LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Mykofenolatmofetil Actavis 500 mg film-coated tablets (mycophenolate mofetil)

SE/H/709/01/DC

This module reflects the scientific discussion for the approval of Mykofenolatmofetil Actavis 500 mf film-coated tablets procedure was finalised at 18 December 2008. 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 500 mg film-coated tablets claiming essential similarity to Cellcept 500 mg tablets 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 bio-equivalence study is Cellcept 500 mg tablet from the German market.

II. QUALITY ASPECTS

II.1 Introduction

Mykofenolatmofetil Actavis is presented in the form of film-coated tablets containing 500 mg of mycophenolate mofetil. The excipients are microcrystalline cellulose, povidone, hydroxypropyl cellulose, croscarmellose sodium, talc, magnesium stearate, hypromellose, titanium dioxide, macrogol, red iron oxide, black iron oxide and indigocarmine aluminium lake. The film-coated tablets are packaged in Al/PVC/PVDC blisters.

II.2 Drug Substance

Mycophenolate mofetil has a monograph in the Ph Eur. Mycophenolate mofetil 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 500 mg film-coated tablets is formulated using excipients described in the current Ph Eur, except for iron oxide red and black which are controlled according USP/JP and indidocarmine aluminium lake which is controlled according to acceptable 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

Two single-dose bioequivalence studies were submitted. The first study was performed using a test product from a batch with a size similar to the proposed commercial tablet batch size. The second, smaller bioequivalence study was performed with a test product with a larger batch size and was considered supportive.

The two studies were of similar design. They were open-label, randomised, two-treatment, two-period, and two-sequence crossover studies conducted in healthy adult human male subjects. In each study period, subjects received a single dose of 500 mg mycophenolate mofetil (MMF) under fasting conditions. Blood sampling was made for 48 hr post-dose. There was at least 7 days washout between periods. Plasma samples were analysed for MMF and MPA concentrations using an adequately validated LC-MS/MS method.

The bioequivalence evaluation was based on pharmacokinetic parameters for the active metabolite MPA since after absorption, the conversion of MMF to MPA is rapid and complete and MMF concentrations are barely measurable in plasma after oral administration. The protocol pre-specified that bioequivalence was to be concluded if the 90% confidence intervals (CIs) for the ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for MPA were within 80-125% for AUC parameters and within 75-133% for C_{max}. However, the wider acceptance criteria for Cmax were not specifically justified in the protocol and could not be considered retrospectively justifiable from a clinical efficacy/safety perspective.

The results from the first and second bioequivalence studies are presented in Table 1 and Table 2, respectively. In both studies, the 90% CI for MPA AUC were within the 80-125% limits. In the first study, with the commercial tablet batch size, also the 90% CI for MPA C_{max} was within the 80-125% limits. In the supportive study, the 90% CI for C_{max} was just outside the upper acceptance limit. Based on the results of the studies it was concluded that the generic mycophenolate mofetil tablet intended for marketing is bioequivalent with the originator tablet.

Table 1. Geometric Least Squares Mean and results of statistical evaluation for Mycophenolic Acid, MPA. Test batch size 30,000 tablets (n=45)

Parameters	Geometric Least Squares Mean			90% CI (Parametric)
	Reference Product (A)	Test Product (B)	Ratio (B/A) %	
C_{max} (ng/ml)	14869	15833	106.5	96.06-118.03
AUC_{0-t} (ng.h/ml)	27686	27382	98.9	95.65-102.26
$AUC_{0-\infty}$(ng.h/ml)	29027	28693	98.8	95.69-102.11

Table 2. Geometric Least Squares Mean and results of statistical evaluation for Mycophenolic Acid, MPA. Test batch size 115,000 tablets (n=39)

Parameters	Geometric Least Squares Mean			90% CI (Parametric)
	Reference Product (A)	Test Product (B)	Ratio (B/A) %	
C_{max} (ng/ml)	12727	12130	104.9	85.5 - 128.8
AUC_{0-t} (ng.h/ml)	26614	24985	106.5	102.7 - 110.4
$AUC_{0-\infty}$(ng.h/ml)	28255	26627	106.1	102.3 - 110.1

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.

During the procedure, the SPC was updated with the latest approved variations of the originator SPC.

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 Actavis 500 mg film-coated tablets is recommended for approval.

VI. APPROVAL

The Decentralised Procedure for Mykofenolatmofetil Actavis 500 mg film-coated tablets was successfully finalised on 2008-12-18.

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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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