

Public Assessment Report

Scientific discussion

**Zofenoprilcalcium Mylan 30 mg,
film-coated tablets**

(zofenopril calcium)

NL/H/3770/001/DC

Date: 11 April 2016

This module reflects the scientific discussion for the approval of Zofenoprilcalcium Mylan 30 mg, film-coated tablets. The procedure was finalised on 19 January 2011 with Sweden as RMS (SE/H/0987/001/DC). The current RMS is the Netherlands (NL/H/3770/001/DC). For information on changes after this date please refer to the module 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zofenoprilcalcium Mylan 30 mg film-coated tablets from Mylan B.V.

The product is indicated for:

Hypertension

Zofenoprilcalcium Mylan is indicated for the treatment of mild to moderate essential hypertension.

Acute Myocardial Infarction

Zofenoprilcalcium Mylan is indicated for the treatment initiated within the first 24 hours of patients with acute myocardial infarction with or without signs and symptoms of heart failure, who are haemodynamically stable and have not received thrombolytic therapy.

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 Zofenil, film-coated tablet, 30 mg authorised in the UK by Menarini International.

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

The RMS of the initial procedure was Sweden, and the concerned member states (CMS) were France, Italy, the Netherlands, Portugal and Romania. The role of RMS was transferred to the Netherlands on 4 april 2016. Consequently, the MA in Sweden was withdrawn.

II. QUALITY ASPECTS

II.1 Introduction

Zofenoprilcalcium Mylan is presented in the form of tablets containing 30 mg of zofenopril calcium which corresponds to 28.7 mg of zofenopril. The excipients are microcrystalline cellulose, magnesium stearate, pregelatinised starch, macrogol, hypromellose, polysorbate and titanium dioxide. The tablets are packed in blister or bottles.

II.2 Drug Substance

The active substance zofenopril calcium does not have a monograph in the Ph Eur.

Zofenopril calcium is a white, crystalline powder which is very slightly soluble in water and methanol and practically insoluble in acetonitrile and 2-propanol. The structure of zofenopril calcium 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 the limits for impurities/ degradation products have been justified. 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 proposed retest period.

II.3 Medicinal Product

Zofenoprilcalcium Mylan, 30 mg, film-coated tablet is formulated using excipients described in the current Ph Eur, except for Opadry white YS-1R-7003 which is controlled according to acceptable in house specifications. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the active substance, such as poor aqueous solubility.

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 no special storage precautions.

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

To support the application, the applicant has submitted one single-dose bioequivalence study of Zofenoprilcalcium Mylan 30 mg film-coated tablets. The reference product used was Zopranol 30 mg, tablets from Italy.

The study was an open-label randomised, two-treatment, two-period, two-sequence single-dose crossover single-dose study conducted in 44 (42 completed) healthy male volunteers under fasting conditions. Plasma concentrations of zofenopril and zofenoprilat were determined with a validated LC/MS/MS method. The 90% CI for the test/reference ratio for AUC_{0-t} and C_{max} for zofenopril were within the conventional acceptance range of 80-125%. Bioequivalence has been demonstrated.

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. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report, making reference to a user test carried out on the product Enalapril maleate 2.5 mg, 5 mg, 10 mg, 20 mg tablets accepted by MHRA in procedure UK/H/383/01-04/E01. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zofenoprilcalcium Mylan 30 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Zofenil 30 mg film-coated tablets. Zofenil 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.

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 Zofenoprilcalcium Mylan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 19 January 2011.

**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
Updated ASMF for zofenopril calcium	SE/H/0987/IB/001/G	IB	9-6-2011	17-6-2011	Approval	No
Addition of a primary and secondary packaging site	SE/H/0987/IA/003/G	IA	21-7-2011	19-8-2011	Approval	No
Correction of SmPC in line with registered packaging details	SE/H/0987/001/IB/002	IB	27-7-2011	29-8-2011	Approval	No
Minor changes in the HPLC assay method	SE/H/0987/001/IA/005	IA	9-1-2013	29-1-2013	Approval	No
Name change finished product manufacturer	SE/H/0987/IA/004/G (included in supergroup procedure SE/H/xxxx/IA/132/G)	IA	6-2-2013	1-3-2013	Approval	No
Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	SE/H/0987/001/IB/007	IB	16-4-2013	25-4-2013	Approval	No
Substantial changes to the ASMF of an already approved manufacturer	SE/H/0987/001/II/006	II	19-4-2013	1-7-2013	Approval	No
Change in the name and/or address of the marketing authorisation holder in Portugal	SE/H/0987/001/IA/008/G (included in supergroup procedure SE/H/xxxx/IA/178/G)	IA	11-9-2013	25-9-2103	Approval	No
Shelf life extended from 2 years to 3 years.	SE/H/0987/001/IB/009	IB	19-5-2014	18-6-2014	Approval	No
Product information updated to implement the outcome of Article 31 referral for renin-angiotensin system (RAS)-acting agents (EMA/H/A-31/1370)	SE/H/0987/001/IB/010	IB	15-10-2014	14-11-2014	Approval	No
Addition of manufacturing site (finished product, primary and secondary packaging)	SE/H/0987/IB/011/G	IB	18-11-2014	18-12-2014	Approval	No
Addition of a manufacturing site for a manufacturing step. A Minor change to the restricted part of an ASMF. Other changes to a test procedure were made (including replacement or addition) for the active substance or a starting material/intermediate	SE/H/0987/IB/012/G	IB	25-2-2015	27-3-2015	Approval	No
Renewal procedure.	SE/H/0987/001/R/001	R	23-5-2015	2-11-2015	Approval	No
Introduction of a summary of the pharmacovigilance system	SE/H/0987/001/IA/013	IA	23-12-2015	22-1-2016	Approval	No
Addition of a site where batch control takes place	SE/H/0987/001/IA/014	IA	2-2-2016	3-3-2016	Approval	No