Public Assessment Report

Decentralised Procedure

Timolol 0.25% w/v Eye Drops Solution
Timolol 0.5% w/v Eye Drops Solution

PL 25298/0054
PL 25298/0055

UK/H/4103/001/DC
UK/H/4103/002/DC

Brown & Burk UK Ltd
Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Brown & Burk UK Ltd Marketing Authorisations for the medicinal products Timolol 0.25% w/v Eye Drops Solution and Timolol 0.5% w/v Eye Drops Solution (product licence numbers: PL 25298/0054 and PL 25298/0055) on 3 December 2012. These medicines are available on prescription only.

Timolol 0.25% w/v and 0.5% w/v Eye Drops Solution belongs to a group of medicines called beta-blockers. Timolol lowers pressure in the eye. It is used to treat glaucoma when pressure in the eye is raised.

No new or unexpected safety concerns arose from this application. It was judged that the benefits of taking Timolol 0.25% w/v and 0.5% w/v Eye Drops Solution outweigh the risks; hence Marketing Authorisations have been granted.
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Module 1

Information about Decentralised Procedure

| Name of the products in the Reference Member State | Timolol 0.25% w/v Eye Drops Solution  
Timolol 0.5% w/v Eye Drops Solution |
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Type of application</td>
<td>Article 10.3 (hybrid)</td>
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<tr>
<td>Name of the drug substance</td>
<td>Timolol maleate</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code) of the medicinal products</td>
<td>Pharmacotherapeutic group: Anti-glaucoma preparations and miotics, beta-blocking agents, selective (S01ED01)</td>
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<tr>
<td>Pharmaceutical form and strengths of the medicinal products</td>
<td>Eye drops solution; 0.25% w/v and 0.5% w/v</td>
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</table>
| Reference numbers for the Decentralised Procedure | UK/H/4103/001/DC  
UK/H/4103/002/DC |
| Reference Member State                             | United Kingdom                                                                 |
| Member States concerned                            | Ireland                                                                         |
| Start date of the Decentralised Procedure          | 28 July 2010                                                                    |
| End date of the Decentralised Procedure            | 26 September 2012                                                               |
| Marketing Authorisation numbers                    | PL 25298/0054  
PL 25298/0055 |
| Name and address of the authorisation holder       | Brown & Burk UK Ltd  
5 Marryat Close  
Hounslow West  
Middlesex  
TW4 5DQ  
UK |
Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

Product Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

Timolol 0.25% w/v Eye Drops Solution

Label:

Timolol 0.25% w/v Eye Drops Solution

Timolol maleate
Each ml contains Timolol Maleate equivalent to 2.5 mg of Timolol.

Keep out of the sight and reach of children. 5 mL Eye Drops solution.
Read the package leaflet before use. Discard 28 days after first opening. For ocular use only.

MA Holder: Brown & Burk UK Ltd.
PL 25298/0054

Timolol 0.5% w/v Eye Drops Solution

Labels:

**Timolol 0.5% w/v Eye Drops Solution**

5 ml

Timolol maleate
Each ml contains Timolol Maleate equivalent to 5 mg of Timolol.

Keep out of the sight and reach of children. 5 mL Eye Drops solution.
Read the package leaflet before use. Discard 28 days after first opening. For ocular use only.
MA Holder: Brown & Burk UK Ltd.
PL 25298/0055

**Timolol 0.5% w/v Eye Drops Solution**

10 ml

Timolol maleate
Each ml contains Timolol Maleate equivalent to 5 mg of Timolol.

Keep out of the sight and reach of children. 10 mL Eye Drops solution. Read the package leaflet before use. Discard 28 days after first opening. For ocular use only.
MA Holder: Brown & Burk UK Ltd.
PL 25298/0055
Timolol 0.5% w/v Eye Drops Solution

Each ml contains Timolol Maleate equivalent to 0.5 mg of Timolol.
Also contains: Sodium chloride, Disodium phosphate dodecahydrate, Sodium dihydrogen phosphate dihydrate, Sodium metabisulphite, Water for injections.

Use as directed by the physician.

Keep out of the sight and reach of children.

This medication procedure does not require any special physical precautions or first opening. Do not store above 30°C after first opening. Store bottle in the outer carton. Discard 28 days after first opening.

10 ml Eye Drops solution. For oculor use only.
Read the package leaflet before use.

DO NOT USE THE EYE DROPS WHILST WEARING CONTACT LENSES.
EXTERNAL USE ONLY. STERILE UNTIL OPENED.

MA Holder:
Brown & Burk UK Ltd. 5 Marryat Close, Hounslow West Middlesex, TW4 1DQ United Kingdom

PL 25298/0055
CODE: K123DROGS/KTK/28/357/2006

MHRA PAR; TIMOLOL 0.25% W/V AND 0.5% W/V EYE DROPS SOLUTION, PL
25298/0054-0055
Module 5

Scientific Discussion

1. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Timolol 0.25% w/v Eye Drops Solution and Timolol 0.5% w/v Eye Drops Solution for the treatment of ocular hypertension and glaucoma could be approved.

This Decentralised application was submitted under Article 10.3 of Directive 2001/83/EC, as amended, as a hybrid application. The reference products for this application are Timoptol® 0.25% w/v Eye Drops Solution (PL 0025/0134) and Timoptol® 0.5% w/v Eye Drops Solution (PL 0025/0135), which were first licensed to Merck Sharp & Dohme Limited in the UK on 15 March 1984. The reference products have been authorised in the EEA for at least 10 years, therefore, the legal basis of this application is acceptable.

With the UK acting as RMS in this Decentralised Procedure (DCP), Brown & Burk UK Ltd sought Marketing Authorisations for Timolol 0.25% w/v and 0.5% w/v Eye Drops Solution in Ireland.

About the Product

Timolol is a β-adrenergic blocker that decreases intraocular pressure by decreasing aqueous humour formation. It has been in clinical use as an antiglaucoma agent for many years.

General Comments on the Submitted Dossier

The submitted documentation in relation to the proposed products is of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall quality, non-clinical and clinical overviews have been submitted. They represent an adequate summary of the dossier.

General Comments on Compliance with GMP, GLP, GCP and Agreed Ethical Principles

GMP

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable
standards of GMP are in place at those non-Community sites.

**GLP and GCP**
No new non-clinical or clinical studies were conducted, which is acceptable given that this is a hybrid application cross-referring to products that have been licensed for over 10 years. No therapeutic studies have been performed and none are required for this application, in line with the “Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products Containing Known Constituents” CPWP/EWP/239/95 (see Clinical Aspects).

2. QUALITY ASPECTS

**Drug Substance**

**INN:** Timolol maleate  
**Molecular Formula:** C$_{17}$H$_{28}$N$_{4}$O$_{7}$S  
**RMM:** 432.5

**Structure:**

![Structure of Timolol Maleate](image)

**General Properties:**
A white to practically white, crystalline powder or colourless crystals. Freely soluble in water, soluble in ethyl alcohol and methyl alcohol, sparingly soluble in chloroform and propylene glycol, practically insoluble in ether and cyclohexane.

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

**Drug Products**

**Description and Composition of the Drug Products**
The drugs product are clear, colourless to light yellow, sterile eye drop solutions containing timolol maleate equivalent to 0.25% w/v or 0.5% w/v timolol and the pharmaceutical excipients disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, sodium hydroxide (for pH adjustment), benzalkonium chloride and water for injections. All excipients comply with their respective Ph Eur monograph.

Certificates of Analysis are provided for each excipient showing compliance with their respective monographs.

None of the excipients contain materials of animal or human origin. No genetically modified organisms have been used in the preparation of these excipients.
Pharmaceutical Development of the Drug Products
Details of the pharmaceutical development of the drug products have been supplied and are satisfactory. The objective was to develop stable, generic eye drop solutions that are pharmaceutically equivalent to the reference products.

Manufacture of the Drug Products
A satisfactory batch formula has been provided for the manufacture of the drug products, together with a description and flow-chart of the manufacturing method. In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies have been conducted on pilot scale batches and results were acceptable. A process validation scheme for commercial scale batches is also presented in accordance with CPMP/QWP/848/96 and is acceptable.

Control of the Drug Products
The finished product specifications provided are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided; the data demonstrate that the batches are compliant with the proposed release specifications.

Container Closure System
The drug products are licensed for marketing in a 3020 D sterile, opaque, LDPE container with sterile, translucent, LDPE 3020D block nozzle and a sterile, double safe, HDPE white cap. The 0.25% w/v strength eye drops are licensed for storage in 5 ml bottles and the 0.5% w/v strength eye drops are licensed for storage in 5 ml or 10 ml bottles. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Stability of the Drug Products
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been approved.

After the container is first opened the products should be used within 28 days and the storage precautions ‘Do not store above 25°C after first opening’ and ‘Store bottle in the outer carton’ should be applied.

Bioequivalence/bioavailability Study
As the products provide local therapeutic activity, investigations of bioequivalence/bioavailability are not necessary and none have been provided. Sufficient evidence was provided to demonstrate that the physicochemical properties of Timolol 0.25% w/v and 0.5% w/v Eye Drops Solution and of the reference products Timoptol 0.25% w/v and 0.5% w/v Eye Drops Solution are equivalent. As satisfactory evidence of pharmaceutical equivalence to the reference products was provided, no non-clinical or clinical studies were required or provided.
Quality Overall Summary
A satisfactory Quality Overall Summary prepared by an appropriately qualified expert has been provided. The CV of the expert has also been supplied.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and product labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Forms
The MAA forms are satisfactory.

Quality Conclusion
There are no objections to approval of Timolol 0.25% w/v Eye Drops Solution and Timolol 0.5% w/v Eye Drops Solution from a pharmaceutical point of view.

3. NON-CLINICAL ASPECTS

The pharmacological, pharmacokinetic and toxicological properties of timolol maleate are well known. As timolol maleate is a well known drug substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

Non-clinical Overview
The Non-clinical Overview has been written by a suitably qualified expert. The overview, dated 2 January 2010, refers to 16 references from the published literature dated up to 2008. In view of the fact that the pharmaco-toxicological properties of timolol maleate are well known, the overview is acceptable.

Environmental Risk Assessment
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all timolol maleate-containing products, which, in turn, is unlikely to increase exposure of the environment to timolol maleate.

Product Literature
The product literature is acceptable from a non-clinical point of view.

Non-clinical Conclusion
There are no objections to the approval of Timolol 0.25% w/v Eye Drops Solution and Timolol 0.5% w/v Eye Drops Solution from a non-clinical point of view.

4. CLINICAL ASPECTS
Pharmacokinetics
In accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr) the applicant is not required to submit a therapeutic equivalence study.

Pharmacodynamics
No new pharmacodynamic data were submitted and none are required for this application.

Clinical Efficacy
No new efficacy data are presented for this application and none are required. However, the applicant has provided a review of clinical trials published in the literature regarding the efficacy of timolol maleate.

Clinical Safety
No new safety data are presented for this application and none are required. No new or unexpected safety issues arose during the bioequivalence study. The applicant has provided a review of clinical trials published in the literature regarding the safety of timolol maleate.

Pharmacovigilance System
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk Management Plan
No safety concerns requiring additional risk minimisation activities have been identified. A detailed RMP is not considered necessary for this application.

Clinical Overview
A Clinical Overview written by an appropriately qualified physician has been provided and is a satisfactory summary of the clinical part of the dossier.

Product Literature
All product literature (SmPC, PIL and labelling) is medically satisfactory.

Clinical Conclusion
There are no objections to the approval of Timolol 0.25% w/v and 0.5% w/v Eye Drops Solution from a clinical point of view.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Timolol 0.25% w/v and 0.5% w/v Eye Drops Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

**EFFICACY**
No new clinical data were submitted and none are required for applications of this type. The applicant’s products Timolol 0.25% w/v and 0.5% w/v Eye Drops Solution have been demonstrated to be equivalent to the reference products Timoptol 0.25% and 0.5% w/v Eye Drops Solution.

**SAFETY**
No new clinical data were submitted and none are required for applications of this type.

**PRODUCT LITERATURE**
The SmPCs and PIL are satisfactory and consistent with those of the reference products. Satisfactory product labelling has also been submitted.

**BENEFIT: RISK ASSESSMENT**
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s products and the reference products are interchangeable. Extensive clinical experience with timolol maleate is considered to have demonstrated the therapeutic value of the compound. The benefit: risk balance is, therefore, considered to be acceptable. Marketing Authorisations should be granted.