Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

# Public Assessment Report

# Decentralised Procedure

# Mycophenolate mofetil Sandoz 250mg Capsules, hard

## UK/H/0886/001/DC
## UK licence no: PL 04416/0712

## Sandoz Limited

Medicines and Healthcare Products Regulatory Agency

# LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Mycophenolate mofetil Sandoz 250mg Capsules (PL 04416/0712). It explains how Mycophenolate mofetil Sandoz 250mg Capsules was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

For practical information about using Mycophenolate mofetil Sandoz 250mg Capsules, patients should read the Package Leaflet or contact their doctor or pharmacist.

**What are Mycophenolate mofetil Sandoz 250mg Capsules and what are they used for?**
Mycophenolate mofetil Sandoz 250mg Capsules are used to prevent the body rejecting a transplanted organ (such as a heart, liver or kidney). Mycophenolate mofetil 250mg hard Capsules should be used together with ciclosporins and corticosteroids.

**How do Mycophenolate mofetil Sandoz 250mg Capsules work?**
Mycophenolate mofetil Sandoz 250mg Capsules contains the active substance mycophenolate mofetil. They belong to a group of medicines called “immunosuppressants”.

**How are Mycophenolate mofetil Sandoz 250mg Capsules used?**
The amount you take depends on the type of transplant you have had. Treatment will continue for as long as you need to prevent you from rejecting your transplant organ. Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Swallow your capsules whole with a glass of water.
- Do not break or crush them
- Do not take any capsules that have broken open or split.

Take care not to let any powder from inside a broken capsule get into your eyes or mouth.
- If this happens, rinse with plenty of plain water.

Take care not to let any powder from inside a broken capsule get onto your skin.
- If this happens, wash the area thoroughly with soap and water.

**How have Mycophenolate mofetil Sandoz 250mg Capsules been studied?**
Mycophenolate mofetil Sandoz 250mg Capsules is a “generic” version of the Brand leader product CellCept 250mg Capsules (Roche Registration Limited, UK),. In support of this application, pharmacokinetic data from a study were submitted, comparing levels of the active substance of both products in the blood, to show that the levels are comparable.

**What are the possible side effects of Mycophenolate mofetil Sandoz 250mg Capsules?**
Because Mycophenolate mofetil Sandoz 250mg Capsules is a “generic version of the Brand leader product CellCept 250mg Capsules (Roche Registration Ltd UK), its benefits and possible side-effects are taken as being the same.

For further information, please see Section 4 the Package Leaflet.

**Why is Mycophenolate mofetil Sandoz 250mg Capsules approved?**

It was concluded that Mycophenolate mofetil Sandoz 250mg Capsules could be considered to be a generic medicinal product of the Brand leader product CellCept 250mg Capsules (Roche Registration Ltd UK), with the same benefit/risk profile.

**What measures are being taken to ensure the safe and effective use of Mycophenolate mofetil Sandoz 250mg Capsules?**
A risk management plan (RMP) has been developed to ensure that Mycophenolate mofetil Sandoz 250mg Capsules is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Mycophenolate mofetil Sandoz 250mg Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Mycophenolate mofetil Sandoz 250mg Capsules**
The UK first granted a marketing authorisation for this product on 01 November 2010.

The full PAR for Mycophenolate mofetil Sandoz 250mg Capsules follows this summary.

For more information about treatment with Mycophenolate mofetil Sandoz 250mg Capsules, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in March 2016.

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# I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Portugal, Slovenia and the Slovak Republic have granted marketing authorisations for Mycophenolate mofetil Sandoz 250mg Capsules to Sandoz Limited, for use in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

This is an application made under Article 10(1) of 2001/83 EC, as amended, for Mycophenolate mofetil Sandoz 250mg Capsules, claiming to be a generic medicine to CellCept 250mg Capsules (Roche Registration Limited UK), which was registered via the Centralised Procedure on 14 February 1996. The reference product has been authorised in the European Community for more than 10 years, so the period of data exclusivity has expired.

Mycophenolate mofetil belongs to the immunosuppressant group. Its active metabolite, mycophenolate acid, is a potent inhibitor of guanosine nucleotide synthesis. Due to its potent cytostatic effect on lymphocytes, the proposed indication is in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogenic renal, cardiac or hepatic transplants.

With the exception of the bioequivalence study, no new non-clinical or clinical studies were conducted, which is acceptable given that the application is for a product that is identical to a reference product that has been granted in the UK for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

Since this product will be used in place of other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

The Reference Member State (RMS) has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of this product.

The pharmaceutical, non-clinical and clinical expert reports have been written by appropriately qualified persons and are suitable summaries of the data submitted.

The Marketing Authorisation Application (MAA) form submitted is satisfactory.

The application was submitted via the decentralised procedure (DCP), with the UK as Reference Member State (RMS), and Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Portugal, Slovenia and the Slovak Republic as Concerned Member States (CMS – UK/H/0886/001/DC). The UK granted a marketing authorisation for this product on 24 April 2007 (PL 04416/0712).

# II. QUALITY ASPECTS

## II.1 INTRODUCTION

This is an abridged application for Mycophenolate mofetil Sandoz 250mg Capsules, submitted under Article 10(1) of Directive 2001/83/EC. The proposed MA holder is Sandoz Limited, Frimley Business Park, Frimley, Camberley, GU16 7SR, UK.

The application cross-refers to CellCept 250mg Capsules (Roche Registration Limited UK), which was registered via the Centralised Procedure on 14 February 1996.

Other ingredients consist of the following pharmaceutical excipients:

**Capsule content:**
Starch, pregelatinised
Croscarmellose sodium
Povidone (K-90F)
Magnesium stearate

**Capsule shell:**
Gelatine
Red iron oxide (E172)
Yellow iron oxide(E172)
Titanium dioxide (E171)
Indigo carmine (E132)

The finished product is packaged in:

- a polyvinylidene chloride / polyvinylchloride / polyethylene / aluminium blister, which is stored in a cardboard container in pack sizes of 50, 100 and 300 capsules.
- a high-density polyethylene containers of 250 capsules.

Not all pack sizes may be marketed.

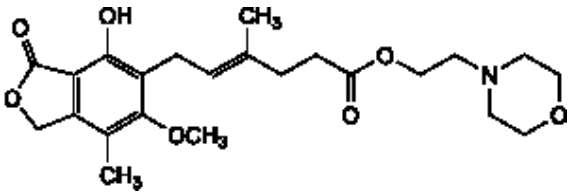
Specifications and certificates of analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with relevant regulations regarding the contact of materials with foodstuff.

## II.2 DRUG SUBSTANCE

INN: Mycophenolate mofetil

Chemical name: i. 2-(morpholin-4-yl)ethyl-(4*E*)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl-4-methylhex-4-enoate
ii. mycophenolic acid 2-(4-morpholinyl)ethyl ester

Structure:




Physical form: White to off-white or almost white, crystalline powder. Practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol.

Molecular formula: $C_{23}H_{31}NO_7$

Molecular weight: 433.5

Mycophenolate mofetil is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of mycophenolate mofetil are controlled by a European Directorate for the Quality of Medicines (EDQM) certificate of suitability.

## II.3 DRUG PRODUCT

### Pharmaceutical development

The applicant has provided a suitable product development section. Dissolution data and impurity profiles support the pharmaceutical equivalence of the proposed product with the reference product CellCept 250mg Capsules (Roche Registration Limited UK).

All excipients comply with their respective European Pharmacopoeia monograph. Suitable batch analysis data have been provided for each excipient, showing compliance with its respective monograph. The suppliers of indigo carmine, titanium dioxide and the iron oxide red/yellow provided suitable confirmation that these comply with EC Directives 78/25/EC (concerning use in foodstuff) and 95/45/EC (concerning purity).

With the exception of gelatin, none of the excipients contain materials of animal or human origin. Certificates of Suitability from the European Directorate for the Quality of Medicines has been provided for the suppliers of gelatin, showing that they comply with current guidelines concerning the minimising of TSE/BSE transmission. No genetically modified organisms (GMO) have been used in the preparation of this product.

There were no novel excipients used and no overages.

### Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out on batches of the finished product. The results appear satisfactory.

### Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Satisfactory certificates of analysis have been provided for all working standards used.

### Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set for both pack types, with the storage conditions “Do not store above 30°C.” The shelf-life after opening for product packed in the HDPE container is 2 months.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance used in the proposed and reference products. In addition, similar dissolution and impurity profiles have been demonstrated for the proposed and reference products.

# III NON-CLINICAL ASPECTS

## III.1 Introduction

This is an abridged application for Mycophenolate mofetil Sandoz 250mg Capsules, submitted under Article 10(1) of Directive 2001/83/EC. As mycophenolate mofetil is a well-known active substance, no further studies are required and the applicant has not provided any.

## III.2 Pharmacology

## III.3 Pharmacokinetics

## III.4 Toxicology

No new data have been submitted and none are required.

## III.5 Environmental Risk Assessment

Since this product will be used in place of other products that are currently on the market, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

## III.6 Discussion on non-clinical aspects

It is recommended that a Marketing Authorisation is granted for this application.

# IV CLINICAL ASPECTS

## IV.1 Introduction

This is an abridged application for Mycophenolate mofetil Sandoz 250mg Capsules, submitted under Article 10(1) of Directive 2001/83/EC. With the exception of a bioequivalence study, no further studies are required and the applicant has not provided any.

The bioequivalence study was performed in accordance with Good Clinical Practice (GCP).

Mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (MPA). MPA is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase and, therefore, inhibits the *de novo* pathway of guanosine nucleotide synthesis, without incorporation into DNA. As T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilise salvage pathways, MPA has more potent cytostatic effects on lymphocytes than on other cells.

Mycophenolate mofetil is rapidly and extensively absorbed from the gastrointestinal tract. It undergoes presystemic metabolism to active mycophenolic acid (MPA). MPA undergoes enterohepatic recirculation and secondary increases in plasma MPA concentrations are seen at between 6 to 12 hours after a dose. MPA is metabolised by glucuronidation to the inactive mycophenolic acid glucuronide. The majority of a dose is excreted in the urine as glucuronide, about 6% is recovered in faeces. MPA is 97% bound to plasma albumin. The mean half-life of MPA after oral dose of mycophenolate mofetil has been reported to be 17.9 hours.

## IV.2 Pharmacokinetics

The applicant has conducted a single bioequivalence study comparing the pharmacokinetic profiles of Mycophenolate mofetil Sandoz 250 mg Capsules (test) and CellCept 250 mg capsules (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for both the test and reference product.

***Bioequivalence study***

An open-label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, crossover, comparative oral bioavailability study to compare the pharmacokinetics of the test product Mycophenolate mofetil Sandoz 250 mg Capsules versus the reference product CellCept 250mg capsules (Roche Registration Limited, UK) in healthy, adult male subjects under fasted conditions.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The two treatment arms were separated by a 7-day washout period.

Pharmacokinetic parameters for the concentration of mycophenolate mofetil and its active metabolite mycophenolic acid (MPA) are given below:

**Mycophenolate mofetil**

| Parameters | Mean ± SD (Un-transformed data) | |
|---|---|---|
| | Reference Product | Test Product |
| $T_{max}$ | 0.585 ± 0.3410 | 0.536 ± 0.1854 |
| $C_{max}$ (ng/ml) | 1.508 ± 1.2949 | 1.580 ± 1.1010 |
| $AUC_{0-t}$ (ng.h/ml) | 0.950 ± 0.5842 | 1.043 ± 0.5952 |
| $AUC_{0-\infty}$(ng.h/ml) | 1.254 ± 1.0843 | 1.186 ± 0.7345 |
| t½ (h) | 2.623 ± 7.7508 | 1.445 ± 2.9712 |

$AUC_{0-\infty}$ 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

**Mycophenolic acid (MPA)**

| Parameters | Mean ± SD (Un-transformed data) | |
|---|---|---|
| | Reference Product | Test Product |
| $T_{max}$ | 0.598 ± 0.3946 | 0.572 ± 0.1698 |
| $C_{max}$ (ng/ml) | 10267.461 ± 2921.1997 | 10652.992 ± 2306.2895 |
| $AUC_{0-t}$ (ng.h/ml) | 12772.839 ± 2747.8589 | 13443.624 ± 2845.8685 |
| $AUC_{0-\infty}$(ng.h/ml) | 13940.258 ± 3045.9516 | 14768.306 ± 3092.3628 |
| t½ (h) | 9.294 ± 5.2711 | 11.086 ± 9.2287 |

$AUC_{0-\infty}$ 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

**Geometric Least Squares Mean, Ratios and 90% CI for Mycophenolic Acid (n=46)**

| Parameters | Geometric Least Squares Mean | | | 90% CI (Parametric) |
|---|---|---|---|---|
| | Reference Product (A) | Test Product (B) | Ratio (B/A) % | |
| $C_{max}$ (ng/ml) | 9882.339 | 10397.387 | 105.2% | 97.46-113.58 |
| $AUC_{0-t}$ (ng.h/ml) | 12486.041 | 13179.002 | 105.5% | 102.59-108.59 |
| $AUC_{0-\infty}$(ng.h/ml) | 13626.591 | 14466.647 | 106.2% | 102.65-109.80 |

As mycophenolate mofetil undergoes rapid and complete metabolism to the active metabolite MPA, adequate plasma concentration of mycophenolate mofetil may not be obtained. Therefore, the choice of selecting MPA data for confirmation of bioequivalence between test and reference products and providing data on mycophenolate mofetil as supportive evidence is adequate.

The 90% confidence intervals for $C_{max}$ and AUC for test versus reference product is within predefined acceptance criteria, according to the *Note for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98). The data support the claim that the test product can be considered a generic medicinal product of the reference product.

### IV.3 Pharmacodynamics

No new pharmacodynamic data have been submitted with this application and none are required.

### IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required for this application.

### IV.5 Clinical safety

With the exception of the data collected during the bioequivalence study, no new safety data have been submitted and none are required for this application. No new or unexpected safety issues were raised during the bioequivalence study.

### IV.6 Risk Management Plan (RMP)

No RMP was submitted with this application.

### IV.7 Discussion on the clinical aspects

It is recommended that a Marketing Authorisation is granted for this application.

## V USER CONSULATATION

A user consultation with target patient groups on the PIL has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the patient information leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

## IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

### QUALITY

The important quality characteristics of Mycophenolate mofetil Sandoz 250 mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

### NON-CLINICAL/CLINICAL

With the exception of one bioequivalence study, no new non-clinical or clinical data were submitted and none were required for an application of this type. Bioequivalence has been demonstrated between the applicant's Mycophenolate mofetil 250 mg Sandoz Capsules and CellCept 250 mg capsules (Roche Registration Limited UK).

No new or unexpected safety concerns arise from this application.

### PRODUCT LITERATURE

The summary of product characteristics (SmPC), patient information leaflet (PIL) and labelling are satisfactory, and consistent with that for the innovator product. The current approved UK labelling is provided below.

### BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the originator product are interchangeable. Extensive clinical experience with mycophenolate mofetil is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.

# Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

(Type II variations, PSURs, commitments)

| 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) |
|---|---|---|---|---|---|---|
| IB | UK/H/0886/ 001/IB/030 | SmPC/PIL | 26/01/2016 | 02/03/2016 | Approval | Yes (Annex 1) |
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## ANNEX 1

**Our Reference:** PL 04416/0712-0044

**Product:** Mycophenolate mofetil Sandoz 250mg Capsules

**Marketing Authorisation Holder:** Sandoz Limited
**Active Ingredient(s):** Mycophenolate Mofetil

**Type of Procedure:** Mutual Recognition
**Submission Type:** Variation
**Submission Category:** Type IB
**Submission Complexity:** Standard
**EU Procedure Number (if applicable):** UK/H/0886/001/IB/030

**Reason:**
To update the SmPC to bring it in-line with the reference product. Consequently, the PIL has been updated.

**Supporting Evidence**
Revised SmPC fragments and PILs.

**Evaluation**
The proposed changes to the SmPC and PILs are acceptable. The updated SmPC fragments and PILs have been incorporated into the Marketing Authorisation.

**Conclusion**
The proposed changes are acceptable.

**Decision**- Approved on 02 March 2016.