PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Bisoprololfumaraat 5 mg, film-coated tablets
Bisoprololfumaraat 10 mg, film-coated tablets
Synthon B.V., the Netherlands
bisoprolol hemifumarate

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states. It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation. This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/853/01-02/MR
Registration number in the Netherlands: RVG 33729, 33730

15 August 2008

Pharmacotherapeutic group: Beta blocking agents, selective
ATC code: C07AB07
Route of administration: oral
Therapeutic indication: Hypertension; chronic stable angina pectoris.
Prescription status: prescription only
Date of authorisation in NL: 14 April 2006
Concerned Member States: Mutual Recognition Procedure with IT
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I  INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Bisoprololfumarat 5 mg, film-coated tablets and Bisoprololfumarat 10 mg, film-coated tablets from Synthon B.V., the Netherlands. The date of authorisation was on 14 April 2006 in the Netherlands. The product is indicated for hypertension and chronic stable angina pectoris.

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

Bisoprolol is a potent, highly β₁-selective-adrenoceptor blocking agent devoid of intrinsic sympathomimetic activity. As with other β-blocking agents, the mode of action in hypertension is unclear. However, it is known that bisoprolol markedly depresses plasma renin activity. In patients with angina, the blockade of β-receptors reduces heart action and thus reduces oxygen demand. Bisoprolol possesses similar local anaesthetic properties to propanolol.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Emcor 5 and Emcor 10 film-coated tablets (NL License RVG 12408 and 12409), containing 5 mg and 10 mg bisoprolol hemifumarate respectively, which have been registered in the Netherlands by Merck AG since 1987. In addition, reference is made to Emcor authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Detensiel®, registered in France. Detensiel is the trade name for the innovator product in France, which is identical with the innovator product on the Dutch market. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

II  SCIENTIFIC OVERVIEW AND DISCUSSION

II.1  Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients
The active substance is bisoprolol hemifumarate, an established active substance. Bisoprolol hemifumarate is not described in the Ph.Eur., USP or any other pharmacopoeia. Ph.Eur. and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU or USA, respectively. The active substance specification is considered adequate to control the quality and refers to general monographs on pharmaceutical
substances of the Ph.Eur. The active substance specification includes tests for appearance, identification, solubility, pH value, clarity and colour of solution, loss on drying, assay, microbial contamination, particle size distribution, heavy metals and impurities (HPLC/GC). Batch analytical data demonstrating compliance with this specification have been provided for 3 batches. The MAH committed to provide analytical data demonstrating that dimethylformamide is adequately limited in final batches of the active substance.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Stability data on the active substance have been provided for 6 batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 48 months. Based on the data submitted, a retest period could be granted of 4 years when stored in double polyethylene bags in fibre drum and not stored above 25°C.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs except for colorants iron oxide red and iron oxide yellow for which reference is made to the USP/NF.

**Medicinal Product**

**Composition**

Bisoprolol fumarate 5 mg, film-coated tablets contain as active substance 5 mg bisoprolol hemifumarate, corresponding to 4.24 mg of bisoprolol and are light pink, round, biconvex tablets, scored on both sides and embossed with “BSL5” on one side.

Bisoprolol fumarate 10 mg, film-coated tablets contain as active substance 10 mg bisoprolol hemifumarate, corresponding to 8.49 mg of bisoprolol and are yellow to orange, round, biconvex tablets, scored on both sides and embossed with “BSL10” on one side.

The tablets are packed in PVC/PE/PVDC/Al blister, PVC/PE/PVDC/Al blister in Al sachets or HDPE containers.

The excipients are:

**Core:** microcrystalline cellulose, calcium hydrogen phosphate, pregelatinised maize starch, crospovidone, colloidal anhydrous silica, magnesium stearate

**Coating:** hypromellose, macrogol 400, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172)

**Pharmaceutical development**

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be bioequivalent with the innovator product Emcor 5 and Emcor 10 mg film-coated tablets.

**Manufacturing process and quality control of the medicinal product**

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 1 batch of 5 mg and 2 batches of 10 mg in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for tablets in the Ph.Eur. and includes tests for appearance, diameter, thickness, identification, uniformity of mass of whole and subdivided scored tablets, hardness,
disintegration, dissolution, water content, assay, content uniformity, related substances and microbiological purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data for 6 production scaled batches and 3 pilot scale batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 8 batches of 5 mg and 9 batches of 10 mg in accordance with applicable European guidelines. Stability has been demonstrated of the product for 2 years when stored in PVC/PE/PVDC/AI blisters in AI sachet and for 1 year when stored in PVC/PE/PVDC/AI blisters without AI sachet or stored in HDPE tablet containers. The labelled storage conditions are: “Do not store above 25 °C. Store in the original package”, with an additional storage condition when stored in HDPE tablet containers: “Keep the container tightly closed”.

Specific measures concerning 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.

II.2 Non clinical aspects
This product is a generic formulation of Emcor, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of bisoprolol hemifumarate released into the environment. It does not contain any component, which results in additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects
Bisoprolol hemifumarate is a well known active substance with established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Emcor 5 ad 10 mg tablets marketed by Merck AG.

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Bisoprololfumaraat 10 mg tablet is compared with the pharmacokinetic profile of the French reference product Detensiel 10 mg tablet.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

A open, randomised, single-dose, 2-way cross-over, bioequivalence study was carried out under fasted conditions in 24 healthy subjects (13 males and 11 females), aged 18-35 years. For each subject there were 2 dosing periods of one of the 10 mg bisoprolol hemifumarate formulations, separated by a washout period of at least 7 days. The tablet was orally administered with 240 ml water after 10 hours of fasting. Blood samples were collected over a period of 60 hours (17 sampling points). All subjects were eligible for pharmacokinetic analysis.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax (median, range)) of bisoprolol hemifumarate under fasted conditions

<table>
<thead>
<tr>
<th>Treatment N=24</th>
<th>AUC0-t</th>
<th>AUC0-∞</th>
<th>Cmax</th>
<th>tmax</th>
<th>t1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>645 ± 120</td>
<td>669 ± 115</td>
<td>46.8 ± 6.6</td>
<td>2.0 (1.0-3.5)</td>
<td>14.2 ± 1.7</td>
</tr>
<tr>
<td>Reference</td>
<td>636 ± 100</td>
<td>661 ± 100</td>
<td>46.5 ± 4.9</td>
<td>1.75 (1.0-4.0)</td>
<td>9.2 ± 1.1</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>--</td>
<td>0.99 (0.95-1.03)</td>
<td>1.0 (0.96-1.04)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td>--</td>
<td>8.5%</td>
<td>9.0%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

AUC0-∞ area under the plasma concentration-time curve from time zero to infinity
AUC0-t area under the plasma concentration-time curve from time zero to t hours
Cmax maximum plasma concentration
tmax time for maximum concentration
t1/2 half-life

*B^ln-transformed values*

Bisoprolol hemifumarate should be taken once daily without reference to food intake. From the literature it is known that food does not interact with the absorption of bisoprolol hemifumarate. Therefore, no food interaction study is deemed necessary. The 90% confidence intervals calculated for AUC0-∞ and Cmax are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of bisoprolol hemifumarate under fasted conditions, it can be concluded that Bisoprololfumarataat 10 mg tablet and the reference product Detensiel 10 mg tablet are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The Bisoprololfumarataat 5 and 10 mg tablets are not completely dose proportional. Equal amounts of ingredients are used for both tablets except for the calcium hydrogen phosphate. This is allowed in case of a small concentration of active substance.

The pharmacokinetics of amlodipine is linear in the range 5-10 mg and both tablets have similar dissolution profiles. The results of the bioequivalence study performed with the 10 mg tablet therefore apply to the other tablet’s strength.

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).

**Risk Management Plan**

Bisoprolol was first approved in 1986, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of bisoprolol can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Readability test**

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 patient leaflet has been adapted sufficiently taking into account the results of the test.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Bioequivalence has been shown to be in compliance with the European guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. Bisoprololfumaraat 5 and 10 mg were authorised in the Netherlands on 14 April 2006. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Bisoprololfumaraat 5 and 10 mg with the reference product, and have therefore granted a marketing authorisation.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure.

The first PSUR will cover the period from December 2006 till August 2009. Hereafter, the PSUR submission cycle is 3 years.

The date for the first renewal will be: 6 December 2011

The following post-approval commitments have been made during the procedure:

**Quality - Active substance**
- The MAH committed to provide analytical data demonstrating that dimethylformamide is adequately limited in final batches of the active substance.
List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
</tr>
<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
</tr>
<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
</tr>
<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
</tr>
<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
</tr>
</tbody>
</table>
**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 procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for batch release. Not including batch control/testing.</td>
<td>NLH/0853/001-002/IA/001</td>
<td>IA</td>
<td>11-12-2007</td>
<td>25-12-2007</td>
<td>Approval</td>
<td>N</td>
</tr>
</tbody>
</table>