METOPROLOL TARTRATE 50 MG AND 100 MG FILM-COATED TABLETS

PL 17907/0129-30

UKPAR

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METOPROLOL TARTRATE 50 MG AND 100 MG FILM-COATED TABLETS

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LAY SUMMARY

On 31st December 2012, the MHRA granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Metoprolol Tartrate 50 mg and 100 mg Film-coated Tablets. These medicines are only available on prescription from your doctor.

Metoprolol tartrate, the active ingredient in Metoprolol tartrate tablets, is one of a group of medicines called beta blockers. Beta blockers slow the heart beat, lessen the force with which the heart muscle contracts and reduced blood vessel contraction in the heart, brain, and throughout the body.

• Metoprolol tartrate tablets are used to treat a number of different conditions including:
  - High blood pressure
  - Angina (chest pain)
  - Some heart disorders, for example, heart attack or irregular heart beats.

• They can also be used as part of the treatment for an overactive thyroid gland.
• Metoprolol tartrate tablets can be taken to help prevent migraine attacks.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Metoprolol Tartrate 50 mg and 100 mg Film-coated Tablets outweigh the risks. Hence, Marketing Authorisations have been granted.
METOPROLOL TARTRATE 50 MG AND 100 MG FILM-COATED TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted Marketing Authorisations for the medicinal products Metoprolol Tartrate 50 mg and 100 mg Film-coated Tablets (PL 17907/0129-30) on 31st December 2012. These prescription only medicines are used for the treatment of the following indications:

- Hypertension and angina pectoris, cardiac arrhythmias especially supraventricular tachyarrhythmias.
- Adjunct to treatment of thyrotoxicosis.
- Early intervention with Metoprolol Tartrate in myocardial infarction reduces infarct size and the incidence of ventricular fibrillation.
- Pain relief may also decrease the need for opiate analgesics.
- Metoprolol Tartrate has been shown to reduce mortality when administered to patients with acute myocardial infarction.
- Prophylaxis of migraine.

These are national abridged applications for Metoprolol Tartrate 50 mg and 100 mg Film-coated Tablets submitted under Article 10(1) of Directive 2001/83/EC, as amended. These products are generic versions of Lopresor 50 mg and 100 mg film-coated tablets (PL 00101/0418-9), authorised to Novartis, UK on 6th June 1997.

Metoprolol Tartrate is a cardioselective beta-adrenergic blocking agent. It has a relatively greater blocking effect on beta1-receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of free fatty acids from fat stores) than on beta2-receptors which are chiefly involved in broncho and vasodilation. It has no membrane-stabilising effect or partial agonist (intrinsic sympathomimetic) activity.

The stimulant effect of catecholamines on the heart is reduced or inhibited by metoprolol. This leads to a decrease in heart rate, cardiac contractility and cardiac output.

A pharmacovigilance system has been provided with these applications and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Metoprolol tartrate

Chemical Names: Bis [(2RS)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]2-propanol] (2R,3R)-2,3-dihydroxybutanedioate

Structure:

[Chemical Structure Image]

Metoprolol Tartrate

Molecular Formula: C\textsubscript{34}H\textsubscript{56}N\textsubscript{2}O\textsubscript{12}

Molecular Weight: 685

Appearance: White or almost white, crystalline powder or colourless crystals.

Solubility: Very soluble in water, freely soluble in alcohol

Metoprolol tartrate is the subject of a European Pharmacopoeia monograph.

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

DRUG PRODUCT

Other ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, sodium starch glycolate, silica colloidal anhydrous, crosscarmellose sodium, starch pregelatinised, magnesium stearate, hypromellose, talc, macrogol 400, titanium dioxide (E171) and ferric oxide red (E172) (50 mg).

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.
Lactose monohydrate is the only material of animal origin used in the manufacture of the drug product. A declaration has been provided by the supplier which confirms that the lactose monohydrate is sourced from healthy animals in accordance with EMEA/410/01 Rev 02 which is acceptable.

**Pharmaceutical development**

Suitable pharmaceutical development data have been provided for these applications. Comparable dissolution and impurity profiles are provided for these products versus the originator products.

**Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished product specification**

The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container Closure System**

The tablets are packed in polyvinylchloride(PVC)/ aluminium (Al) foil blisters containing 14, 28 and 56 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**

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

Based on the results, a shelf-life of 2 years with storage condition “Store in the original packaging below 25°C” is set. This is satisfactory.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SmPCs, PIL and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Atenolol Tablets (PL 11311/0014, 0015, 0019). The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification of the rationale for bridging is accepted.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille
on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

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

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of metoprolol tartrate are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

Suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of these products from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

BIOEQUIVALENCE

To support these applications, the applicant has submitted a bioequivalence study under fasting condition comparing the test product with the reference product.

This was an open-label, randomised, two-treatment two-period, two sequences, crossover, single dose comparative bioequivalence study of Metoprolol Tartrate Tablets 100 mg (Ipca Laboratories Ltd.,) and Lopressor® Tablets 100 mg (Novartis Pharma GmbH) in healthy adult human subjects under fasting conditions.

Serial blood sampling pre-dose and at 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 3.00, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00 16.00, 24.00, 36.00 and 48 hours after drug administration was carried out in each group. A washout period of 9 days was maintained between the two dosing periods in each group.

Results

Summary of Geometric mean and 90% confidence intervals, for Test and Reference products (N=23)

<table>
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<tr>
<th>Parameters</th>
<th>Geometric Mean*</th>
<th>% Ratio</th>
<th>90% Confidence Interval for Log-transformed data</th>
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<tr>
<td></td>
<td>Test (A)</td>
<td>Reference (B)</td>
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<tr>
<td>AUC₀⁻inf</td>
<td>1119.28</td>
<td>1081.58</td>
<td>103.49</td>
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<td>AUC₀⁻t</td>
<td>1073.88</td>
<td>1039.59</td>
<td>103.30</td>
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</table>

The results show that the 90% confidence intervals for AUC₀⁻t and AUC₀⁻inf fell within the acceptable range (80-125%). Bioequivalence has been demonstrated between the test formulation (Metoprolol Tartrate Tablets 100 mg) and the reference formulation (Lopressor® Tablets 100 mg). According to the Committee for Proprietary Medicinal Products Notes for Guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev.1 Corr**), the results of the study for 100 mg formulation can be extrapolated to the other strength i.e 50 mg Film-coated Tablets.

Efficacy

No new efficacy data have been submitted and none are required for these applications.

Safety

No new safety data have been submitted and none are required for these applications.

Expert Report

The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.
SUMMARY OF PRODUCT CHARACTERISTICS
These are satisfactory.

PATIENT INFORMATION LEAFLET
This is satisfactory.

LABELLING
These are satisfactory.

MAA FORMS
These are satisfactory.

CONCLUSIONS
There are no objections to the approval of these products from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The quality characteristics of Metoprolol Tartrate 50 mg and 100 mg Film-coated Tablets 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 data have been submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Metoprolol Tartrate Tablets 100 mg and the reference product, Lopressor® Tablets 100 mg. According to the Committee for Proprietary Medicinal Products Notes for Guideline on “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QEWP/1401/98 Rev.1 Corr**), the results of the study for 100 mg formulation can be extrapolated to the other strength i.e 50 mg Film-coated Tablets.

SAFETY
No new or unexpected safety concerns arise from these applications.

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

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with metoprolol tartrate is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
## STEPS TAKEN FOR ASSESSMENT

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<td>The MHRA received the Marketing Authorisation applications on 20th August 2010</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 13th September 2010.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossier on 20th April 2011, 19th December 2011 and on the clinical section on 19th May 2011, 12th January 2012 and 26th September 2012.</td>
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<td>The applications were determined on 31st December 2012</td>
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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
Patient 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.
Metoprolol Tartrate 50 mg and 100 mg Film-coated Tablets

PL 17907/0129-30

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UKPAR Metoprolol Tartrate 50 mg and 100 mg Film-coated Tablets
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