COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Mycofenolaatmofetil Aurobindo 500 mg, film-coated tablets (mycophenolate mofetil)

NL/H/5131/001/DC

Date: 17 March 2023

This module reflects the scientific discussion for the approval of Mycofenolaatmofetil Aurobindo 500 mg, film-coated tablets. The procedure was finalised on 18 December 2008 in Portugal (PT/H/2079/001/DC). After a transfer on 9 Augustus 2000, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
EMA	European Medicines Agency
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Mycofenolaatmofetil Aurobindo 500 mg, film-coated tablets, from Aurobindo Pharma B.V.

The MAH has applied for a marketing authorisation for Mykofenolatmofetil Aurobindo 500 mg, film-coated tablets claiming essential similarity to Cellcept 500 mg tablets marketed in the EU (EU/1/96/005) 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.

The concerned member states (CMS) involved in this procedure were Spain and the Netherlands.

This product was originally authorised in several Members States of the European Union under the decentralised procedure SE/H/0709/001/DC with Sweden as RMS. Subsequently, a RMS transfer to Portugal (PT/H/2079/001/DC) took place. The current RMS is the Netherlands.

II. QUALITY ASPECTS

II.1 Introduction

Mycofenolaatmofetil Aurobindo 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 indigo carmine 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.

Manufacturing process

The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

Quality control of drug substance
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 of drug substance
Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Mycofenolaatmofetil Aurobindo 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 indigo carmine 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).

Pharmaceutical development
The product development has taken into consideration the physico-chemical characteristics of the active substance.

Manufacturing process
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.

Quality control of drug product
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 of drug product
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.

Bioequivalence studies

Design

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.

The bioequivalence evaluation was based on pharmacokinetic parameters for the active metabolite mycophenolic acid (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 $AUC0_{-\infty}$ for MPA were within 80-125% for AUC parameters and within 75-133% for C_{max}. However, the wider acceptance criteria for C_{max} were not specifically justified in the protocol and could not be considered retrospectively justifiable from a clinical efficacy/safety perspective.

Analytical/statistical methods

Plasma samples were analysed for MMF and MPA concentrations using an adequately validated LC-MS/MS method.

Results

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 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.**

Parameters	Geometric Least Squares Mean (n=45)			
	Reference Product (A)	Test Product (B)	Ratio (%) (B/A)	90% CI (Parametric)
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
$AUC0_{-\infty}$ (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.**

Parameters	Geometric Least Squares Mean (n=39)			
	Reference Product (A)	Test Product (B)	Ratio (%) (B/A)	90% CI (Parametric)
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
$AUC0_{-\infty}$ (ng.h/ml)	28255	26627	106.1	102.3 - 110.1

IV.1 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. USER CONSULTATION

User testing of the package leaflet has not been performed, but an acceptable bridging to a test for a similar product has been made.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and the application for Mycofenolaatmofetil Aurobindo 500 mg, film-coated tablets is recommended for approval. The Decentralised Procedure for Mycofenolaatmofetil Aurobindo 500 mg, film-coated tablets was successfully finalised on 2008-12-18.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5131/ IB/031/G	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product: - Minor change in the manufacturing process. Change to in-process tests or limits applied during the manufacture of the finished product: - Tightening of in-process limits.	No	10-09-2020	Approved	N/A
NL/H/5131/ 001/IB/033	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/ hybrid/ biosimilar medicinal products following assessment of the same change for the reference product: - Implementation of change(s) for which no new additional data are submitted by the MAH.	Yes	05-11-2020	Approved	N/A
NL/H/5131/ IA/035/G	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph: - Updated certificate from an already approved manufacturer.	No	29-09-2020	Approved	N/A
NL/H/5131/ 001/IB/034	Changes in the composition (excipients) of the finished product: - Other variation.	Yes	12-11-2020	Approved	N/A
NL/H/5131/ 001/IA/036	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under	Yes	13-07-2021	Approved	N/A

	Articles 45 or 46 of Regulation 1901/2006SmPCSmPC: - Implementation of wording agreed by the competent authority.				
NL/H/5131/001/IB/037	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product: - Implementation of change(s) for which no new additional data are submitted by the MAH.	Yes	11-05-2022	Approved	N/A
NL/H/5131/001/II/038	Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required.	No	23-01-2023	Approved	N/A