LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Mykofenolatmofetil Actavis 250 mg hard capsules
(mycophenolate mofetil)

SE/H/790/01/DC

This module reflects the scientific discussion for the approval of Mykofenolatmofetil 250 mg hard capsules. The procedure was finalised on 21 April 2009. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Actavis Group PTC ehf, Iceland has applied for a marketing authorisation for Mykofenolatmofetil Actavis 250 mg hard capsules claiming essential similarity to Cellcept 250 mg hard capsules marketed in the EU by Roche. The product contains mycophenolate mofetil as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bioequivalence study is Cellcept 250 mg hard capsule from the German market.

II. QUALITY ASPECTS

II.1 Introduction

Mykofenolatmofetil Actavis is presented in the form of hard capsules containing 250 mg of mycophenolate mofetil. The excipients of the capsule content are microcrystalline cellulose, hydroxypropyl cellulose, talc, croscarmellose sodium, povidone, and magnesium stearate. The capsules are made of gelatine and contain sodiumlauril sulfate and the colorants indigocarmine, titanium dioxide and iron oxides.
The capsules are packaged in Al/PVC/PVDC blisters.

II.2 Drug Substance

Mycophenolate mofetil has a monograph in the Ph Eur. The drug substance is a white, crystalline powder which is practically insoluble in water, freely soluble in acetone and sparingly soluble in anhydrous ethanol. The structure of mycophenolate mofetil has been adequately proven and its physico-chemical properties have been 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 retest period.

II.3 Medicinal Product

Mykofenolatmofetil Actavis 250 mg hard capsules are formulated using excipients described in the current Ph Eur, or are controlled by suitable in-house specifications. All raw materials used in the product have been demonstrated to be in 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 product development has taken into consideration the physico-chemical characteristics of the active substance. 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 and the analytical methods have been suitably validated.
Stability studies under ICH conditions have been performed and data presented support the shelf life and storage conditions claimed in the SPC.

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

A randomised, single-dose, open-label, 2-way crossover bioequivalence study with mycophenolate mofetil 250 mg hard capsules was performed under fasting conditions. A total of 54 healthy adult subjects were included. Blood sampling was made for 60 hours post-dosing and a wash-out period of eight days was used.

Plasma samples were analysed for mycophenolate mofetil (MMF) and the active metabolite mycophenolic acid (MPA) with a validated LC-MS-MS method. Since the plasma levels of MMF are barely detectable, the bioequivalence evaluation was based on the active metabolite MPA.

The results from the bioequivalence study are presented in Table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **mycophenolic acid** (n=50).

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	12840 ± 4301	13557 ± 4553	10891 ± 3324	0.50 (0.33-0.83)	7.75 ± 4.32
Reference	12653 ± 4235	13421 ± 4468	10802 ± 3751	0.500 (0.33-1.25)	8.40 ± 4.70
***Ratio (90% CI)**	101.5 (98.02-105.19)	101.2 (97.64-104.88)	101.7 (93.46-110.67)		

$AUC_{0-\infty}$ 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***

Based on the results of the studiy it was concluded that the generic mycophenolate mofetil capslue intended for marketing is bioequivalent with the originator.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refers 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 not been performed, but an acceptable bridging to a test for a similar product has been made.

The risk/benefit ratio is considered positive and the application for Mykofenolatmofetil 250 mg hard capsules is recommended for approval.

VI. APPROVAL

The Decentralised procedure for Mykofenolatmofetil 250 mg hard capsules was successfully finalised on 20090421.

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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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