Public Assessment Report

Decentralised Procedure

Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets

(Bisoprolol Fumarate)

Procedure Nos: UK/H/1100/001-5/DC

UK Licence Nos: PL 18110/0013-17

Chanelle Medical UK Limited
LAY SUMMARY

Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets
(Bisoprolol fumarate)

This is a summary of the Public Assessment Report (PAR) for Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets (PL 18110/0013-17; UK/H/1100/001-5/DC). It explains how Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg 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 Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets.

These products will be referred to as Bisoprolol Fumarate Tablets in this lay summary for ease of reading.

For practical information about using Bisoprolol Fumarate Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Bisoprolol Fumarate Tablets and what are they used for?
Bisoprolol Fumarate Tablets are ‘generic medicines’. This means that Bisoprolol Fumarate Tablets are similar to ‘reference medicines’ already authorised in the UK called Cardicor 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg (Merck Limited, UK).

Bisoprolol Fumarate Tablets are used:
- To treat stable chronic heart failure. It is used in combination with other medicines suitable for this condition (such as ACE-inhibitors, diuretics and heart glycosides)
- In treatment of coronary heart disease and chest pain (angina pectoris) caused by shortage of oxygen in the heart muscle.
- In treatment of high blood pressure (hypertension).

How do Bisoprolol Fumarate Tablets work?
This medicine contains the active ingredient bisoprolol fumarate which belongs to a group of medicines called beta-blockers. This medicine works by affecting the body’s response to some nerve impulse 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 Fumarate Tablets used?
The pharmaceutical form of this medicine is a tablet and the route of administration is oral (by mouth).

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

Bisoprolol Fumarate Tablets should be taken in the morning, before with or after breakfast. The tablets should be swallowed whole with water and should not be chewed or crushed. The 2.5 mg, 5 mg and 10 mg tablets can be divided into equal doses. The 1.25 mg and 3.75 mg Tablets should not be broken.

The maximum daily dose in adults and the elderly with hypertension or angina pectoris is 20 mg once a day.
Stable chronic heart failure
The treatment should be managed by a doctor experienced in treating chronic heart failure. Treatment with bisoprolol must be started at a low dose and increased gradually. A 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 one week
- 2.5 mg bisoprolol once daily for one week
- 3.75 mg bisoprolol once daily for one week
- 5 mg bisoprolol once daily for four weeks
- 7.5 mg bisoprolol once daily for four weeks
- 10 mg bisoprolol once daily for maintenance (on-going) therapy.

The maximum recommended dose is 10 mg once daily.

Patients with kidney or liver disease
Patients with hypertension or angina pectoris; the dosage should not exceed 10 mg once daily in patients with severe kidney or liver problems.

Children and adolescents
Bisoprolol Fumarate Tablets are not recommended for use in children and adolescents.

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

For further information on how Bisoprolol Fumarate Tablets are used, refer to the package leaflet and Summaries of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Bisoprolol Fumarate Tablets have been shown in studies?
Because Bisoprolol Fumarate Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines Cardicor 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg (Merck Limited, UK). 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 Fumarate Tablets?
Because Bisoprolol Fumarate Tablets are generic medicines and are bioequivalent to the reference medicines Cardicor 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets, 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 Fumarate Tablets, see section 4 of the package leaflet available on the MHRA website.

Why was Bisoprolol Fumarate Tablets approved?
It was concluded that, in accordance with EU requirements, Bisoprolol Fumarate Tablets have been shown to have comparable quality and to be bioequivalent to Cardicor 10mg Tablets. Therefore, the MHRA decided that, as for Cardicor 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets; 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 Fumarate Tablets?
Safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflet for Bisoprolol Fumarate 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 Fumarate Tablets
Hungary, Italy, Poland and the UK agreed to grant Marketing Authorisations for Bisoprolol Fumarate Tablets on 29 October 2009. Marketing Authorisations were granted in the UK on 27 November 2009.

The full PAR for Bisoprolol Fumarate Tablets follows this summary.

For more information about treatment with Bisoprolol Fumarate Tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in September 2016.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Hungary, Italy, Poland and the UK considered that the applications for Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets are approvable. These products are prescription only medicines (POM) and are indicated in adults for the treatment of:

- stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides
- chronic, stable angina pectoris.
- essential hypertension.

These applications for Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets are submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of 10mg Emcor Tablets, first authorised in the UK to E. Merck Limited in February 1988. The UK reference products are Cardicor 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets. In both formulations, the active component is bisoprolol fumarate.

Bisoprolol fumarate is a long acting selective beta-1 adrenergic blocker without either intrinsic agonist or membrane stabilising action. Its use in hypertension and treatment of angina pectoris is well established for a number of years.

Bisoprolol is absorbed well (90% bioavailable) with little first pass metabolism. It has the advantage of having a dual excretion/elimination pathway (50% renal and 50% liver) and therefore offers certain advantages.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies with the exception of the bioequivalence study have been performed and none are required for these applications as the pharmacology of bisoprolol fumarate is well-established.

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.

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant 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 either in the Community or in a third country.

The Marketing Authorisation Holder (MAH) has provided adequate justification for not submitting a risk management plan (RMP).
II QUALITY ASPECTS
II.1 INTRODUCTION
Each tablet contains 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg bisoprolol fumarate as active ingredient.

Other ingredients consist of pharmaceutical excipients cellulose microcrystalline, silica colloidal anhydrous, croscarmellose sodium, sodium starch glycolate (Type A) and magnesium stearate.

All excipients comply with their relevant European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. The magnesium stearate contained in these products is sourced from vegetable origin and therefore no European Pharmacopoeia Certificates of suitability for TSE is required.

No genetically modified organisms (GMO) have been used in the preparation of these products.

These products are packaged in blisters composed of white polyvinyl chloride (PVC), polyvinylidene chloride (PVdC) and aluminium. The pack sizes are 20, 21, 28, 30, 50, 56, 60, 90 and 100 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary product packaging complies with EU legislation regarding contact with food.

II.2 DRUG SUBSTANCE
Bisoprolol fumarate

INN: Bisoprolol fumarate
Chemical names:
- (RS)-1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]propan-2-ol fumarate
- (±)-1-[4-[[2-(1-methylethoxy)ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-Propanol,(E)-2-butenedioate (2:1) (salt)
- (±)-1-[[α-(2-Isoproproxyethoxy)-p-tolyl]oxy]-3-isopropylamino)-2-propanol Fumarate (2:1)(salt)

Structure:

Molecular formula: $C_{40}H_{66}N_2O_{12}$
Molecular Mass: 767.0 g/mol
Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets

Appearance: White or almost white powder, slightly hygroscopic powder
Solubility: Very soluble in water and freely soluble in methanol.

An Active Substance Master File (ASMF) has been provided covering the manufacture and control of the active substance bisoprolol fumarate.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied.

Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

All potential known impurities have been identified and characterised. Appropriate proof of structure data has been supplied for the active pharmaceutical ingredient.

An appropriate specification is provided for the active substance bisoprolol fumarate, with suitable test methods and limits. 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 specifications and certificates of analysis have been provided for all aspects of the container-closure system. A declaration has been provided that the primary packaging complies with current regulations concerning contact with foodstuff.

Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

II.3. Medicinal Product
Pharmaceutical development
The objective of the development programme was to produce products that could be considered generic medicinal products of Emcor and Cardicor Tablets (E. Merck Limited).

The reference product used in the bioequivalence study is qualitatively and quantitatively identical to the UK reference product.

The applicant has provided suitable product development sections. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished products versus the reference products.

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

Manufacture of the products
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. Process validation data on two pilot scale batches per strength have been provided. The applicant has committed to perform process validation on the first three production-scale batches of each strength.
Finished Product Specification
The finished product specification proposed for the products is acceptable. Test methods have been described and have been 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 3 years with no special storage instructions.

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

III NON-CLINICAL ASPECTS
III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of bisoprolol fumarate are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ non-clinical pharmacology, pharmacokinetics and toxicology.

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)
Since the proposed products are intended for a generic substitution, their use will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

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

IV CLINICAL ASPECTS
IV.1 Introduction
This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.
IV.2  Pharmacokinetics
To support these applications, the marketing authorisation holder submitted the following single dose bioequivalence study.

A randomised, analyst blind (open label), single dose, two period, two sequence, cross over, bioequivalence study of Bisoprolol Fumarate 10mg Tablets versus Cardicor (bisoprolol fumarate) 10mg Tablets in normal, healthy, male subjects.

All subjects were in a fasted state before dosing. Blood sampling was performed at baseline and up to 72 hours post dose in each treatment period. The washout period between phases was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-4} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
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<tbody>
<tr>
<td>Bisoprolol Fumarate:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test</td>
<td>571.56</td>
<td>620.47</td>
<td>43.37</td>
</tr>
<tr>
<td>Reference</td>
<td>560.51</td>
<td>612.58</td>
<td>43.25</td>
</tr>
<tr>
<td>Ratio (90% CI)</td>
<td>101.97 (98.44 – 105.6)</td>
<td>101.29 (97.94 – 104.75)</td>
<td>100.30 (96.69 – 104.03)</td>
</tr>
</tbody>
</table>

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-4} and C_{max} for bisoprolol fumarate lie within 80-125% boundaries.

Although bioequivalence has been shown between the test and reference products in this study, it was agreed a repeat biostudy at a different CRO which is FDA approved and has been satisfactorily inspected by the IMB should be conducted. This is due to outstanding concerns centered around the performance of the bioanalytical method used in the bioequivalence study at the lowest end of the calibration range specifically at the limit of quantification and the lowest quality control level employed in the validation and in the course of sample analysis.

2nd Bioequivalence study:

A comparative, randomised, single-dose, two-period, two-sequence, two-way cross-over open label study to determine the bioequivalence of Bisoprolol Fumarate 10mg Tablets versus Cardicor (bisoprolol fumarate) 10mg Tablets in normal, healthy, male subjects under fasting conditions.

All subjects were in a fasted state before dosing. Blood sampling was performed at baseline and up to 72 hours post dose in each treatment period. The washout period between phases was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.
Results from this study are presented below as non-transformed values:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(\text{AUC}_{0-t}) (ng/ml/h)</th>
<th>(\text{AUC}_{0-\infty}) (ng/ml/h)</th>
<th>(\text{C}_{\text{max}}) (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol Fumarate:</td>
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</tr>
<tr>
<td>Test</td>
<td>504.33 ± 116.85</td>
<td>521.97 ± 124.43</td>
<td>34.99 ± 7.57</td>
</tr>
<tr>
<td>Reference</td>
<td>476.94 ± 85.85</td>
<td>491.47 ± 91.22</td>
<td>31.94 ± 5.87</td>
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<tr>
<td>Ratio (90% CI)</td>
<td>104.96 (100.63–109.47)</td>
<td>105.44 (101.17–109.90)</td>
<td>108.81 (103.21–114.70)</td>
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The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for \(\text{AUC}_{0-t}\) and \(\text{C}_{\text{max}}\) for bisoprolol fumarate lie within 80-125% boundaries.

As the 10mg strength product meets all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 10mg strength can be extrapolated to Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg and 5mg Tablets.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for applications of this type.

IV.4 Clinical efficacy
The efficacy of bisoprolol fumarate is well-known. No new efficacy data have been submitted and none are required for applications of this type.

IV.5 Clinical safety
With the exception of the safety data generated during the bioequivalence study, no new safety data were submitted and none are required for applications of this type. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant 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 either in the Community or in a third country.

The applicant has provided a suitable justification for not submitting a risk management plan for these products.

IV.7 Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

V User consultation
User testing results have been submitted for typical PILs for these products. The results indicate that the PILs are 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 they contain.
VI OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg 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. As the pharmacokinetics, pharmacodynamics and toxicology of bisoprolol fumarate are well-known, no additional data were required.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets and the originator products.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with that for the innovator products.

BENEFIT/RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical concerns have been identified. The data provided support the claim that these products are generic medicinal products of the reference products, Cardicor 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets (Merck Limited, UK). Extensive clinical experience with bisoprolol fumarate is considered to have demonstrated the therapeutic value of the products. The benefit/risk is, therefore, considered to be positive.
Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

The Summaries of Product Characteristics and Patient Information Leaflets (PIL) are consistent with the details registered for the cross-reference products.

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

The current approved labelling mock-ups are presented below:
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>
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<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
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<td>UK/H/1100/01-05/1B/011 SmPC and PIL</td>
<td>29/04/2016</td>
<td>10/08/2016</td>
<td>Approved on 10/08/2016</td>
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**Reason:**
To update sections 1, 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.1, 5.2, 5.3, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6 of the SmPCs in line with the QRD template. Consequently the leaflet has been updated.

**Supporting Evidence**
Revised SmPC fragments and PIL.

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

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

**Decision** - Approved on 10 August 2016.