CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Bisoprololfumaraat Deco Aurobindo 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, film-coated tablets Aurobindo Pharma 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.
It reflects the scientific conclusion reached by the MEB 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.

Registration number in the Netherlands: RVG 106054 - 106059

5 March 2013

Pharmacotherapeutic group:	Beta blocking agents, selective
ATC code:	C07AB07
Route of administration:	oral
Therapeutic indication:	stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, diuretics, and optionally cardiac glycosides
Prescription status:	prescription only
Date of authorisation in NL:	28 June 2011
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 Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Bisoprololfumaraat Deco Aurobindo 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, film-coated tablets, from Aurobindo Pharma B.V. The date of authorisation was on 28 June 2011 in the Netherlands.

The product is indicated for the treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, 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 national procedure concerns a generic application claiming essential similarity with the innovator product Emcor Deco 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg tablets (NL License RVG 24502 - 24507) which were registered in the Netherlands by Merck in 1999. Emcor Deco film-coated tablets has been withdrawn from the Dutch market.

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 two bioequivalence studies in which the pharmacokinetic profile of the products is compared with the pharmacokinetic profile of the reference products Cardicor 1.25 mg and 10 mg tablets, registered in the United Kingdom. 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.*). The active substance is a white or almost white powder, which is very soluble in water and freely soluble in methanol. Bisoprolol possesses an asymmetric carbon and is a racemic mixture. According the Ph.Eur., bisoprolol fumarate is known to exhibit polymorphism. A test for polymorphism in the active substance specifications involving DSC has 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 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 specification is in line with the CEP. Additional requirements for particle size, density and microbiological quality are included. 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 scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 full scaled batches stored at 25°C/60%RH (24 months) and at 40°C/75%RH (6 months). A retest period of 3 years in the proposed packaging materials has been granted.
The MAH committed to complete the stability, to obtain a retest period fully supported by stability data. Additionally, at least one commercial scale batch (if manufactured) shall be added annually to the stability program and shall be tested at least once in year to confirm the re-test period through the proposed stability duration.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Bisoprololfumaraat Deco Aurobindo 1.25 mg are white, round, biconvex, film-coated tablets debossed ‘P’ on one side and ‘1’ on the other side.
Bisoprololfumaraat Deco Aurobindo 2.5 mg are white, round, biconvex, film-coated tablets debossed ‘P’ on one side and ‘2’ on the other side.
Bisoprololfumaraat Deco Aurobindo 3.75 mg are white, round, biconvex, film-coated tablets debossed ‘P’ on one side and ‘3’ on the other side.

Bisoprololfumaraat Deco Aurobindo 5 mg are white, round, biconvex, film-coated tablets debossed 'P' on one side and '5' on the other side.
Bisoprololfumaraat Deco Aurobindo 7.5 mg are white, round, biconvex, film-coated tablets debossed 'P' on one side and '7' on the other side.
Bisoprololfumaraat Deco Aurobindo 10 mg are white, round, biconvex, film-coated tablets debossed 'P' on one side and '10' on the other side.
The tablets - except for the 1.25 mg strength - can be divided into equal halves.
The tablets are packed in aluminium/aluminium blister packs or HDPE bottles. The packaging is usual for this type of dosage form.

The excipients are:
Tablets core: microcrystalline cellulose (E460), calcium hydrogen phosphate (E341), colloidal anhydrous silica (E551), crospovidone (E1202), magnesium stearate (E572).
Film-coating: opadry white mixture consisting of hypromellose 6cP (E464), titanium dioxide (E171), macrogol 400.

The used excipients are well known and safe in the proposed concentrations. For the strengths 1.25 mg and 2.5 mg the increasing content of the active has been evenly reduced from calcium hydrogen phosphate. The 2.5-3.75-5-7.5-10.0 strengths are fully dose-proportional.

Pharmaceutical development
The development of the product has been described adequately, the choice of excipients is justified and their functions explained. The tablets are considered bioequivalent on quality grounds with the innovator product based upon the closely similar composition and the results of the dissolution study. The Dutch and UK innovator products of Merck are registered by a MRP with Sweden as RMS and both NL and UK as CMS. Therefore, the composition of the innovator products of UK and NL can be accepted as identical. Use of the UK reference in the bioequivalence study is therefore justified.
Breakability of the scored tablets is evaluated and in conformity with Ph.Eur. requirements.

Manufacturing process
The manufacturing comprises a well-known process of premixing and mixing, 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 of two batches of each strength are available at pilot-scale. The dosage uniformity results comply with the Ph. Eur. requirements.
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.

Control of excipients
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.

Quality control of drug product
The product specification includes tests for appearance, uniformity of dosage units, subdivision of tablets, water content, dissolution, identity, assay, degradation, and microbiological purity. The analytical methods have been adequately described and validated. Batch analytical data have been provided on 2 pilot scaled batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Two batches of all tablet strengths were stored under controlled conditions (25°C/60% R.H. for 24 months). Additionally the batches were stored under intermediate conditions (30°C/65% R.H.) for 12 months and accelerated conditions (40°C/75% R.H.) for 6 months.
The claimed shelf life is 2 years for all strengths in both containers with the storage conditions 'Store below 25°C' and 'Store in the original package in order to protect from light'.

The drug product complied with the specification after 45days of in-use stability in HDPE container of 30's count and for up to18 months in HDPE container of 500's count at long term conditions.

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 Deco 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg tablets which is available on the European market. 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 Board agreed that no further non-clinical studies are required.

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.
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 Board agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Bisoprololfumaraat Deco Aurobindo 1.25 mg and 10 mg, film-coated tablets (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Cardicor 1.25 mg and 10 mg tablets (Merck Ltd. UK).

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. The studies submitted with the highest and lowest strength formulations are considered appropriate for this application.

Study I – 1.25 mg strength
Design
An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19 - 41 years with normal weight and BMI. Each subject received a single dose (2 tablets x 1.25 mg) of one of the 2 bisoprolol fumarate formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected prior to dosing and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after administration of the products.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods

The analytical method has been adequately validated and is 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 both treatments.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of bisoprolol fumarate 1.25 mg under fasted conditions.

Treatment N=28	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	148 ± 21.5	154 ± 23.8	9.90 ± 1.41	2.84	10.2 ± 1.2
Reference	158 ± 24.2	164 ± 27.0	10.6 ± 1.59	2.84	9.95 ± 1.4
***Ratio (90% CI)**	0.94 (0.91 – 0.97)	0.94 (0.91 – 0.97)	0.94 (0.89 – 0.98)	-	-
CV (%)	6.9	7.3	9.9	-	-

$AUC_{0-\infty}$ 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 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 Deco Aurobindo 1.25 mg, film-coated tablets and the Cardicor 1,25 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Study II – 10 mg strength
Design
An open label, randomized, two-treatment, two-sequence, two-period, crossover, single-dose comparative oral bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 20 - 34 years with normal weight and BMI. 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 two dosing periods, separated by a washout period of 12 days.

Blood samples were collected prior to dosing and at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.33, 3.67, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after administration of the products.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods
The analytical method has been adequately validated and is 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
. One subject did not check in for the second period and was therefore withdrawn from the study. 27 subjects completed both treatments.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of bisoprolol fumarate 10 mg under fasted conditions.

Treatment N=27	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	612 ± 113	633 ± 122	40.8 ± 5.88	3.00	9.3 ± 1.2
Reference	609 ± 102	631 ± 110	39.5 ± 5.0	3.00	9.5 ± 1.2
***Ratio (90% CI)**	1.00 (0.97 – 1.03)	1.00 (0.97 – 1.03)	1.03 (0.99 – 1.07)	-	-
CV (%)	6.2	6.3	9.1	-	-

$AUC_{0-\infty}$ 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 Deco Aurobindo 10 mg, film-coated tablets and the Cardicor 10 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bisoprolol fumarate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of bisoprololfumarate. 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.

Biowaiver
The results of this study can be extrapolated to the other strengths of 2.5 mg, 3.75 mg, 5mg and 7.5 mg since:

- the pharmaceutical products are manufactured by the same manufacturer and process
- the pharmacokinetics has been shown to be linear over the therapeutic range
- the qualitative composition of the different strengths is the same
- the ratio between amounts of active substance and excipients is the same
- the dissolution profile is similar under identical conditions for the additional strengths and the strength of the biobatch.

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 fumarate 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 fumarate 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 the national procedure is in accordance with that accepted for the reference product Emcor Deco 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg tablets marketed by Merck.

Readability test
The MAH submitted a bridging report in which the PIL of Bisoprololfumaraat Deco Aurobindo 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, film-coated tablets (Daughter PIL) was bridged with the already user tested PIL of Ramipril Aurobindo (Parent PIL).
Both Parent and Daughter PIL have the same layout and design (same in-house style), same fontsize, paper size and text colour. In both Parent PIL and Daughter PIL the headings are presented as white letters with black back ground which enhances the findability of the PIL. The critical safety sections (contraindications and warnings) in both PILs are laid out in bullet points. The paper weight of both Parent and Daughter PIL is the same, both have been prepared according to the current QRD template. The PIL text is in line with the PIL text for the originator product Emcor. Therefore, separate user testing for the leaflet of Bisoprololfumaraat Deco Aurobindo is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Bisoprololfumaraat Deco Aurobindo 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 Emcor Deco 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg tablets. 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 is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other bisoprolol fumarate containing products.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated with the reference product, and has therefore granted a marketing authorisation. Bisoprololfumaraat Deco Aurobindo 1.25 mg, 2.5 mg, 3.75 mg, 5 mg, 7.5 mg and 10 mg, film-coated tablets were authorised in the Netherlands on 28 June 2011.

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

- The MAH committed to perform prospective validation studies on the first three production-scale batches of each strength.

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
Change in the name of the medicinal product due to the transfer of MAH.	-	IB	01-08-2011	02-09-2011	Approval	N
Change in bossing details on the tablets	-	IA	17-10-2011	07-12-2011	Approval	N
Submission of an updated certificate from an already approved manufacturer	-	IA	05-03-2012	14-03-2012	Approval	N