LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Carveratio
Carvedilol

SE/H/853/01-04/MR

This module reflects the scientific discussion for the approval of Carveratio. Please note that the marketing authorisation was first approved with the name "Carvira" and therefore this name is used throughout the document. The procedure was finalised at 2008-10-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Alfred E Tiefenbacher (GmbH & Co. KG) has applied for a marketing authorisation for Carvira, filmcoated tablets, 3.125 mg, 6.25 mg, 12.5 mg and 25 mg claiming essential similarity to Kredex tablets marketed by Roche, which were first authorised in August 1992 in Sweden. Kredex tablets are available on the Swedish market in the strengths 3.125 mg, 6.25 mg, 12.5 mg and 25 mg. The product contains carvedilol as active substance. For approved indications see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Carvira is presented in the form of film-coated tablets containing 3.125 mg, 6.25 mg, 12.5 mg and 25 mg of carvedilol.
The excipients are microcrystalline cellulose, lactose monohydrate, crospovidone, povidone, anhydrous colloidal silicon dioxide, magnesium stearate, hypromellose, titanium dioxide (E 171), triethyl citrate, macrogol and polydextrose.
The tablets are packed in white HDPE bottles with polypropylene caps or in white opaque PVC/aluminium foil blisters.

II.2 Drug Substance

Carvedilol has a monograph in the Ph. Eur.

Carvedilol is a white, off-white powder which is practically insoluble in water, slightly soluble in alcohol and practically insoluble in dilute acids. The structure of carvedilol has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and limits for impurities/degradation products. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Carvira is formulated using excipients described in the current Ph Eur, except for polydextrose which is controlled according to acceptable in house specifications. All raw materials used in the product have demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with the special storage precautions "Do not store above 30°C (for blisters) and "Do not store above 25°C" (for bottles).

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The relative bioavailability of Carvedilol 12.5 mg tablets manufactured by Pharmascience Inc compared with Coreg 12.5 mg tablets from SmithKline Beecham Inc, Canada, and Dilatrend, Hoffmann-LaRoche, Germany, was determined in a randomised, three-way, cross-over single dose study in healthy volunteers performed under fasting conditions.

The bioequivalence study contained two reference arms, however, only the comparison with the European reference product, Dilatrend, is relevant for the approval.

Bioequivalence was demonstrated regarding C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ using the normal acceptance range, 80-125%, as seen below.

The results are given in the following table as arithmetic mean (CV%)

Treatment	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$T_{1/2}$** h
Test	156.3 (73.3)	164.0 (70.7)	42.66 (47.41)	1.03 (97.72)	6.91 (62.9)
Reference	159.0 (86.4)	170.5 (81.8)	43.97 (59.48)	0.86 (64.81)	9.45 (131.0)
***Ratio (90% CI)**	105 (96-115)	103 (94-112)	101 (87-118)		

$AUC_{0-\infty}$	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

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User testing of the package leaflet has been performed and the result of the user testing is considered acceptable.

The SPC, package leaflet and labelling are acceptable.

The risk/benefit ratio is considered positive and Carvira film-coated tablets in the strengths 3.125 mg, 6.25 mg, 12.5 mg and 25 mg is recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Carvira film-coated tablets in the strengths 3.125 mg, 6.25 mg, 12.5 mg and 25 mg were successfully finalised on 2008-10-09.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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