Public Assessment Report

Scientific discussion

Carvedilol Aurobindo 6.25 mg and 25 mg, film-coated tablets (carvedilol)

NL/H/2609/001-002/MR

Date: 26 May 2014

This module reflects the scientific discussion for the approval of Carvedilol Aurobindo. The procedure was finalised on 6 August 2012. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Carvedilol Aurobindo 6.25 mg and 25 mg, film-coated tablets from Aurobindo Pharma B.V.

The product is indicated for:

- Essential hypertension.
- Chronic stable angina pectoris
- Adjunctive treatment in moderate to severe stable heart failure.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Eucardic 6.25 mg and 25 mg film-coated tablets (NL License RVG 19808 and 14491), which have been registered since 1991 (25 mg) and 1997 (6.25 mg) by Roche Nederland B.V.

The concerned member state (CMS) involved in this procedure was Italy.

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

II. QUALITY ASPECTS

II.1 Introduction

Carvedilol Aurobindo 6.25 mg is a white to off-white, oval film-coated tablet engraved with "F57" on one side and scored on the other side. The tablet can be divided into equal doses.
Carvedilol Aurobindo 25 mg is a white to off-white, oval, film-coated tablet engraved with "F59" on one side and scored on the other side. The tablet can be divided into equal doses.

The tablets are packed in PVC/PE/PVDC–Aluminum blisters and HDPE bottles.

The excipients are:
Tablet core - lactose monohydrate, silica colloidal anhydrous, crospovidone, povidone 30,sucrose, magnesium stearate.
Tablet coating - macrogol 400, polysorbate 80, titanium dioxide (E 171), hypromellose.

The tablets are dose-weight proportional in terms of all excipients.

II.2 Drug Substance

The active substance is carvedilol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white, crystalline powder, which is practically insoluble in water, slightly soluble in alcohol and practically insoluble in dilute acids. The molecule shows polymorphism. Form II is manufactured.

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.
A brief narrative of the manufacturing process was included together with a reaction scheme which identifies all reagents used during the process.

Quality control of drug substance
The control tests and specifications for drug substance product are adequately drawn up being based on the current monograph of the Ph.Eur. with additional tests for particle size. Certificates of analysis from for 3 batches of drug substance have been provided. All batches comply with the specification.

Stability of drug substance
Stability studies have been performed with the drug substance under long-term (30 ± 2°C//65 ± 5%) and accelerated (40 ± 2°C//75 ± 5% RH) . No significant changes in any parameters were observed. The proposed retest period of 2 years is justified.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. Satisfactory breakability data are provided. *In vitro* dissolution profiles of the test and innovator products used in the bioequivalence study are comparable under two different dissolution conditions. The pharmaceutical conditions for a bio-waiver for the lower strength have been satisfactorily fulfilled. The profiles of the different strengths are similar.

Manufacturing process
Manufacture of the product uses a wet granulation process. The method is adequately described, includes appropriate in-process controls and is supported by satisfactory process validation at pilot scale. Further process validation will be performed.

Control of excipients
All excipients are controlled according to the relevant Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specifications cover appropriate parameters, and include test for identification, average weight, water, dissolution, uniformity of dosage units, related substances, assay, thickness, identification of titanium dioxide and microbial contamination. Validations of the analytical methods have been presented. Batch analysis has been performed on 2 batches of each tablet strength. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product
Stability data on the drug product have been provided during storage at 25°C/60% RH (24 months), 30°C/75% RH (up to 12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The tablets were packed in PVC/PE/PVDC-Al blisters and HDPE containers (30's count and1000's count). The control tests and specifications for drug product are adequately drawn up. The drug product was demonstrated to be photostable.
The proposed shelf-life of 2 years is acceptable for both packages based on the stability data presented, with the storage precautions 'Store below 25 °C'.

An in-use stability was performed for 24 months at 25°C/60% RH for all strengths packed in 1000's count HDPE containers. During the study sample withdrawal was simulated. All parameters remain within the specified limits.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Appropriate TSE statements have been provided to confirm that lactose is in accordance with EMEA/410/01 Rev. 2.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Carvedilol Aurobindo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

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

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Eucardic 6.25 mg and 25 mg film-coated tablets, which are available on the European market. Reference is made tot the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Carvedilol is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Carvedilol Aurobindo 25 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Eucardic 25 mg film-coated tablets (Roche Products Ltd, UK).

The choice of the reference product in the bioequivalence study has been justified by comparison of compositions of reference products in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A bio-waiver has been granted for Carvedilol Auborindo 6.25 mg tablets as per the following considerations of the *CPMP Note for Guidance on Investigation of Bioavailability and Bioequivalence*:

- Carvedilol Aurobindo 6.25 mg & 25 mg tablets are manufactured by the same manufacturer and using the same manufacturing process.
- The pharmacokinetics of carvedilol is linear. Plasma concentrations achieved are proportional to the oral dose administered.
- The qualitative composition of the 6.25 mg tablets is the same as that of the 25 mg tablets.
- Carvedilol Aurobindo 6.25 mg is dose proportional (*i.e* step-down formula) with the 25 mg tablets. Thus, the ratio of amount of active substance and the excipients is the same for both the strengths.
- The dissolution profiles of the 6.25 mg are similar to the 25 mg tablets.

Bioequivalence study
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 42 healthy male subjects, aged 18-40 years. After a supervised overnight fast of approximately 10 hours, subjects were given a high-calorie, high fat, standardized, pre dose meal of 985.0 Kcal. (60% fat of total calories). Subjects received a single oral

dose of the assigned formulation 30 minutes after the pre-dose high-fat breakfast according to the randomization schedule. There were 2 dosing periods, separated by a washout period of 12 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours after administration of the products.

The study design, considering the pharmacokinetic characteristics of carvedilol, is acceptable. Although the rate of absorption is decreased slightly when carvedilol was taken with food (t_{max} increased from 0.97 to 1.3 h), the extent of absorption is unaffected, as shown by unchanged AUC and C_{max} values. The delay in absorption of carvedilol when administered with food and the lower serum concentrations attained may help control side effects. Moreover, in the SmPC the recommendation is included that heart failure patients take their carvedilol medication with food to allow the absorption to be slower and the risk of orthostatic hypotension to be reduced.

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 was withdrawn due to vomiting after dosing in period-I and 5 subjects were dropped out in the second period as they did not show up. Thirty-six subjects completed the study and were included in the pharmacokinetic analysis.

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

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	374 ± 191	382 ± 192	78.2 ± 37.1	1.75 (0.5-5.0)	6.65± 1.9
Reference	413 ± 252	423 ± 255	87.9 ± 45.4	2.13 (0.5-5.0)	6.63 ± 2.8
***Ratio (90% CI)**	0.93 (0.88 -0.99)	0.93 (0.87 -0.98)	0.90 (0.83 – 0.98)	--	--
CV (%)	14.9	14.7	21.2	--	--

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 4-hydroxyphenyl-carvedilol under fed conditions

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	53.18 (18.006)	56.94 (17.926)	13.60 (5.639)	1.75 (0.5-5.0)	8.87 (3.3)
Reference	56.47 (17.666)	60.54 (18.153)	14.20 (5.194)	1.75 (0.5-5.0)	9.16 (3.4)
***Ratio (90% CI)**	0.94 (0.88-1.01)	0.94 (0.88-1.01)	0.94 (0.86-1.03)	--	--
CV (%)	18.03	17.14	22.12	--	--

$AUC_{0-\infty}$	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*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} of carvedilol and its metabolite 4-hydroxyphenyl-carvedilol are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Carvedilol Aurobindo 25 mg is considered bioequivalent with Eucardic 25 mg film-coated tablets.

Ten adverse events were reported during the entire duration of the study, out of which one adverse event was reported during the study and nine adverse events as post study lab abnormalities; out of nine, seven adverse events were resolved and two still under follow-up.

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

IV.3 Risk Management Plan

The MAH submitted a statement on the absence of a Risk Management Plan, and indicated that the application concerns a generic product, for which the active ingredient has a well-established safety profile and has been in use for many years. As the safety profile of the drug is well-established, a Risk Minimisation Plan was required at the time of this application.

IV.4 Discussion on the clinical aspects

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

V. USER CONSULTATION

The MAH has not conducted a user consultation on the package leaflet (PL) with target patient groups
For the readability test the MAH refers to user test results of the PL of Carvedilol Aurobindo (UK/H/1170/001-004/DC).

An adequate justification was provided for referring to the User Testing Report. The MAH clearly explained the reason why the results of this test are also justified for the PL of Carvedilol Aurobindo. The bridging report also critically appraises the similarities/differences between both PLs and addresses the relevance of test results with the PL used in the user test by including a document which indicates the exact differences between the tested PL and the submitted PL. In conclusion, bridging is justified, and no separate user testing is required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Carvedilol Aurobindo 6.25 mg and 25 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Eucardic 6.25 mg and 25 mg film-coated. Eucardic 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 Board followed the advice of the assessors and granted a marketing authorization on 25 November 2010.

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 Carvedilol Aurobindo 6.25 mg and 25 mg with the reference product. The mutual recognition procedure was finalised with a positive outcome on 6 August 2012.

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
Submission of an updated/renewed Ph.Eur certificate of suitability for carvedilol drug substance. Minor change in the test procedure of related substances method in Carvedilol tablets.	NL/H/2609/ 001-002/IA/ 001/G	IA/G	4-4-2013	6-5-2013	Approval	N
Introduction of the Pharmacovigi-ance System Master File (PSMF)	NL/H/2609/ 001-002/IA/ 002/G	IA/G	26-6-2013	26-7-2013	Approval	N
Update Summary of Product Characteristics and Package Leaflet for Carvedilol Aurobindo 6.25 mg & 25 mg film-coated tablets with reference to the Core safety profile following the recent PSUR work sharing procedure of Carvedilol [FI/H/PSUR/0017/002]	NL/H/2609/ 001-002/IB/ 003	IB	8-11-2013	21-11-2013	Approval	N