CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Bisoprololfumaraat Accord 2.5 mg, 5 mg and 10 mg film-coated tablets
Accord Healthcare B.V., the Netherlands

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/2224/001-003/DC
Registration number in the Netherlands: RVG 108798-108800

16 March 2012

Pharmacotherapeutic group:	beta blocking agents, selective
ATC code:	C07AB07
Route of administration:	oral
Therapeutic indication:	hypertension; stable chronic angina; stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides
Prescription status:	prescription only
Date of authorisation in NL:	22 December 2011
Concerned Member States:	Decentralised procedure with AT, BE, DE, FR, IT, PL, PT and UK
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 Accord 2.5 mg, 5 mg and 10 mg film-coated tablets, from Accord healthcare B.V. The date of authorisation was on 22 December 2011 in the Netherlands.

The product is indicated for:

- treatment of hypertension
- treatment of stable chronic angina
- 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 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 decentralised procedure concerns a generic application claiming essential similarity with the innovator product Cardicor 2.5 mg marketed in the UK by Merck (authorised in the UK on 4 June 1999), Emconcor Mitis 5 marketed in BE by Merck N.V. (authorised in BE on 27 September 1991) and Emconcor 10 marketed in BE by Merck N.V. (authorised in BE on 7 July 1987). In the Netherlands, Emcor Deco 2.5 mg, 5 mg and 10 mg tablets (NL license RVG 24503, 24505, and 24507 respectively) have been registered by Merck B.V. since 1 November 1999 through the MRP (SE/H/0184-0187/002;004;006/MR. In addition, reference is made to Emcor Deco 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 Cardicor 10 mg tablets, registered in the UK. 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, as this is not required for generic medicinal 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 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 powder. The drug substance is available as a racemic mixture. The Ph.Eur. specifies that polymorphism exists for the drug substance. However, the MAH stated that nothing can be found in literature on this subject. In addition, the drug substance manufacturer does not specify any reference for existence of polymorphism of bisoprolol fumarate either. This statement is accepted. Bisoprolol fumarate exhibits poor flow properties and is hygroscopic in nature. The drug substance is very soluble in water and methanol, freely soluble in chloroform, glacial acetic acid and alcohol, and slightly soluble in acetone and ethyl acetate.

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

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 new 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities in Europe.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur., with additional requirements for identification, residual solvents and fumaric acid content. 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 two pilot scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for three pilot scaled batches stored at 25°C/60%RH (60 months) and 40°C/75%RH (6 months). Additionally, three full scaled batches were stored at 25°C/60%RH (48 months) and 40°C/75%RH (6 months). No up or downward trends were observed during the stability tests. The claimed re-test period of 5 years when stored in the original container is acceptable.

Medicinal Product

Composition
The drug product concerns bisoprolol fumarate 2.5 mg, 5 mg, and 10 mg tablets which are white to off white, round, biconvex, film-coated tablets with a break line on one side and on the other side a debossing of b1, b2 or b3 (respectively). The tablets can be divided into equal halves. The three different tablet strengths are fully dose proportional and can be distinguished by means of their embossing and size.
The excipients used are cellulose microcrystalline, sodium starch glycolate (type-A), povidone K-30, silica colloidal anhydrous and magnesium stearate (E572). The film-coating consists of hypromellose E-15 (E464), macrogol 400 (E553), titanium dioxide (E171) and talc.

The tablets are packed in PVC/PVDC-Alu blisters or Alu-Alu blisters. The secondary packaging material is a carton pack. The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The contents of the three tablet formulations, 2.5 mg, 5 mg and 10 mg, are dose proportional. Optimisation of the physico-chemical properties of the tablets was reached by a series of experimental trials during which excipients and/or processes were varied. Subdivision testing of the tablets has been satisfactorily performed in line with Ph.Eur.
Dissolution profiling has been performed in media with pH 1.2, 4.5 and 6.8. Profiles for all strength tablets were comparable and more than 85% was dissolved within 15 minutes. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of sifting, blending, and direct compression. Subsequently the tablets are film-coated and packed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scale batches for each strength.

Excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, average weight of tablets, identification (UV, HPLC, titanium dioxide), loss on drying, dissolution, related substances, uniformity of dosage units, assay, microbial examination, and subdivision of tablets. Release and shelf-life limits are equal for majority of the parameters, with exception of limits for loss on drying, and related substances. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on two pilot scaled batches, demonstrating compliance with the release specification. For every tablet strength, the MAH committed to validate all process parameters of three batches of two different batch sizes.

Stability of drug product
Stability data on the product have been provided for two pilot scaled batches for each strength. Stability was tested for three packaging materials.
The Alu-Alu blister was tested for storage at 25°C/60%RH (18 months) and 40°C/75%RH (6 months), showing upward trends for one specified impurity and unidentified/unspecified impurities. All batches however stayed within limits. Based on a calculated worst case scenario, a maximum shelf-life of 18 month when stored below 30°C can be granted for storage in the Alu-Alu blisters.
The PVC/PVDC-Alu blister was tested for storage at 25°C/60%RH (18 months), 30°C/65%RH (12 months) and 40°C/75%RH (3 months). When stored under accelerated conditions the tablets ran out of specification. Storage at both long term and intermediate conditions demonstrated upward trends for one specified impurity and unidentified/unspecified impurities. However, all batches remain within limits. Based on a calculated worst case scenario, a maximum shelf-life of 18 months, when stored below 30°C can be granted for storage in the PVC/PVDC-Alu blisters.
Storage of the bulk at long-term conditions did not show any trends.
Forced degradation studies have been performed and showed that the methods used indicate stability and that the drug product is photo stable. The MAH committed to subject at least one batch from any of the approved batch size to stability trials per year of production.

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.

** USP and Ph.Eur. are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the United states and Europe respectively.*

II.2 Non clinical aspects

This product is a generic formulation of Cardicor/Emcor Deco (i.a.), 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 Accord 10 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Cardicor 10 mg tablets (Merck KGaA).

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 (if applicable) in different member states.

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

Study design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy non-smoking male subjects, aged 18-55 years, with a Body Mass Index (BMI) between 18.5-24.9 kg/m2. Each subject received a single dose (10 mg) of one of the 2 bisoprolol fumarate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 21 days.
In each study period, 25 blood samples, including one pre dose sample, were collected to analyse the pharmacokinetic profile of the test as well as the reference drug. Blood samples were collected at pre dose and at 0.5, 1, 1.333, 1.667, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours post-dose administration.
The analytical method is adequately validated and considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All subjects completed the study and therefore samples of 26 subjects were analysed.

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

Treatment N=26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	658.0 ± 115.0	671.1 ± 116.3	47.7 ± 7.0	2.5	8.9± 1.6
Reference	642.8 ± 96.0	655.9 ± 97.4	48.2 ± 7.8	2.4	8.8 ± 1.2
***Ratio (90% CI)**	1.02 (0.99-1.05)	1.02 (0.99-1.05)	0.99 (0.95 –1.02)	-	-

$AUC_{0-\infty}$ 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 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 fumarate under fasted conditions, it can be concluded that Bisoprololfumaraat Accord 10 mg film-coated tablets and Cardicor 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Extrapolation to different strengths
According to the CPMP guideline "Note for guidance on the investigation of bioavailability and bioequivalence" (CPMP/EWP/QWP/1401/98), a bioequivalence study investigating only one tablet strength may be acceptable if all of the following conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the composition of the different strengths is dose proportional
- the dissolution profiles for the additional strengths and the strength of the biobatch are similar under identical conditions

All these conditions apply for Bisoprololfumaraat Accord 2.5 mg, 5 mg and 10 mg film-coated tablets, manufactured by Accord Healthcare B.V. Therefore the results of the bioequivalence study with the 10 mg strength formulation can be extrapolated to the other strengths.

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.

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 post-authorisation 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

SPC
The content of the SPC approved during this decentralised procedure is in accordance with that accepted for the the innovator Emcor Deco/Cardicor marketed by Merck.

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 test consisted of two rounds with 10 participants each. Fourteen questions about the most critical parts of the package leaflet and general questions about the lay out of the package leaflet were asked. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.
After the first and the second test the MAH did not adapt the package leaflet, as there were no significant difficulties experienced with any of the questions.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bisoprololfumaraat Accord 2.5 mg, 5 mg and 10 mg film-coated tablets have a proven chemical-pharmaceutical quality and are a generic form of Emcor Deco/Cardicor 2.5 mg, 5 mg and 10 mg tablets. Emcor Deco 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Bisoprololfumaraat Accord 2.5 mg, 5 mg and 10 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 18 November 2012. Bisoprololfumaraat Accord 2.5 mg, 5 mg and 10 mg film-coated tablets were authorised in the Netherlands on 22 December 2011.

The date for the first renewal will be: 31 May 2014.

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

Quality - medicinal product

- The MAH committed to subject at least one batch from any of the approved batch sizes to stability trials per year of production.
- For every tablet strength, the MAH committed to validate all process parameters of three batches with two different batch sizes.

- **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
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