Public Assessment Report

Scientific discussion

Byblok 5 mg and 10 mg, film-coated tablets
(bisoprolol fumarate)

NL/H/3569/001-002/DC

Date: 9 May 2017

This module reflects the scientific discussion for the approval of Byblok 5 mg and 10 mg film-coated tablets. The procedure was finalised on 22 September 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.
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<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CMS</td>
<td>Concerned Member State</td>
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<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<tr>
<td>ERA</td>
<td>Environmental Risk Assessment</td>
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<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PL</td>
<td>Package Leaflet</td>
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<td>RH</td>
<td>Relative Humidity</td>
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<td>RMP</td>
<td>Risk Management Plan</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<tr>
<td>USP-NF</td>
<td>United States Pharmacopoeia – National Formulary</td>
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</table>
I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Byblok 5 mg and 10 mg film-coated tablets from Sandoz B.V.

The product is indicated for:

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

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application. Reference is made to the innovator product Emcor 5 mg tablets (NL License RVG 12408), registered in the Netherlands by Merck B.V. since 6 October 1987. Emcor has been approved for the treatment of hypertension and angina pectoris.

In addition, the MAH refers to Emcor Deco 5 mg and 10 mg film-coated tablets (NL License RVG 24505, 24507) as reference product. Emcor Deco has been approved for the treatment of chronic stable heart failure. It was registered in the Netherlands by Merck B.V. on 1 November 1999, through MRP SE/H/0184/004;006/MR. The marketing authorisation of these two products has been withdrawn. However, Emcor Deco 2.5 mg and 7.5 mg are still authorised in the Netherlands.

All three indications (hypertension, angina pectoris and chronic stable heart failure) have been combined in the SmPC/PL of this generic product, which is accepted as the innovator product Emcor with the indication ‘hypertension’ and ‘angina pectoris’ belongs to the same global marketing authorisation as the innovator product Emcor Deco with the indication ‘chronic stable heart failure’.

The concerned member states (CMS) involved in this procedure were Czech Republic, Romania and Slovakia.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Byblok 5 mg is a pink coloured, round, biconvex, film-coated tablet with “U5” debossed on one side and scored notch on the other side, containing 5 mg bisoprolol fumarate.

Byblok 10 mg is a white to off-white coloured, round, biconvex, film-coated tablet with “U10” debossed on one side and scored notch on other side, containing 10 mg bisoprolol fumarate.

Both tablets can be divided into equal doses.

The film-coated tablets are packed in opaque PVC/PVDC-aluminium blister.

The excipients are:

- Tablet core - microcrystalline cellulose (Avicel PH 112), anhydrous calcium hydrogen phosphate, pregelatinised starch (Starch 1500LM), colloidal anhydrous silica, crospovidone Type B, magnesium stearate
- Tablet coating - hypromellose- 5cps, macrogol 6000 (PEG 6000), polysorbate 80, titanium dioxide (E171), 5 mg additionally: ferric oxide red (E172)

The two strengths are fully dose proportional.
II.2 Drug Substance

The active substance is bisoprolol fumarate, an established active substance described in the European Pharmacopoeia (Ph.Eur). Bisoprolol fumarate is very soluble in water and freely soluble in methanol. It is slightly hygroscopic. In literature, it is reported that bisoprolol fumarate exhibits polymorphism. However it does not occur under the manufacturing conditions applied by manufacturer.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance is tested in accordance with the Ph. Eur. monograph with an additional test on a residual solvent, as covered by the CEP, and with an additional test on particle size. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
A retest period of 2 years is applied, when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Subdivision of tablets is tested in line with Ph. Eur. monograph for tablets. Divisibility into equal halves has been adequately demonstrated. The proposed products and the reference product contain the same amounts of the same active substance and concern the same pharmaceutical form. Results of a bioequivalence study have been provided. The products used in the bioequivalence study are acceptable.

The submitted comparative in vitro dissolution data support bioequivalence. The biowaiver for 5 mg is considered acceptable based on comparative in vitro dissolution data.

Manufacturing process
The drug product is prepared by a direct compression process followed by film-coating. The process is a standard manufacturing process. Relevant process parameters have been included in the description. The in-process controls are appropriate.

Process validation has been adequately performed on three blend batches and on three tablet batches per strength on production scale. The first three commercial batches per tablet strength will be validated.

Control of excipients
The excipients comply with Ph. Eur. or USP-NF requirements. These specifications are acceptable.

Quality control of drug product
The product specification includes routine tests for description, identity of bisoprolol and of colourants, average mass, disintegration, dissolution, loss on drying, uniformity of dosage units by content uniformity, assay, related substances, and non-routine tests for subdivision of tablets and microbiological quality. The limits are justified. The analytical methods have been adequately described and validated.

Batch analysis data have been provided for six validation batches, three for each strength. The results are consistent and comply with the proposed specifications.
Stability of drug product

Stability studies at accelerated (40°C/75% RH, 6 months), intermediate (30°C/65% RH, 12 months) and long-term conditions (25°C/60% RH, 24 months) were performed on three batches per strength in transparent blisters. Accelerated stability data show significant changes in related substances, with out of specification results for one impurity and individual unknown impurity. Intermediate conditions and available long-term stability data show that the results are well within the specifications.

Photostability studies show that the tablets are sensitive for light and only just meet the specifications if stored in (clear) blister packaging only and are not sensitive for light if stored in the secondary carton packaging.

The proposed shelf-life of two years and the proposed storage condition 'Do not store above 25°C. Keep the blister in the outer carton in order to protect from light' are acceptable for the drug product packed in opaque PVC/PVDC blister material.

For future commercial scale batches, the clear PVC/PVDC foil will be replaced by an opaque foil with comparable moisture protection, but improved protection to light transmission.

Stability studies will be carried out on three commercial scale batches of the product packed in the packaging material proposed for marketing.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Byblok has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Byblok is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Emcor (Deco), which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Bisoprolol fumarate is a well-known active substance with established efficacy and tolerability.

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.
IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Byblok 10 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Cardicor 10 mg, film-coated tablets (Merck Serono Ltd, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified. Cardicor is identical to the product Emcor Deco 10 mg (SE/H/0184/006/MR) previously authorised in the Netherlands. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The bioequivalence study has been performed with the 10 mg film-coated tablet. For the 5 mg strength a biowaiver has been granted, as the following criteria are met:

- The 5 mg and 10 mg film-coated tablet are manufactured by the same manufacturing process and manufacturing site.
- The qualitative composition of the strengths are same.
- The formulation of the strengths are dose proportional.
- The in-vitro dissolution profile is comparable between the strengths
- The pharmacokinetics of bisoprolol are linear and independent of age.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy adult male subjects. Each subject received a single dose (10 mg) of one of the 2 bisoprolol fumarate formulations. The tablet was orally administered after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 8, 12, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable, the sampling period was long enough, the sampling scheme adequate to estimate the pharmacokinetic parameters. The washout period of 7 days is considered sufficient to avoid carry over effects. Bisoprolol tablets can be taken with food. Therefore the study under fasted conditions is appropriate.

Analytical/statistical methods

The analytical method used is considered acceptable and appropriately validated (pre-study and within study). The bioequivalence study had a two stage design, with three sections. In section A the power was determined. The 90% confidence intervals for the ratio of test/reference for \( C_{\text{max}} \) and \( \text{AUC}_{0-t} \), should be within 0.80 to 1.25 to conclude the test product is bioequivalent to the reference product. If the power was to be greater than or equal to 80% in stage 1, Bioequivalence was to be evaluated using alpha level of 0.05 (at 90% confidence interval) and study was to be stopped, whether the Bioequivalence Criteria are met. If the power was less than 80% section B was applied. In section B Bioequivalence was to be evaluated using alpha level of 0.0294 (at 94.12% confidence interval) and if the Bioequivalence Criteria are met, then the study was to be stopped regardless of the power achieved. If the power was to be less than 80% and the Bioequivalence Criteria are not met in stage 1 section C was applied. In Section C Bioequivalence was to be evaluated at stage 2 using data from both the stages and alpha level of 0.0294 (at 94.12% confidence interval). The study was to be stopped here whether Bioequivalence Criteria were met or not and regardless of the power achieved.

Results

One subject did not report to the facility for period 2 and hence considered a drop-out. The remaining 27 subjects completed the clinical phase of the study and were included in the final pharmacokinetic and statistical analysis.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of bisoprolol under fasted conditions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) ng/ml</th>
<th>( \text{AUC}_{0-\infty} ) ng/ml</th>
<th>( C_{\text{max}} ) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>733.39 ± 261.58</td>
<td>760.93 ± 267.35</td>
<td>49.96 ± 16.30</td>
<td>3.33</td>
</tr>
<tr>
<td>Reference</td>
<td>730.17 ± 242.53</td>
<td>761.12 ± 254.18</td>
<td>47.85 ± 15.57</td>
<td>3.00 (1.00 – 5.50)</td>
</tr>
</tbody>
</table>

\( ^* \) Ratio (90% CI)

<table>
<thead>
<tr>
<th>CV (%)</th>
<th>Power (%)</th>
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</thead>
<tbody>
<tr>
<td>9.19</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

\( ^* \) ln-transformed values

Conclusion on bioequivalence studies

The study medication was well tolerated when administered under fasting condition and no significant safety issues emerged.

As the power for \( C_{\text{max}} \) and \( \text{AUC}_{0-t} \) was >99.9%, which was greater than 80% in stage 1, the applicant did not perform a stage 2. The 90% confidence intervals for \( C_{\text{max}} \) and \( \text{AUC}_{0-t} \) lie within the bioequivalence range 80% to 125%.

However, the statistical method used for the 2-stage design study and the bioequivalence evaluation is not in line with the recommended 2-stage design approach mentioned in the EMA bioequivalence guideline. By applying a two stage design and looking into the data, the overall alpha of 5% should be kept over both stages. Decision based upon power calculation and keeping the alpha at 5% at the first stage is considered not acceptable.

The MAH therefore provided the statistical outcome after applying a 94.12% confidence interval over the first stage for \( \text{AUC}_{0-t} \) and \( C_{\text{max}} \).

Table 2. Ratio, 94.12% Confidence intervals, intra-subject variability and power (n=27)

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Ratio of geometric means (%)</th>
<th>94.12% CI</th>
<th>Intra-subject %CV</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{AUC}_{0-t} )</td>
<td>99.39</td>
<td>94.60 to 104.43</td>
<td>9.19</td>
<td>&gt;99.9</td>
</tr>
<tr>
<td>( C_{\text{max}} )</td>
<td>104.68</td>
<td>99.81 to 109.79</td>
<td>8.85</td>
<td>&gt;99.9</td>
</tr>
</tbody>
</table>

The 94.12% confidence interval was within the bioequivalence range of 80-125% as well bioequivalence is sufficiently proven. Based on the submitted bioequivalence study Byblok 10 mg is considered bioequivalent with Cardicor 10 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).
IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Byblok.

- Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Cardiac failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Bronchospasm, airway obstruction</td>
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<tr>
<td></td>
<td>Hypoglycaemia</td>
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<tr>
<td></td>
<td>Anaphylactic shock</td>
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<td></td>
<td>Severe hypotension</td>
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<table>
<thead>
<tr>
<th>Important potential risks</th>
<th>None</th>
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<tbody>
<tr>
<td>Missing information</td>
<td>Exposure during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Use in the paediatric population</td>
</tr>
</tbody>
</table>

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Emcor/Emcor Deco. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 testing process involved: one pilot test and two main tests on ten participants each. Sixteen questions about the most critical parts of the package leaflet and three general questions about the PL were used. The package leaflet has been adapted after the pilot phase but no adaptations have not been made between two tests and after the last test. There were sufficient questions about the critical sections. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Taking into account the results for each question more than 90% of the participants finds the section and answered the question correctly. 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

Byblok 5 mg and 10 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Emcor and Emcor Deco. These are well-known medicinal products with an established favourable efficacy and safety profile

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.
There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Byblok with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 September 2016.
**STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY**

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ Non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
</table>
