LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Mycophenolate mofetil Hexal
(mycophenolate mofetil)

SE/H/2240/01-02/DC

This module reflects the scientific discussion for the approval of Mycophenolate mofetil Hexal. The procedure was finalised on 2023-04-26. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Mycophenolate mofetil Hexal, 250 mg, capsule, hard and 500 mg, film-coated tablet.

The active substance is mycophenolate mofetil. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Mycophenolate mofetil Hexal, 250 mg, capsule, hard and 500 mg, film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, FI, NO as concerned member states (CMS).

The reference medicinal products chosen for the purposes of establishing the expiry of the data protection period are CellCept 250 mg, capsule, hard and CellCept 500 mg, film-coated tablet authorised in the Union since 1996, with Roche Registration GmbH as marketing authorisation holder.

The reference products used in the bioequivalence studies are CellCept 250 mg, capsule, hard and CellCept 500 mg, film-coated tablet from UK with Roche Registration Limited, UK as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products the following medicinal product(s) has/have been designated as orphan medicinal products, but not yet been granted a marketing authorisation in the EU: EU/3/13/1171, EU/3/14/1253, EU/3/15/1479, EU/3/18/2114, EU/3/17/1939, EU/3/18/2063, EU/3/17/1866, EU/3/17/1869, EU/3/17/1931, EU/3/21/2521.

The applicant should monitor these products during the entire procedure to check if a marketing authorisation has been granted. In case a marketing authorisation is granted, the applicant should update the report on similarity (Module 1.7.1) and, if applicable, submit the data to support derogation from orphan market exclusivity (Module 1.7.2).

The applicant has provided a similarity report (Module 1.7.1) due to potential similarity with authorised orphan medicinal product(s) under market exclusivity. The detailed RMS assessment of similarity was circulated by the RMS at day 70.

Conclusion

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Mycophenolate mofetil Hexal is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Idefirix. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Idefirix in the *Prevention of graft rejection following solid organ transplantation*, does not prevent the granting of the marketing authorisation of Mycophenolate mofetil Hexal. This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of active substance are well known. As active substance is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Mycophenolate mofetil Hexal is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Mycophenolate mofetil Hexal from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted two bioequivalence studies comparing Mycophenolate mofetil Hexal (Mycophenolate mofetil) with the reference product CellCept.

Pharmacokinetic properties of the active substance
Absorption: Following oral administration, mycophenolate mofetil (MMF) undergoes rapid and extensive absorption and complete pre-systemic metabolism to the active metabolite, mycophenolic

acid (MPA). As evidenced by suppression of acute rejection following renal transplantation, the immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil, based on MPA AUC, is 94% relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption (MPA AUC) of mycophenolate mofetil when administered at doses of 1.5 g BID to renal transplant patients. However, MPA C_{max} was decreased by 40% in the presence of food. Mycophenolate mofetil is not measurable systemically in plasma following oral administration.

Study 044-07 (250 mg capsule)

Methods

This was a single-dose, two-way crossover study conducted in 52 healthy volunteers (50 completed), comparing Mycophenolate mofetil, 250 mg, capsule with CellCept, 250 mg, capsule under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 60 hours post-dose. Plasma concentrations of parent MMF and active metabolite MPA were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 07 June 2007 and 29 June 2007.

Results

The results from the pharmacokinetic and statistical analysis are presented below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **mycophenolic acid (MPA)** (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	0.50 (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*

For MPA AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The data of MMF was analysed and provided as supporting evidence.

Study 60207 (500 mg tablet)

Methods

This was a single-dose, two-way crossover study conducted in 68 healthy volunteers (57 completed), comparing Mycophenolate mofetil, 500 mg, film-coated tablet with CellCept, 500 mg, film-coated tablet under fasting conditions. A single dose of two tablets of 500 mg (total dose of 1 g) of either test or reference was administered in each period. Blood samples for concentration analysis were collected pre-dose and up to 24 hours (MMF) and 96 hours (MPA) post-dose. Plasma concentrations of parent MMF and active metabolite MPA were determined with a LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}. The study was conducted between 02 November 2006 and 08 January 2007.

Results

The results from the pharmacokinetic and statistical analysis are presented below.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for **mycophenolic acid (MPA)** (n=57).

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	63130 ± 17507	66617 ± 18261[#]	19964 ± 6720	0.683 (0.333-4.00)	16.90 ± 5.69[#]
Reference	65773 ± 18624	68917 ± 18606[#]	19868 ± 7471	0.667 (0.333-4.02)	16.49 ± 3.96[#]
***Ratio (90% CI)**	96.16 (92.20-100.30)	96.48 (93.00-100.08)[#]	100.83 (94.20-107.92)		

$AUC_{0-\infty}$	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*
[#]n=56

For MPA AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The data of MMF was analysed and provided as supporting evidence.

Discussion and overall conclusion
The bioequivalence studies and the statistical evaluation were in accordance with accepted standards for bioequivalence testing, as outlined in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). The bioanalytical methods were adequately validated. The applicant has justified for the lack of incurred sample reanalysis (ISR) data.

The bioequivalence evaluation was based on the active metabolite MPA. Since the plasma levels of MMF are barely detectable this is acceptable. The data of MMF was analysed and provided as supporting evidence.

Based on the submitted bioequivalence studies, Mycophenolate mofetil Hexal is considered bioequivalent with CellCept.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Risk Management Plan
The MAH has submitted a risk management plan for 250 mg hard capsules and
500 mg film-coated tablets version 5.0 in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Mycophenolate mofetil Hexal.

Safety specification Mycophenolate mofetil Hexal

Table 9-1 Part II SVIII.1: Summary of safety concerns

Important identified risks	Bone marrow depression resulting in cytopenias and associated infections or hemorrhages
	Gastrointestinal disorders including ulceration and hemorrhage
	Hypersensitivity
	Drug-drug interaction (DDI) -- Drugs that interfere with enterohepatic recirculation and may lead to reduced efficacy of mycophenolate mofetil
	Adverse pregnancy outcomes
	Lymphomas and other malignancies, particularly of the skin
Important potential risks	Exacerbation of hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT)
	DDI – Risk of activation of live vaccines
	DDI – Lack of effect of any vaccination
	DDI – Potential interaction with azathioprine leading to increased bone marrow suppression
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and the following additional routine pharmacovigilance activity is proposed by the applicant, which is endorsed:

Routine pharmacovigilance activities beyond ADRs reporting and signal detection

Specific adverse reaction follow-up questionnaires for teratogenic effects (spontaneous abortion and congenital malformations):

Intensive monitoring of teratogenic effects (spontaneous abortion and congenital malformations) will be performed through targeted follow up questionnaires of pregnancies and outcomes for health care professionals (HCP's) and patients. These questionnaires aim at further characterizing the nature of events, demographics of patients at risk, and the presence of risk factors and confounding factors

Risk minimisation measures

The applicant has in the RMP Part V3 included the table of "Summary of risk minimization measures Table 6-2 Summary of PhV activities and risk minimization activities by safety concerns"

All but one of the safety concerns included are handled by Routine risk minimization measures. (For the full list, see RMP.)

Additional Risk minimisation measures

The safety concern "Teratogenic effects (spontaneous abortion and congenital malformations in women)" shall be handled by Additional risk minimization measures, educational material:

- Guide for HCPs
- Guide for patients

The key safety messages for the eductional material in Annex 6 of the RMP are in alignment with the recent Annex II D of the originator 'Cellcept' available on the European Medicines Agency (EMA) webpage.

The approval of wording and layout of educational material is a matter for each MS.

The wording of the conditions for marketing authorisation are given in section VIII of the Overview.

Summary of the RMP
The submitted Risk Management Plan, version 5.0 and (electronically) signed date 13 Sep 2022 is considered acceptable. Conditions for marketing authorisation are given in section VIII below.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Mycophenolate mofetil Sandoz 250 mg Capsules, hard. UK/H/0886/001/DC.
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Mycophenolate mofetil Hexal, is found adequate. There are no objections to approval of Mycophenolate mofetil Hexal, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

Additional risk minimisation measures (including educational material)
The educational material should contain the following key elements:
Copy from annex II for the centrally authorised reference product Cellcept.
The RMP for Mycophenolate mofetil Hexal is aligned with this.

The Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme and a follow-up pregnancy questionnaire, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at ensuring that the health professionals and patients are aware of the teratogenicity and mutagenicity, the need for pregnancy tests before starting therapy with <product name>, the contraceptive requirements for both male and female patients and what to do in case of pregnancy during treatment with <product name>.

The MAH shall ensure that in each MS where <product name> is marketed, all healthcare professionals and patients who are expected to prescribe, dispense or use <product name> are provided with the following educational package:

- Physician educational material
- Patient information pack

The health professional educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

The patient information pack should contain:

- The Package Leaflet
- Guide for patients

The educational materials shall contain the following key elements:

Separate guides for healthcare professionals and patients should be provided. For patients, the text should be appropriately separated for men and women. The following areas should be covered in these guides:

- An introduction in each guide will inform the reader that the purpose of the guide is to tell them that a foetal exposure must be avoided and how to minimise the risk of birth defects and miscarriage associated with mycophenolate mofetil. It will explain that although this guide is very important it does not provide full information on mycophenolate mofetil and that the SmPC (healthcare professionals) and package leaflet (patients) supplied with the medicine must also be read carefully.

- Background information on mycophenolate mofetil teratogenicity and mutagenicity in humans. This section will provide important background information concerning the teratogenicity and mutagenicity of mycophenolate mofetil. It will provide details about the nature and magnitude of the risk, in line with the information provided in the SmPC. The information provided in this section will facilitate a correct understanding of the risk and explain the rationale for the following pregnancy prevention measures. Guides should also mention that patients should not to give this drug to any other person.

- Counselling of patients: This section will emphasise the importance of a thorough, informative and ongoing dialogue between patient and healthcare professional about the pregnancy risks associated with mycophenolate mofetil and the relevant minimisation strategies including alternative treatment choices, if applicable. The need to plan a pregnancy will be highlighted.

- The need to avoid foetal exposure: Contraceptive requirements for patients of reproductive potential prior to, during and after treatment with mycophenolate mofetil. Contraceptive requirements for sexually active male patients (including vasectomised men) and female patients of childbearing potential will be explained. The need for contraception prior to, during and after treatment with mycophenolate mofetil, including details of the duration of time for which contraception must be continued after cessation of therapy, will be clearly stated.

In addition, the text relating to women should explain the pregnancy test requirements prior to and during therapy with mycophenolate mofetil; including the advice for two negative pregnancy tests prior to starting therapy and the importance of the timing of these tests. The need for subsequent pregnancy tests during treatment will also be explained.

- Advice that patients should not donate blood during therapy or for at least 6 weeks following discontinuation of mycophenolate. Furthermore, men should not donate semen during therapy or for 90 days following discontinuation of mycophenolate.

- Advice on action if a pregnancy occurs or is suspected during or shortly after being treated with mycophenolate mofetil. Patients will be informed that they should not stop taking mycophenolate mofetil but must contact their doctor immediately. It will be explained that the correct course of action, based on an assessment of the individual benefit-risk, will be determined on a case-by-case basis through a discussion between the treating physician and the patient.

In addition, a pregnancy follow-up questionnaire including details of exposure during pregnancy, including timing and dose; duration of therapy, before and during pregnancy; concomitant drugs; known teratogenic risks and full details of congenital malformations should be agreed to with the national competent authorities.

VII. APPROVAL

The decentralised procedure for Mycophenolate mofetil Hexal, 250 mg, capsule hard and 500 mg, film-coated tablet was positively finalised on 2023-04-26.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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