CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Bisoprololfumaraat 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg, and 10 mg film-coated tablets Hexal AG, Germany

bisoprolol fumarate

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/673/001-006/MR
Registration number in the Netherlands: RVG 33088-93

8 July 2009

Pharmacotherapeutic group:	selective ß$_1$-blocking agents
ATC code:	C07AB07
Route of administration:	oral
Therapeutic indication:	hypertension, angina pectoris, stable chronic moderate to severe heart failure with reduced systolic ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.
Prescription status:	prescription only
Date of first authorisation in NL:	9 March 2006
Concerned Member States:	Mutual recognition procedure with AT, CZ, DE, ES, HU, PT (1.25, 2.5, 5, and 10 mg). AT, DE (3.75 and 7.5 mg)
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 Bisoprololfumaraat 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg, and 10 mg film-coated tablets, from Hexal AG. The date of authorisation was on 9 March 2006 in the Netherlands.

The product is indicated for the treatment of hypertension, angina pectoris, and of stable chronic moderate to severe heart failure with reduced systolic ventricular function (ejection fraction ≤ 35 %, based on echocardiography) in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

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

Bisoprolol is a highly $beta_1$-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the $beta_2$-receptor of the smooth muscles of bronchi and vessels as well as to the $beta_2$-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and $beta_2$-mediated metabolic effects. Its $beta_1$-selectivity extends beyond the therapeutic dose range.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Emcor (NL license RVG 12408-9) which has been registered in the Netherlands by Merck since 1987. Emcor Deco (NL license RVG 24502-7) has been registered in the Netherlands since 1999. In addition, reference is made to Emcor and Concor 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 10 mg Concor, registered in Germany. 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, and no paediatric development programme has been submitted.

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 this product type 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
The active substance is bisoprolol fumarate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Bisoprolol fumarate is a white or almost white crystalline substance which is soluble in water and methanol. Bisoprolol is a racemic mixture with equal ratio of both isomers of bisoprolol fumarate: full scale batches show that bisoprolol fumarate exists as a single crystal modification; the drug substance is not a polymorph.

Manufacture
The route of synthesis is described in sufficient detail by the active substance manufacturers, and includes amongst information on the yields and reaction conditions. The active substance is manufactured in a multi-stage route of synthesis with purification steps.

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.

Specification
The drug substance specification has been established in-house by the applicant based on the Ph.Eur. monograph. Additional specifications for residual solvents and for particle size are laid down. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full scaled batches of each source.

Stability
Stability data on the active substance have been provided for 6 full scaled batches stored at 25°C/60%RH (varying from 18 to 48 months) and 3 full scaled batches, stored at 40°C/75%RH (6 months). The batches were stored in PE bags in fibre drum. A retest period of 4 years in the proposed packaging material has been granted.
From another active substance manufacturer, stability data on the active substance have been provided for 3 full scaled batches stored at 25°C/60%RH (36 months), 2 full scaled batches stored at 40°C/75%RH (6 months) and 1 full scaled batch, stored at 4°C (36 months). A retest period of 2 years in the proposed packaging materials has been granted.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
The product is formulated as a film-coated tablet. The product will be marketed in six different strengths 1.25 mg, 2.5 mg, 3.75 mg, 5.0 mg, 7.5 mg and 10 mg. The 5-7.5-10 mg strengths are dose proportional; for the 1.25-2.5-3.75-5 mg strengths, all with the same total weight per tablet, the differences between the ratio of the core excipients are considered as not essential for the drug release behaviour, taking also into account the small amount of active substance. According to the SPC the maximum dose of the product is 20 mg/day.

The drug product is packaged into blister packs (bottom: OPA/Alu/PVC/Alu, cover: Print primer/Al/Heatseal lacquer. The packaging is usual for this type of dosage form.

The excipients are: calcium hydrogen phosphate (E341b), croscarmellose sodium, microcrystalline, cellulose (E460), hydroxypropyl methylcellulose (E464), lactose monohydrate, macrogol 4000, magnesium stearate (E470b), maize starch, silicon dioxide (E551) (All strengths).
Colouring agent titanium dioxide (E171) (only 1.25 and 2.5 mg strengths)
Colouring agents ferric oxide (E172) and titanium oxide (E171) (only 3.75, 5, 7.5, and 10 mg strengths)

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The composition of the product is qualitatively similar to the composition of the innovator reference product. The tablets are considered bioequivalent with the innovator product based upon the closely similar composition and the results of the dissolution study. Breakability of the scored tablets is evaluated and in conformity with Ph.Eur. requirements.

The excipients comply with Ph.Eur. requirements. For the Opadry White mixture also general specifications have been laid down. The specifications for the excipients are acceptable.

In-vitro studies
The applied dissolution method and the specification is acceptable. The dissolution of the 10.0 mg biobatch and the shown dissolution results of the 1.25 mg, 2.5 mg, 3.75 mg, 5 mg and 7.5 mg batch are well comparable. As it has been shown that the biobatch and the German reference product are considered being bioequivalent, it can be assumed that also all other strengths of the bisoprololfumarate tablets are bioequivalent.
In view of the mutual recognition procedure comparing dissolution studies have been performed between the proposed product and the corresponding strength of originator products from NL, DE and involved CMSs. Among the tested originator products are, besides those from NL and DE(/LU), products from AT, BE, DK, FI, HU, IE, IT, LV/LT, NO, PL, PT, DE and UK; not all strengths are marketed in all these countries.

Manufacturing process
The manufacturing comprises a well-known process of mixing-steps, sieving, compression of the cores, and film-coating. The various steps of the manufacturing process, the process parameters, and the in-process controls have been sufficiently described. Batch results from the manufacturing sites and manufactured with drug substance from all sources are available at pilot-scale and full scale. The 1.25 mg strength possesses an active content of 1.4%, therefore for this strength a process validation has been performed according to the Note for Guidance on Process validation. The content uniformity results comply with the Ph. Eur. requirements of method 2.9.6 on content uniformity. The 1.25 mg strength is considered as the most critical strength.

The MAH committed to perform prospective validation studies on the first three production-scale batches of each strength, results should be available for the Inspectorate. A generalised validation protocol for all dosages is presented.

Product specification
The product specification includes tests appearance, uniformity of dosage units, dissolution, hardness, identity, assay, degradation, and microbiological purity. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production sites have been provided on 2full scaled batches of each strength and each production site, demonstrating compliance with the release specification.

Breakability
The 2.5-3.75-5.0-7.5-10.0 mg tablets are scored; the 2.5 mg tablets possess a single score, the 3.75-7.5 mg tablets a triple score and the 5.0-10.0 mg tablet possess a double score (crossed score). Breakability data has been submitted according to Ph. Eur. 2.9.5 “Uniformity of mass of single-dose preparations”, being the regulatory requirement in force at the time of the submission of the original dossier. The scored tablets are easily breakable by hand. The instruction has been included in the SmPC section 6.6.

Stability tests on the finished product
The claimed shelf life is 24 months for the 1.25-mg strength and 36 months for the 2.5-3.75-5-7.5-10 mg strengths, all without a specific storage condition. Four batches of the 1.25 mg, 5 mg, 7.5 mg and 10 mg film-coated tablets and five batches each of the 2.5 mg and 3.75 mg film-coated tablets are stored under controlled conditions (25°C/60% R.H.). This stability tests are still ongoing. Additionally four batches of 1.25 mg, 5 mg, 7.5 mg and 10 mg and five batches each of the 2.5 mg and of the 3.75 mg film-coated tablets were stored under accelerated conditions (40°C/75% R.H) for 6 months.
With respect to the data obtained it is justified to grant a shelf life of 24 months for the 1.25 mg film-coated tablets and a shelf life of 36 months for the 2.5-3.75-5-7.5-10 mg film-coated tablets. No special storage conditions are required.

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 fumarate released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

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

The choice of the reference product
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 (see also II.1 Quality aspects).

The company explained that at the time of bioequivalence testing (September 1995) the version of 1991 of the NfG on the investigation of bioavailability and bioequivalence was in force. In this guideline a minimum batch-size for the biobatches was not defined. The company provided a comparing dissolution

profile of the biobatch and production scale batch, and similarity was demonstrated considering that both profiles show dissolution results > 85% after 15 min. This is in accordance with the current NfG. The provided reasoning can be accepted.

Bioequivalence study

A single-blind, three treatment, three period, single dose, crossover comparative bioequivalence study was carried out under fasted conditions in 26 healthy male volunteers, aged 18 to 44 years. Of these subjects 2 were stand-byes. Each subject received a single dose (10 mg) of one of the 2 bisoprolol formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Except for water given with the study medication, no fluids were allowed from 1 hour before dosing until 2 hours post dose. There were 3 dosing periods, separated by a washout period of 7 days.
Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 7, 10, 14, 24, 36 and 48 hours after administration of the products. According to the protocol, 24 subjects were eligible for pharmacokinetic analysis.

In this bioequivalence study a product outside the EU was included as a third arm.

The analytical method is adequate validated and considered acceptable for analysis of the plasma samples. The long term stability data are covering the storage period of the plasma samples.

Statistical analysis was performed using the log-transformed pharmacokinetic parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$), They were analysed using a ANOVA model including sequence, period and formulation effects. The 90% confidence intervals for the difference between the drug formulations were calculated for the different parameters. According to protocol, bioequivalence will be concluded when these 90% confidence intervals for bisoprolol fumarate are within 80-125% for AUC_{0-t} and $AUC_{0-\infty}$ and within 70-143% for C_{max}. instead of 80-125%. However, the widening of the 90% confidence interval of C_{max} as proposed by the applicant, was not accepted since bisoprolol fumarate is not considered to be a highly variable drug.

Bisoprolol may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of bisoprolol. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of bisoprolol under fasted conditions.

Treatment N=24	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	558 ± 100	580 ± 102	38 ± 5	2.67 (1.67 – 4.00)	8.5 ± 1.0
Reference	538 ± 100	564 ± 100	38 ± 5	2.67 (1.33 – 5.00)	8.5 ± 1.2
***Ratio (90% CI)**	1.04 (100.7 – 108.4)	1.03 (0.99 – 1.06)	1.02 (0.98 – 1.04)	---	---
CV (%)	26.9	25.7	18.9	---	---

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of bisoprolol under fasted conditions, it can be concluded that Bisoprololfumaraat 10 mg and Concor 10 mg are bioequivalent with

respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The results of this study can be extrapolated to the other strengths, since:

- The different strengths are manufacturered by the same manufacturer and manufacturing process
- Pharmacokinetics for bisoprolol are linear
- Qualitative compositions of the different strengths are the same with the exception of the colorants.
- The ratio between amounts of active substance and excipients is the same for the 5 mg, 7.5 mg and 10 mg strength (dose proportinional). Although the 1.25 mg, 2.5 mg and 3,75 mg tablets are not dose-propotional the differences in the composition are small. Therefore no effect with regard to the bioavailability of bisoprolol fumarate is expected.
- The dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

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.

Product information

Readability test

A readability test was performed. There were two rounds of each ten participants. There were 12 questions about the package leaflet. Furthermore, the participants were asked to rate the leaflet on 5 items (information easy to find, information easy to understand, instructions easy to follow, layout is logical, text large enough). An open question about the positive/negative points of the leaflet was asked. The questions cover all parts of the leaflet including the safety issues. The test criteria was that 81% of the participants must be able to answer correctly, i.e. must be able to find the information and act upon it.
Taking into account the outcome of first test round the package leaflet has been adapted before the second test round. Addional questions from the RMS and CMS's were resolved.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bisoprololfumaraat 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg, and 10 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of the innovator product Emcor. Emcor is a well-known medicinal product with an established favourable efficacy and safety profile.

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

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 and are in agreement with other bisoprolol containing products.

The Board followed the advice of the assessors. Bisoprololfumaraat was authorised in the Netherlands on 9 March 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bisoprololfumaraat with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 2 October 2008.

The first PSUR will cover the period from 1 October 2004 to 30 September 2004. The second PSUR will cover the period from 1 October 2007 to 30 September 2010. Thereafter, the PSUR submission cycle is 3 years.

The date for the first renewal will be 30 may 2011, taking into account the European Data Lock Point (DLP) of bisoprololfumarate, which is September 2010.

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

Quality - active substance
- The MAH has committed to validate the first production scale batches with the new batch sizes and to submit the resulting report.

Quality - medicinal product
- The MAH has committed to validate the first three consecutive production scale batches of the 1.25 mg strength when available.
- Where not available yet, the MAH has committed to put batches of commercial size on stability and generate dissolution profiles. Dissolution profiles will be submitted after production of commercial size batches, stability results will be submitted before renewal of the product.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached