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LAY SUMMARY
Bisoprolol Fumarate 7.5 mg Tablets
(Bisoprolol fumarate)

This is a summary of the public assessment report (PAR) for Bisoprolol Fumarate 7.5 mg Tablets (PL 18110/0021). It explains how Bisoprolol Fumarate 7.5 mg 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 7.5 mg Tablets.

For practical information about using Bisoprolol Fumarate 7.5 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Bisoprolol Fumarate 7.5 mg Tablets and what are they used for?
Bisoprolol Fumarate 7.5 mg Tablets are a ‘generic medicine’. This means that Bisoprolol 7.5 mg Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Cardicor 7.5 mg Tablets.

Bisoprolol Fumarate 7.5 mg Tablets are used to treat stable chronic heart failure. They are used in combination with other medicines suitable for this condition. Bisoprolol Fumarate 7.5 mg Tablets are also used in the treatment of coronary heart disease and chest pain (angina pectoris) and in the treatment of high blood pressure (hypertension).

How are Bisoprolol Fumarate 7.5 mg Tablets used?
Bisoprolol Fumarate 7.5 mg Tablets should be taken in the morning, before, with or after breakfast. They should be swallowed whole with liquid and should not be chewed or crushed.

In adults (including the elderly) the maximum dose for the treatment of hypertension or angina pectoris is 20 mg once a day. The dosage should not exceed 10 mg once daily in patients with severe kidney or liver problems. The maximum recommended dose for the treatment of stable chronic heart failure is 10 mg once daily.

This medicine can only be obtained with a prescription.

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

How have Bisoprolol Fumarate 7.5 mg Tablets been studied?
Because Bisoprolol Fumarate 7.5 mg Tablets are a generic medicine, studies in patients have been limited to tests to determine that a higher strength of the product, which is already available on the market, called Bisoprolol Fumarate 10 mg Tablets, is bioequivalent to a higher strength of the reference medicine, called Cardicor 10 mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body. It was deduced from these tests that Bisoprolol Fumarate 7.5 mg Tablets are comparable to Cardicor 7.5 mg Tablets.

What are the benefits and risks of Bisoprolol Fumarate 7.5 mg Tablets?
Because Bisoprolol Fumarate 7.5 mg Tablets are a generic medicine that is comparable to the reference medicine, their benefits and risks are taken as being the same as the reference medicine.
Why are Bisoprolol Fumarate 7.5 mg Tablets approved?
It was concluded that, in accordance with EU requirements Bisoprolol Fumarate 7.5 mg Tablets have been shown to have comparable quality and to be comparable to the reference medicine Cardicor 7.5 mg Tablets. Therefore, the view was that, as for Cardicor 7.5 mg Tablets, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Bisoprolol Fumarate 7.5 mg Tablets?
A risk management plan has been developed to ensure that Bisoprolol Fumarate 7.5 mg 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 Bisoprolol Fumarate 7.5 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Bisoprolol Fumarate 7.5 mg Tablets
The UK agreed to grant a Marketing Authorisation for Bisoprolol Fumarate 7.5 mg Tablets on 06 March 2014.

The full PAR for Bisoprolol Fumarate 7.5 mg Tablets follows this summary. For more information about treatment with Bisoprolol Fumarate 7.5 mg Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2014.
BISOPROLOL FUMARATE 7.5 MG TABLETS
PL 18110/0021

SCIENTIFIC DISCUSSION

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Pharmaceutical assessment Page 6
Non-clinical assessment Page 8
Clinical assessment (including statistical assessment) Page 9
Overall conclusions and benefit-risk assessment Page 11
INTRODUCTION

The MHRA granted Chanelle Medical (UK) Limited a Marketing Authorisation (licence) for the medicinal product Bisoprolol Fumarate 7.5 mg Tablets (PL 18110/0021) on 06 March 2014.

This is a prescription-only medicine (POM) indicated for the following:

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

The application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The originator product is Emcor 10 mg Tablets (PL 00493/0127; E Merck Limited), which was granted a licence in the UK on 11 February 1988. The UK reference product is Cardicor 7.5 mg film-coated Tablets (PL 00493/0183; E Merck Limited), which was initially granted a licence on 24 December 1999. The reference product used in the bioequivalence study is Cardicor 10 mg film-coated Tablets (PL 00493/0184; E Merck Limited).

Chanelle Medical (UK) Limited also holds Marketing Authorisations for Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets (PL 18110/0013-17; UK/H/1100/001-5/DC), which were granted licences in the UK on 27 November 2009.

Bisoprolol Fumarate 7.5 mg Tablets contain the active ingredient bisoprolol fumarate, which is a highly selective beta 1-adrenoceptor blocking agent. 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. As with other beta1-blocking agents, the mode of action in hypertension is not clear but it is known that bisoprolol markedly depresses plasma rennin levels. In acute administration in patients with coronary heart disease without chronic heart failure, bisoprolol reduces the heart rate and stroke volume and thus the cardiac output and oxygen consumption. In chronic administration the initially elevated peripheral resistance decreases.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on the product being a generic medicinal product of and originator product that has been licensed for over 10 years.

Bioequivalence studies were performed, which compared the pharmacokinetics of the applicant’s Bisoprolol Fumarate 10 mg Tablets (PL 18110/0017) with those of Cardicor 10 mg film-coated Tablets (E Merck Limited). The bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of this product.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Bisoprolol fumarate
INN: Bisoprolol fumarate
Chemical name: i) (R,S)1-[4-[(2-(1-Methylethoxy)ethoxy)methyl]phenoxy]-3[(1-methylethyl)amino]-2-propanol hemifumarate

ii) (±)-1-(4-((2-(1-Methyl-ethoxy)ethoxy)methyl)phenoxy)-3-((1-methylethyl)amino)-2-propanol(E)-2-butenedioate (2:1) salt

iii) (±)-1-[[α-(2-Isopropyethoxy)-p-tolyl]oxy]-3-(Isopropylamino)-2-propanol fumarate (2:1) salt

Structure:

![Structure of Bisoprolol Fumarate](image)

Molecular formula: \((C_{18}H_{31}NO_4)_2\) \(C_4H_4O_4\)
Molecular weight: 767.0
Physical form: White or almost white powder, slightly hygroscopic
Solubility: Very soluble in water and freely soluble in methanol

With the exception of the packaging and stability data, which have been submitted separately, all aspects of the manufacture and control of the active substance from its starting materials are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
DRUG PRODUCT

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

All excipients used comply with their respective European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. The magnesium stearate is of vegetable origin.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce safe, tolerable tablets that could be considered a generic medicinal product of Cardicor 7.5 mg Tablets (E. Merck Limited). The applicant has provided a suitable product development rationale and data.

Comparative in vitro dissolution and impurity profiles have been provided for the applicant’s product versus the reference product.

Manufacture
A Satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

Process validation has been carried out on two batches of finished product. The results are satisfactory.

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

Container Closure System
The finished products are packaged in polyvinylchloride/polyvinylidene chloride/aluminium blisters in a pack size of 28 capsules.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided.

Stability
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years, with no special storage conditions.

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

The results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC (as amended) for the package leaflet for Bisoprolol Fumarate 7.5 mg Tablets were provided. 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.
MAA forms
The MAA form is pharmaceutically satisfactory.

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

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

NON-CLINICAL ASSESSMENT
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 product’s pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As this product is intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of this product from a non-clinical viewpoint.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence studies. These studies were previously submitted in support of the Marketing Authorisation applications for Bisoprolol Fumarate 1.25mg, 2.5mg, 3.75mg, 5mg and 10mg Tablets (PL 18110/0013-17; UK/H/1100/001-5/DC), which were granted licences in the UK on 27 November 2009.

Study 1

A randomised, analyst-blind (open-label), single-dose, two-period, two-sequence, crossover bioequivalence study of Bisoprolol Fumarate 10mg Tablets versus Cardicor (bisoprolol fumarate) 10mg Tablets (E Merck Limited) 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.

The main pharmacokinetic results are presented in the table below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} (ng/ml/h)</th>
<th>AUC_{0-∞} (ng/ml/h)</th>
<th>C_{max} (ng/ml)</th>
</tr>
</thead>
<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>(98.44 – 105.6)</td>
<td>(97.94 – 104.75)</td>
<td>(96.69 – 104.03)</td>
</tr>
</tbody>
</table>

Compared with the reference product, the 90 % confidence intervals for the test product are within 80.00-125.00 % for AUC and Cmax. Bisoprolol Fumarate 10mg Tablets can, therefore, be considered to be bioequivalent with Cardicor (bisoprolol fumarate) 10mg Tablets.

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 was 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.

Study 2: Fasting conditions

A comparative, randomised, single-dose, two-period, two-sequence, two-way crossover, open-label study to determine the bioequivalence of Bisoprolol Fumarate 10mg Tablets versus Cardicor (bisoprolol fumarate) 10mg Tablets (E Merck Limited) 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.
The main pharmacokinetic results are presented in the table below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\text{AUC}_{0-4}$ (ng/ml/h)</th>
<th>$\text{AUC}_{0-\infty}$ (ng/ml/h)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol Fumarate:</td>
<td></td>
<td></td>
<td></td>
</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>
</tr>
<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>
</tr>
</tbody>
</table>

Compared with the reference product, the 90% confidence intervals for the test product are within 80.00-125.00 % for AUC and $C_{\text{max}}$. Bisoprolol Fumarate 10mg Tablets can, therefore, be considered to be bioequivalent with Cardicor (bisoprolol fumarate) 10mg Tablets.

As these products meet the bio-waiver criteria specified in the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 10 mg strength can be extrapolated to the 7.5 mg strength tablets.

**Efficacy**

No new data on efficacy have been submitted and none are required for this type of application.

**Safety**

With the exception of the data submitted during the bioequivalence studies, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

**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.

A suitable risk management plan has been provided for this product.

**Expert Report**

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Summary of Product Characteristics (SmPC)**

This is consistent with the SmPC for the reference product and is satisfactory.

**Patient Information Leaflet (PIL)**

This is consistent with that for the reference product and is satisfactory.

**Labelling**

This is satisfactory.

**Application Forms (MAA)**

This is satisfactory.

**Conclusion**

The grant of a Marketing Authorisations is recommended for this application.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Bisoprolol Fumarate 7.5 mg 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 an application of this type.

CLINICAL
Bioequivalence has been demonstrated between Bisoprolol Fumarate 10mg Tablets and Cardicor 10 mg film-coated Tablets (E Merck Limited). As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 10 mg strength tablets can be extrapolated to the 7.5 mg tablets.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with bisoprolol fumarate is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.
**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation application on 15 October 2012.</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 22 November 2012.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information on 13 March 2013.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 24 December 2013.</td>
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<td>5</td>
<td>The application was approved on 06 March 2014.</td>
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BISOPROLOL FUMARATE 7.5 MG TABLETS
PL 18110/0021

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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Summary of Product Characteristics and Patient Information Leaflet

In accordance with Directive 2010/84/EU, the current approved UK versions of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) for this product are available on the MHRA website.
Labelling

Carton:

Blister: