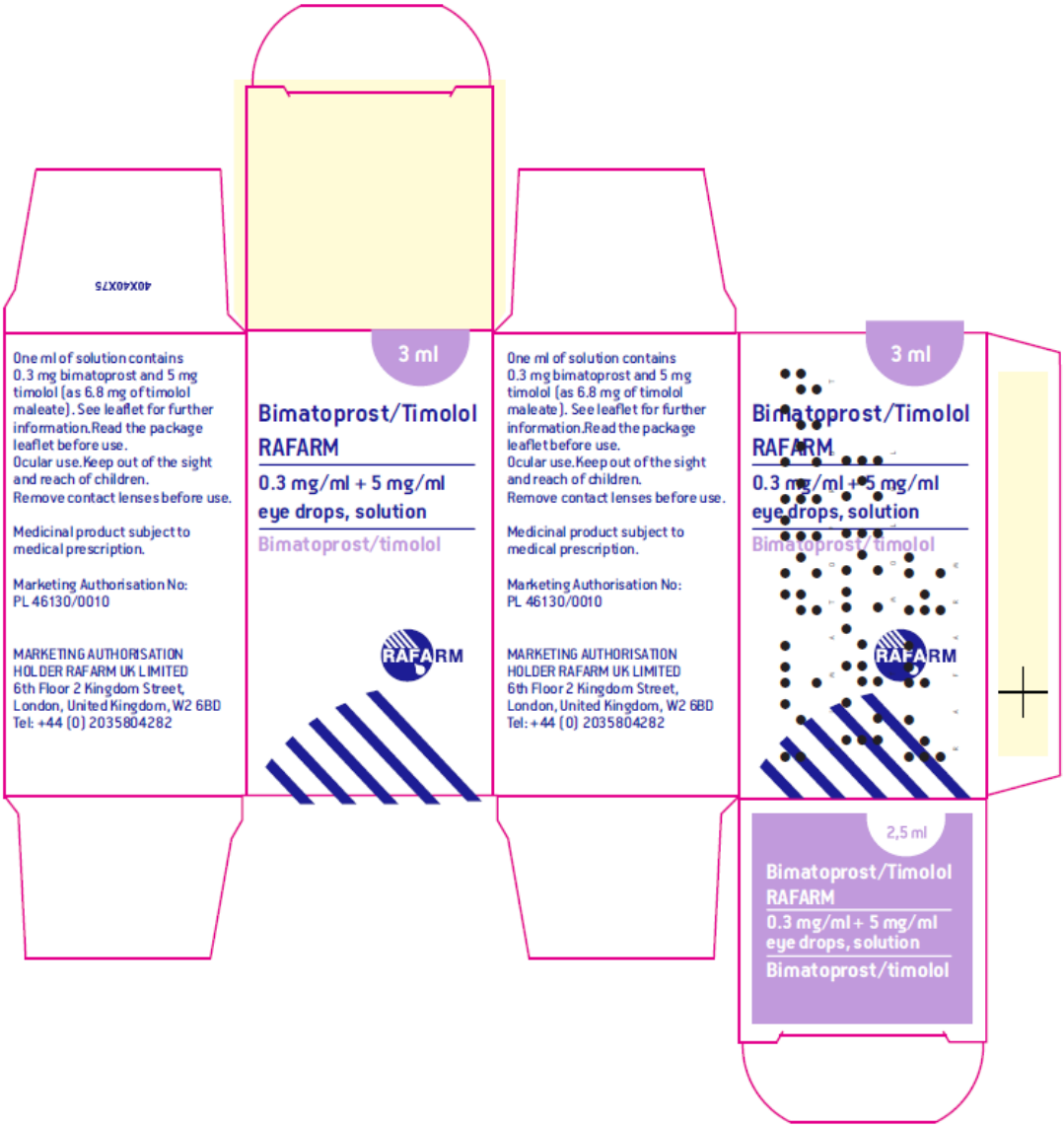
The benefit/risk is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), PIL and labelling are satisfactory, in line with current guidelines and consistent with the reference product.

In accordance with legal requirements, the current approved versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of licensing are provided below.


One ml of solution contains 0.3 mg bimatoprost and 5 mg timolol (as 6.8 mg of timolol maleate).
See leaflet for further information. Read the package leaflet before use.
Ocular use. Keep out of the sight and reach of children. Remove contact lenses before use.
Medicinal product subject to medical prescription.
Marketing Authorisation No: PL 46130/0010
MARKETING AUTHORISATION HOLDER: RAFARM UK LIMITED
6th Floor 2 Kingdom Street, London, United Kingdom, W2 6BD, Tel: +44 (0) 2035804282
1
3 vials
3ml
Bimatoprost/Timolol®
RAFARM
0.3 mg/ml + 5 mg/ml,
eye drops, solution
Bimatoprost/timolol
RAFARM
30804705
Bimatoprost/Timolol®
RAFARM
Bimatoprost/timolol
3 vials
3ml


40X40X75
One ml of solution contains 0.3 mg bimatoprost and 5 mg timolol (as 6.8 mg of timolol maleate). See leaflet for further information. Read the package leaflet before use.
Ocular use. Keep out of the sight and reach of children.
Remove contact lenses before use.
Medicinal product subject to medical prescription.
Marketing Authorisation No:
PL 46130/0010
MARKETING AUTHORISATION HOLDER RAFARM UK LIMITED
6th Floor 2 Kingdom Street,
London, United Kingdom, W2 6BD
Tel: +44 (0) 2035804282
3 ml
Bimatoprost/Timolol
RAFARM
0.3 mg/ml + 5 mg/ml
eye drops, solution
Bimatoprost/timolol
RAFARM
2,5 ml


Bimatoprost/Timolol ®
RAFARM
0.3 mg/ml + 5 mg/ml,
Bimatoprost/timolol
Ocular use. Read the package leaflet
before use. Discard 28 days after first opening
3ml
RAFARM
Lot:
Exp:

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**