Public Assessment Report

UKPAR

BISOPROLOL 1.25 MG, 2.5 MG, 3.75 MG, 5 MG, 7.5 MG AND 10 MG FILM-COATED TABLETS

UK Licence Numbers: PL 21880/0127-32

Medreich Plc.
LAY SUMMARY

Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets.
(bisoprolol fumarate, film-coated tablet, 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg)

This is a summary of the Public Assessment Report (PAR) for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets (PL 21880/0127-32). It explains how Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets.

For practical information about using Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets and what are they used for?
Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets are ‘generic’ medicines. This means that Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets are similar to ‘reference’ medicines already authorised in the European Union (EU), called Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets (Merck Serono Limited).

These medicines are used to treat stable chronic heart failure. They are used in combination with other suitable medicines.

How do Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets work?
These medicines contain the active ingredient bisoprolol fumarate, which belongs to a group of medicines called beta-blockers. These medicines work by affecting the body’s response to some nerve impulses, especially in the heart. As a result, bisoprolol slows down the heart rate and makes the heart more efficient at pumping blood around the body.

Heart failure occurs when the heart muscle is weak and unable to pump enough blood to supply the body’s needs.

How are Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets used?
The pharmaceutical form is a film-coated tablet and the route of administration is oral (by mouth).

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

Treatment with these medicines requires regular monitoring by the patient’s doctor. This is particularly necessary at the start of treatment and during dose increase.

The tablet should be taken with some water in the morning, with or without food. Do not crush or chew the tablet.
Treatment with these medicines is usually long-term.

**Dosage in adults including the elderly:**
Treatment must be started at a low dose and increased gradually. The patient’s doctor will decide how to increase the dose, and this will normally be done in the following way:

- 1.25 mg bisoprolol once daily for the first week of treatment
- 2.5 mg bisoprolol once daily for the second week of treatment
- 3.75 mg bisoprolol once daily for the third week of treatment
- 5 mg bisoprolol once daily for the fourth, fifth, sixth and seventh weeks of treatment
- 7.5 mg bisoprolol once daily for the eighth, ninth, tenth and eleventh week of treatment
- 10 mg bisoprolol once daily from the twelfth week for maintenance (on-going) therapy.

Depending on how well the patient tolerates the medicine; their doctor may also decide to lengthen the time between dose increases. If the patient’s condition gets worse or they no longer tolerate the drug, it may be necessary to reduce the dose again or to interrupt treatment. In some patients a maintenance dose lower than 10 mg bisoprolol may be sufficient.

If the patient has to stop treatment entirely, their doctor will usually advise them to reduce the dose gradually, as otherwise their condition may become worse.

The maximum recommended daily dose of this medicine is 10 mg.

**Children**
These medicines are not recommended for use in children.

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

These medicines can only be obtained with a prescription.

**What benefits of Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets have been shown in studies?**
Because Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets (Merck Serono Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the possible side effects of Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets?**
Because Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets are generic medicines, their benefits and possible side effects are taken as being the same as the reference medicines.

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

For the full list of all side effects reported with Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets, see section 4 of the package leaflet available on the MHRA website.
Why were Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets approved?
It was concluded that, in accordance with EU requirements, Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets have been shown to have comparable quality and to be bioequivalent to Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets (Merck Serono Limited). Therefore, the MHRA decided that, as for Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets (Merck Serono Limited), the benefits are greater than the risks and recommended that they can be approved for use.

What measures are being taken to ensure the safe and effective use of Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets?
A risk management plan (RMP) has been developed to ensure that Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPCs) and the package leaflet for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated 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 Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets
The Marketing Authorisations for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets were granted in the UK to Medreich PLC on 06 August 2012 (PL 21880/0127-32).

The full PAR for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets follows this summary.

For more information about use of Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2016
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I  INTRODUCTION

Please note that the below scientific discussion consists of the original assessment of this product licence, plus a summary of key post approval changes at the end of this introduction section to improve the accuracy of this Public Assessment Report.

The UK granted Medreich PLC Marketing Authorisations for the medicinal products Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets (PL 21880/0127-32) on 6th August 2012.

Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets are prescription only medicines (POM) and are indicated for the treatment of stable chronic heart failure with reduced systolic left ventricular function, in addition to angiotensin-converting-enzyme (ACE) inhibitors, diuretics, and (optionally) cardiac glycosides.

These applications for Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets are submitted under Article 10.1 of Directive 2001/83/EC, claiming to be generic medicinal products to Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets, authorised in the UK to E Merck Limited on 24th December 1999 (PL 00493/0179-84). These licences underwent changes of ownership to Merck Serono Limited on 2nd February 2010 (PL 11648/0071-6).

Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic sympathomimetic and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation.

Summary of key post-approval changes:
The following post-approval variations have been granted for these licences:

1. To extend the shelf life from 24 months to 36 months granted on 23 October 2014 (PL 21880/0127-0015, PL 21880/0129-0016, PL 21880/0130-0016, PL 21880/0131-0016 & PL 21880/0132-0016).
II.1 QUALITY ASPECTS

II.1 Introduction
Each film-coated tablet contains 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg or 10 mg of the active ingredient bisoprolol fumarate. Other ingredients are the pharmaceutical excipients microcrystalline cellulose (PH-102), maize starch, crospovidone (Type B), colloidal anhydrous silica, magnesium stearate, purified water, hypromellose, macrogol 400 and titanium dioxide.

Bisoprolol 3.75 mg, 5 mg, 7.5 mg film-coated Tablets have the additional excipient ferric oxide yellow (E172).

Bisoprolol 10 mg film-coated Tablets has the additional excipients ferric oxide yellow (E172) and ferric oxide red (E172).

The products are packaged in blisters composed of aluminium, polyvinyl chloride (PVC) and polyvinylidene chloride (PVdC). The blisters are packed in cartons. Pack sizes are 20, 28, 30, 50, 56, 60, 90 and 100 film-coated tablets. Not all pack sizes are marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with current legislation and the EU directives regarding contact with food stuffs.

II.1 DRUG SUBSTANCE

INN: Bisoprolol fumarate

Chemical name: \((RS)-1-[4-[2-(1-Methylethoxy) ethoxy] methyl] phenoxy]-3-[(1-methylethyl) amino] propan-2-ol fumarate

Structure:

Physical form: A white or almost white, slightly hygroscopic powder.

Solubility: Very soluble in water and in methanol. Freely soluble in alcohol.

Molecular formula: \(C_{40}H_{66}N_2O_{12}\)
Molecular weight: 767

The bisoprolol fumarate used in the product complies with its European Pharmacopoeia monographs.

The manufacturer of the drug substance holds a valid European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability. The quality of the substance is
suitably controlled, in line with the current edition of the European Pharmacopoeia Monograph for bisoprolol fumarate.

The manufacturing process, control of materials, control of critical steps, validation and process development for bisoprolol fumarate were assessed and approved by the EDQM in relation to the granting of the Certificate of Suitability and are therefore satisfactory.

An appropriate specification with suitable test methods and limits has been provided for the drug substance. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

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

Stability studies have been performed with the drug substance and no significant changes were observed. On the basis of the results, a suitable re-test period could be approved.

II.3. MEDICINAL PRODUCT
Pharmaceutical development
The objective of the development programme was to produce safe, efficacious products containing bisoprolol fumarate that could be considered generic medicinal products of Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets.

Suitable product development information has been provided. Valid justifications for the use and amounts of each excipient have been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and reference products.

With the exception of ferric oxide yellow (E172) and ferric oxide red (E172), all the ingredients comply with their relevant European Pharmacopoeia monographs. Ferric oxide yellow (E172) and ferric oxide red (E172) comply with the United States Pharmacopoeia – National Formulary.

None of the excipients used contain material of animal or human origin. The magnesium stearate used in this product is of plant origin.

Manufacture of the product
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. In-process controls are satisfactory based on batch data and controls on the finished products. Process validation data on commercial-scale batches of each strength have been provided and are satisfactory.

Finished Product Specification
The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.
Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 24 months with no special requirements for storage.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved SmPCs, PIL and labelling are included in modules 2, 3 and 4 of this report.

MAA Forms
These are pharmaceutically satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

II.4 Discussion on chemical, pharmaceutical and biological aspects
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamics, pharmacokinetics and toxicological properties of bisoprolol fumarate are well-known. As bisoprolol fumarate is a widely used, well-known drug substance, no new non-clinical data have been provided and none are required. An overview based on literature is therefore appropriate.

Non-Clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

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)
A satisfactory justification for the absence of an ERA was provided.

III.6 Discussion on the non-clinical aspects
From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.
IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of bisoprolol fumarate is well-known. With the exception of data from the bioequivalence studies detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of bisoprolol fumarate.

Based on the data provided, Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets can be considered bioequivalent to Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets (Merck Serono).

IV.2 Pharmacokinetics
To support the applications, a single bioequivalence study has been provided:

A single-dose, two-period, crossover bioequivalence study comparing the pharmacokinetics of the test product Bisoprolol 10 mg film-coated Tablets versus the reference product Cardicor (bisoprolol fumarate) 10 mg film-coated Tablets (Merck Serono) in healthy volunteers under fasted conditions.

Blood sampling was performed pre-dose and up to 72 hours post dose in each treatment period. There was a washout period of 8 days. Pharmacokinetic parameters were calculated and statistically analysed.

Results from this study are presented below as log-transformed values:

Geometric Least Mean Squares and 90% Confidence Interval

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-\infty}$ (ng.hr/ml)</th>
<th>$\text{AUC}_{0-t}$ (ng.hr/ml)</th>
<th>$\text{C}_{\text{max}}$ (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>Test</td>
<td>571.098</td>
<td>585.682</td>
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<tr>
<td>Reference</td>
<td>582.449</td>
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<tr>
<td>Ratio (90% CI)</td>
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<td>97.9</td>
<td>98.1</td>
</tr>
<tr>
<td></td>
<td>94.08 – 102.18</td>
<td>94.03 – 101.98</td>
<td>94.47 – 101.81</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to t hours

$\text{C}_{\text{max}}$ maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for $\text{AUC}_{0-\infty}$ and $\text{C}_{\text{max}}$ for bisoprolol fumarate lie within the normal 80-125% limits. Thus, bioequivalence has been shown between the test and reference products.

The applicant provided a satisfactory justification for the application of a biowaiver for the other strengths, which was accepted. Therefore, the results and conclusions of the bioequivalence study on the 10 mg tablet strength can be extrapolated to Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg and 7.5 mg film-coated Tablets.
IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
These are generic applications based on demonstration of bioequivalence and new data relating to efficacy are not required as per EU legislation once bioequivalence has been demonstrated.

IV.5 Clinical safety
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

A satisfactory justification for the absence of a Risk Management Plan has been provided.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products.

MAA Forms
The MAA forms are clinically satisfactory.

Clinical Overview
The clinical overview has been written by a suitably qualified person and is satisfactory.

Conclusion
The bioequivalence study has shown that Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets can be considered as generic medicinal products to the reference products Cardicor 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg film-coated Tablets.

IV.7 Discussion on the clinical aspects
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.

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.
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 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.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Bisoprolol 10 mg film-coated Tablets and the reference product, Cardicor 10 mg film-coated Tablets. This conclusion can be extrapolated to Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg and 7.5 mg film-coated Tablets.

No new or unexpected safety concerns arise from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence studies support the claim that the applicant’s products and the reference products are interchangeable. Clinical experience with bisoprolol fumarate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

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

The current approved labelling for these medicines is presented at the end of Annex 1.
## Steps Taken After Initial Procedure - Summary

The following table lists non-urgent safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>31/03/2016</td>
<td>Type 1B</td>
<td>To update sections 1,2,3,4.1, 4.2, 4.3, 4.4, 4.8, 4.9, 5.1,5.2,5.3,6.1,6.2,6.3,6.4,6.5,6.6,6.7,8,9 of the SmPC in line with the QRD template. Consequently the leaflet and labelling has been updated.</td>
<td>Approved on 02/08/2016- see Annex 1</td>
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ANNEX 1

Our Reference: PL 21880/0127-0025
PL 21880/0128-0026
PL 21880/0129-0026
PL 21880/0130-0026
PL 21880/0131-0026
PL 21880/0132-0025

Product: Bisoprolol 1.25 mg Film-coated Tablets
Bisoprolol 2.5 mg Film-coated Tablets
Bisoprolol 3.75 mg Film-coated Tablets
Bisoprolol 5 mg Film-coated Tablets
Bisoprolol 7.5 mg Film-coated Tablets
Bisoprolol 10 mg Film-coated Tablets

Marketing Authorisation Holder: Medreich Plc
Active Ingredient(s): Bisoprolol fumarate

Type of Procedure: National
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): Not applicable

Reason:
To update sections 1,2,3,4.1, 4.2, 4.3, 4.4, 4.8, 4.9, 5.1,5.2,5.3,6.1,6.2,6.3,6.4,6.5,6.6,7,8,9 of the SmPC in line with the QRD template. Consequently the leaflet and labelling has been updated.

Supporting Evidence
Revised SmPC fragments, PIL and labelling.

Evaluation
The proposed changes to the SmPCs, PIL and labelling are in line with the QRD template. The updated SmPC fragments, PIL and labelling have been incorporated into the Marketing Authorisations.

Conclusion
The proposed changes to the SmPCs, PIL and labelling are acceptable.

The approved labelling for the variations is included below:
UKPAR Bisoprolol 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg Film-Coated Tablets

- **Bisoprolol 7.5 mg Film-coated Tablets**
  - Read the package leaflet before use.
  - **Ingredients**
    - Each tablet contains Bisoprolol Fumarate equivalent to Bisoprolol 7.5 mg.
  - **Dosage**
    - For oral administration, use as directed by the physician.
  - **Packaging**
    - Keep out of sight and reach of children.

- **Braille Reads:**
  - Bisoprolol
  - #7.5 mg
  - film-coated
  - Tablets

- **Colours**
  - Pantone 288 C
  - Pantone 4996 C
  - Pantone Red 032 C
  - Black
  - Braille Embossing

- **Space for Batch Details & 2D Barcode (No Varnish Area)**
- **Box size:** 90 x 53 mm
- **Barcode:**

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Decision - Approved on 02 August 2016.