**Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets**

**PL 15142/0252**

**UKPAR**

**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lay Summary</td>
<td>2</td>
</tr>
<tr>
<td>Scientific Discussion</td>
<td>4</td>
</tr>
<tr>
<td>Steps Taken for Assessment</td>
<td>11</td>
</tr>
<tr>
<td>Summary of Product Characteristics</td>
<td>12</td>
</tr>
<tr>
<td>Patient Information Leaflet</td>
<td>13</td>
</tr>
<tr>
<td>Labelling</td>
<td>14</td>
</tr>
</tbody>
</table>
LAY SUMMARY

Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets

This is a summary of the Public Assessment Report (PAR) for Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets (PL 15142/0252). It explains how the application for Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets.

For practical information about using Timolol maleate/bendroflumethiazide 10 mg/2.5 mg tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Timolol maleate/Bendroflumethiazide tablets’ in this report.

What are Timolol maleate/Bendroflumethiazide tablets and what are they used for?
This medicine is the same as Prestim Tablets (PL 15142/0025) held by Meda Pharmaceuticals Limited, which are already authorised in the UK. The licence holder (Meda Pharmaceuticals Limited) for Prestim tablets (PL 15142/0025) has agreed that its own scientific data can be used as a basis for the grant of an identical licence for Timolol maleate/Bendroflumethiazide tablets (informed consent).

Timolol maleate/Bendroflumethiazide tablets are used to treat raised blood pressure.

How do Timolol maleate/Bendroflumethiazide tablets work?
Timolol maleate/Bendroflumethiazide tablets contain the active ingredients timolol maleate and bendroflumethiazide. Timolol maleate slows the heart rate and bendroflumethiazide increases water removal from the body.

How are Timolol maleate/Bendroflumethiazide tablets used?
Timolol maleate/Bendroflumethiazide tablets are taken by mouth. The tablets should be swallowed whole with water.

Timolol maleate/Bendroflumethiazide tablets should always be taken exactly as advised by the patient’s doctor or pharmacist. The patient should check with his/her doctor or pharmacist if he/she is not sure.

The usual daily dose can vary from 1 to 4 tablets. The tablets can be taken as a single dose in the morning or in two doses, one in the morning and the other in the evening.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

Timolol maleate/Bendroflumethiazide tablets can only be obtained with a prescription.

What benefits of Timolol maleate/Bendroflumethiazide tablets have been shown in studies?
The application for Timolol maleate/Bendroflumethiazide tablets is considered to be identical to the previously authorised licence for Prestim Tablets (Meda Pharmaceuticals Limited), with the same benefits and risks. So, no new studies have been provided for Timolol maleate/Bendroflumethiazide tablets. However, reference is made to the studies for Prestim Tablets (Meda Pharmaceuticals Limited).
What are the possible side effects from Timolol maleate/Bendroflumethiazide tablets?
Like all medicines, Timolol maleate/Bendroflumethiazide tablets can cause side effects, although not everybody gets them.

For the full list of all side effects reported with Timolol maleate/Bendroflumethiazide tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Timolol maleate/Bendroflumethiazide tablets approved?
No new or unexpected safety concerns arose from this application. The MHRA, therefore, considered that the benefits of Timolol maleate/Bendroflumethiazide tablets outweigh their risks; and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Timolol maleate/Bendroflumethiazide tablets?
A Risk Management Plan has been developed to ensure that Timolol maleate/Bendroflumethiazide tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Timolol maleate/Bendroflumethiazide tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Timolol maleate/Bendroflumethiazide tablets.
A Marketing Authorisation was granted in the UK on 15 June 2015.

The full PAR for Timolol maleate/Bendroflumethiazide tablets follows this summary.

For more information about treatment with Timolol maleate/Bendroflumethiazide tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2015.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Introduction Page 5
Pharmaceutical assessment Page 6
Non-clinical assessment Page 8
Clinical assessment Page 9
Overall conclusion and benefit/risk assessment Page 10
INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Meda Pharmaceutical Limited, trading as Beechmere Pharmaceuticals, a Marketing Authorisation for the medicinal product Timolol maleate/Bendroflumethiazide 10mg/2.5 mg tablets (PL 15142/0252) on 15 June 2015. The product is a prescription-only medicine (POM) indicated for the treatment of mild to moderate hypertension.

The application was submitted as a simple abridged (informed consent) application according to Article 10c of Directive 2001/83/EC, as amended, cross-referring to Prestim Tablets (PL 15142/0025), which was granted in the UK to Meda Pharmaceuticals Limited on 05 January 2001 following a series of Change of Ownership procedures of Prestim Tablets (PL 00043/0047; Leo Laboratories Limited). Prestim Tablets (Leo Pharmaceuticals) was granted in the UK on 06 June 1979.

Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets contain the active ingredients timolol maleate and bendroflumethiazide. Timolol maleate is a non-selective beta-adrenoceptor antagonist with marked hypotensive activity. Bendroflumethiazide is a thiazide diuretic, which has a moderate duration of activity. It has been shown that beta-blocking agents used in combination with a thiazide diuretic potentiate the effects of this diuretic giving an enhanced antihypertensive effect. This may be due to the inhibition of renin release or concomitant regional haemodynamic changes. This means that a relatively lower dose of the beta-blocker is required.

No new data were submitted nor were necessary to be submitted for this application, as the data are identical to those of the previously granted cross-reference product.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 15142/0252

PROPRIETARY NAME(S): Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets

ACTIVE(S): Timolol maleate
Bendroflumethiazide

COMPANY NAME: Meda Pharmaceutical Limited, trading as Beechmere Pharmaceuticals

E.C. ARTICLE: Article 10c of Directive 2001/83/EC, as amended

LEGAL STATUS: POM

1. INTRODUCTION
This is an informed consent application for Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets (PL 15142/0252) submitted under Article 10c of Directive 2001/83/EC, as amended.

The application cross-refer to Prestim Tablets (PL 15142/0025; Meda Pharmaceuticals Limited), which was granted a Marketing Authorisation on 05 January 2001 following a series of Change of Ownership Procedures of Prestim Tablets (PL 00043/0047; Leo Pharmaceuticals). Prestim Tablets (Leo Pharmaceuticals) was granted a licence in the UK on 06 June 1979. The application is considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM

2.1. Name
The proposed name of the product is Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets. The product has been named in line with current requirements.

2.2. Strength, pharmaceutical form, route of administration, container and pack sizes
Each tablet contains 10 mg timolol maleate and 2.5 mg bendroflumethiazide. The product is packaged in glass bottles, in pack sizes of 14 (sample pack), 30, 100 and 500 tablets.

Not all pack sizes may be marketed.

The proposed shelf life for the product is 3 years, with the special storage conditions ‘Store below 25°C’.

The packaging, proposed shelf-life and storage conditions are consistent with the details registered for the cross-reference product.

2.3. Legal status
The product is available as a prescription only medicine (POM).

2.4. Marketing Authorisation Holder/Contact Persons/Company
Meda Pharmaceuticals Ltd, Skyway House, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU, UK (trading as Beechmere Pharmaceuticals, Merlin Place, Milton Road, Cambridge, CB4 0DP, UK).

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

2.5 Manufacturers
The proposed manufacturing sites are consistent with that registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.
2.6. Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

2.7. Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch sizes are stated.

2.8. Finished product/shelf-life specification
The proposed finished product specification is consistent with the details registered for the cross-reference product.

2.9. Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

2.10. TSE Compliance
None of the excipients contain materials of animal or human origin. This is consistent with the cross-reference product.

2.11. Bioequivalence
No bioequivalence data are required to support this simple abridged application because the proposed product is manufactured to the same formula and utilise the same processes as the reference product Prestim Tablets (PL 15142/0025; Meda Pharmaceuticals Limited).

3. EXPERT REPORT
The applicant cross-refers to the data for Prestim Tablets (PL 15142/0025; Meda Pharmaceuticals Limited) to which this application is claimed to be identical. This is acceptable.

4. PRODUCT NAME & APPEARANCE
See Section 2.1 for details of the proposed product name. The appearance of the product is identical to the cross-reference product.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The proposed SmPC is consistent with the details registered for the cross-reference product.

6. PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
PIL
The PIL has been prepared in line with the details registered for the cross-reference product.

Meda Pharmaceuticals Limited has previously submitted results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended, for Prestim Tablets (PL 15142/0025). The results indicate that the 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.

User-testing of the PIL for Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets (PL 15142/0252) has been accepted based on the bridging report provided by the applicant making reference to the successful user-testing of the PIL for Prestim Tablets (PL 15142/0025) as the ‘parent PIL’.
Carton and label
The proposed artwork is consistent with the artwork registered for the cross-reference product and complies with statutory requirements. In line with current legislation, the applicant has also included the names of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSION
The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.
NON-CLINICAL ASSESSMENT

As this is an informed consent application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

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

The grant of a Marketing Authorisation is recommended.
CLINICAL ASSESSMENT

As this is an informed consent application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

An acceptable Risk Management Plan (RMP) has been submitted. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

The grant of a Marketing Authorisation is recommended.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The data for this application is consistent with those previously assessed for the cross-reference product and as such have been judged to be satisfactory.

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

EFFICACY
This application is identical to the previously granted licence for Prestim Tablets (PL 15142/0252); Meda Pharmaceuticals Limited).

SAFETY
No new safety data were supplied or required for this application. Timolol maleate and bendroflumethiazide have well-established safety profiles. No new or unexpected safety concerns arose from this application.

PRODUCT LITERATURE
The SmPC and PIL are satisfactory, and consistent with those for the cross-reference product. The labelling complies with statutory requirements and is satisfactory.

BENEFIT/RISK ASSESSMENT
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 timolol maleate and bendroflumethiazide is considered to have demonstrated the therapeutic value of the compounds. The benefit/risk assessment is, therefore, considered to be positive.
Steps taken for assessment

1. The MHRA received the Marketing Authorisation application on 14 August 2014.
2. Following standard checks and communication with the applicant the MHRA considered the application valid on 27 August 2014.
3. Following assessment of the application the MHRA requested further information relating to the dossier on 21 November 2014.
4. The applicant responded to the MHRA’s request, providing further information on the 23 March 2015.
5. The application was granted on 15 June 2015.
SUMMARY OF PRODUCT CHARACTERISTICS

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Timolol maleate/Bendroflumethiazide 10 mg/2.5 mg tablets

For oral use

**Beechmere**

Each tablet contains:

- 10 mg timolol maleate
- 2.5 mg bendroflumethiazide

Do not take this medicine if you have a history of wheezing or asthma. Do not store above 25°C.

**KEEP OUT OF THE SIGHT AND REACH OF CHILDREN.**

To be used as directed by a physician. Read the package leaflet before use.

**Beechmere Pharmaceuticals**, Merlin Place, Milton Road, Cambridge CB4 0DP, UK

Expiration date:

[Barcode]

Batch number:

[Barcode]