Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Mycophenolate Sandoz 250mg Capsules

UK/H/1034/001/DC
UK licence no: PL 04520/0114

Sandoz GmbH

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Mycophenolate Sandoz 250mg Capsules (PL 04520/0114). It explains how Mycophenolate 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 Sandoz 250mg Capsules, patients should read the Package Leaflet or contact their doctor or pharmacist.

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

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

How are Mycophenolate 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 Sandoz 250mg Capsules been studied?
Mycophenolate Sandoz 250mg Capsules is a "generic" version of the Brand leader product CellCept 250mg Capsules (Roche Registration Ltd 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 Sandoz 250mg Capsules?
Because Mycophenolate 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 Sandoz 250mg Capsules approved?

It was concluded that Mycophenolate 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 Sandoz 250mg Capsules?

A risk management plan (RMP) has been developed to ensure that Mycophenolate 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 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 Sandoz 250mg Capsules

The UK first granted a marketing authorisation for this product on 15 September 2008.

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

For more information about treatment Mycophenolate 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, Austria, Spain and Germany have granted marketing authorisations for Mycophenolate Sandoz 250mg Capsules to Sandoz GmbH, 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 Sandoz 250mg Capsules, claiming to be a generic medicine to CellCept 250mg Capsules (Roche Registration Ltd UK), which was granted a marketing authorisation in the UK on 14 February 1996, thus fulfilling the 10-year rule.

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 Austria, Spain and Germany and Concerned Member States (CMS – UK/H/1034/001/DC). The UK granted a marketing authorisation for this product on 15 September 2008 (PL 04520/0114).

II. QUALITY ASPECTS

II.1 INTRODUCTION

This is an abridged application for Mycophenolate Sandoz 250mg Capsules, submitted under Article 10(1) of Directive 2001/83/EC. The proposed MA holder is Sandoz GmbH, Biochemiestrasse 10, 6250 Kundl, Austria.

The application cross-refers to CellCept 250mg Capsules (Roche Registration Ltd UK), which was granted a marketing authorisation in the UK on 14 February 1996.

Other ingredients consist of pharmaceutical excipients in the capsules contents (pregelatinised starch, croscarmellose sodium, povidone and magnesium stearate) and the capsule shell (gelatin, red iron oxide [E172], yellow iron oxide [E172], titanium dioxide [E171] and indigocarmine [E132]).

The finished product is packaged in one of the following:

(i) a polyvinylidene chloride / polyvinylchloride / polyethyelene / aluminium blister, which is stored in a cardboard container in pack sizes of 50, 100, 200, 300 and 600 capsules.

(ii) a high-density polyethylene container with a polypropylene closure containing 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.

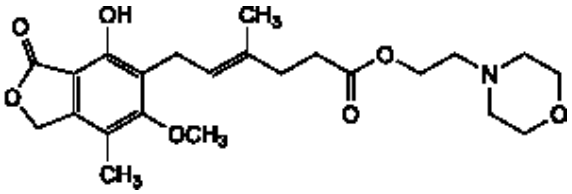
II.2 DRUG SUBSTANCE

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 active mycophenolate mofetil are covered by a certificate of suitability.

Active mycophenolate mofetil is stored in an airtight polyethylene bag, which is contained in polyester/aluminium/polyethylene bags.

An adequate retest period has been defined based on conducted stability studies.

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.

All excipients used comply with their respective European Pharmacopoeia monograph, with the exception of red iron oxide, yellow iron oxide and indigo carmine (which comply with suitable in-house specifications and 95/45/EEC). Satisfactory certificates of analysis have been provided for all excipients.

The only excipient used that contains material of animal origin is gelatin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines (EDQM) to show that they are manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/transmissible Spongiform Encephalopathies (BSE/TSE).

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 packaging types (although the shelf-life changes to 2 months after opening for the high-density polyethylene container).

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 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 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).

IV. 2 Pharmacokinetics
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.

The applicant has conducted a bioequivalence study in order to confirm that the proposed product (Mycophenolate 250mg Capsules) can be considered a generic medicinal product of the reference product (CellCept 250mg Capsules).

Bioequivalence study
This was an open-label, randomised, two-treatment, two-period, two sequence, crossover bioequivalence study conducted in healthy adult human male subjects under fasting conditions, comparing Mycophenolate 250mg Capsules (Test Product) versus CellCept 250mg Capsules (Reference Product).

A single dose of the investigational products was administered orally to each subject in each period with 240 ml of water while in a sitting position, after an overnight fast of at least 10 hours. The subjects were not allowed to lie down for 3 hours after dosing. A washout period of 7 days was maintained between the two dosing days in each group. The plasma samples were analysed for all subjects that completed the trial successfully.
Serial blood sampling before dosing and up to 48 hours after drug administration was carried out in each group. Mycophenolate mofetil and mycophenolic acid (MPA) in plasma were quantified by a validated LC-MS/MS method.

T_{max}, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and half-life were calculated independently for mycophenolate mofetil and MPA by employing a non-compartmental model. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range for ln-transformed C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ for MPA.

ANOVA, two one-sided tests for bioequivalence, power and ratio analysis for untransformed and ln-transformed PK parameters, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ were computed for MPA. Only descriptive statistics were reported for mycophenolate mofetil.

The results for MPA are presented below:

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

No serious or significant adverse events were reported during the study.

Conclusion

The study design is appropriate and the results showed that the test and reference products are bioequivalent as the 90% CI for C_{max} and AUC fall within the acceptance range of 80-125%, in-line with current guidelines.

IV.3 Pharmacodynamics

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.

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.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY

The important quality characteristics of Mycophenolate Sandoz 250mg 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 250mg Capsules and CellCept 250mg Capsules.

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.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON BOX (for blisters)

1. NAME OF THE MEDICINAL PRODUCT

Mycophenolate Sandoz 250 mg Capsules

Mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 250 mg of mycophenolate mofetil

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsules, hard

50 capsules, hard
100 capsules, hard
200 capsules, hard
300 capsules, hard
600 capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The capsules should be handled with care.
Do not open or crush the capsules and breathe the powder inside the capsules or allow it to touch your skin.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

PL 04520/0114

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by your doctor.

16. INFORMATION IN BRAILLE

Mycophenolate Sandoz 250 mg Capsules

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

CARTON BOX (for container)

1. NAME OF THE MEDICINAL PRODUCT

Mycophenolate Sandoz 250 mg Capsules

Mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 250 mg of mycophenolate mofetil

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsules, hard
250 capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The capsules should be handled with care.
Do not open or crush the capsules and breathe the powder inside the capsules or allow it to touch your skin.

8. EXPIRY DATE

EXP

After first opening: use within 2 months

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

PL 04520/0114

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by your doctor.

16. INFORMATION IN BRAILLE

Mycophenolate Sandoz 250 mg Capsules

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

LABEL (for container)

1. NAME OF THE MEDICINAL PRODUCT

Mycophenolate Sandoz 250 mg Capsules

Mycophenolate mofetil

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 250 mg of mycophenolate mofetil

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsules, hard
250 capsules, hard

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

The capsules should be handled with care.
Do not open or crush the capsules and breathe the powder inside the capsules or allow it to touch your skin.

8. EXPIRY DATE

EXP

After first opening: use within 2 months

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH
Biochemiestrasse 10
6250 Kundl
Austria

12. MARKETING AUTHORISATION NUMBER(S)

PL 04520/0114

13. MANUFACTURER'S BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

Use as directed by your doctor.

16. INFORMATION IN BRAILLE

Mycophenolate Sandoz 250 mg Capsules

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Mycophenolate Sandoz 250 mg Capsules

Mycophenolate mofetil

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Sandoz GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PL 04520/0114

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/1034/ 001/IB/024	SmPC/PIL	26/01/2016	25/02/2016	Approval	Yes (Annex 1)

ANNEX 1

Our Reference: PL 04520/0114-0035

Product: Mycophenolate Sandoz 250mg Capsules

Marketing Authorisation Holder: Sandoz GmbH
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/1034/001/IB/024

Reason:
To update sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3 and 6.3 of the SPC in line with the reference text, Cell Cept 250mg film-coated tablets, Roche, UK. Consequently, the PIL has been updated.

Supporting Evidence
Revised SmPC fragments and PIL.

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 25 February 2016.