



Medicines & Healthcare products
Regulatory Agency



Public Assessment Report

Decentralised Procedure

Mycophenolate mofetil Tillomed 250 mg Capsules

Procedure No: UK/H/6783/001/DC

UK Licence No: PL 11311/0591

Tillomed Laboratories Limited

LAY SUMMARY

Mycophenolate mofetil Tillomed 250 mg Capsules

This is a summary of the Public Assessment Report (PAR) for Mycophenolate mofetil Tillomed 250 mg Capsules (PL 11311/0591; UK/H/6783/001/DC). It explains how the application for Mycophenolate mofetil Tillomed 250 mg Capsules was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Mycophenolate mofetil Tillomed 250 mg Capsules. For ease of reading, the product may be referred to as 'Mycophenolate mofetil' or 'Mycophenolate mofetil Capsules' in this lay summary.

For practical information about using Mycophenolate mofetil, patients should read the package leaflet or contact their doctor or pharmacist.

What is Mycophenolate mofetil and what is it used for?

Mycophenolate mofetil is a 'generic' medicine. This means that Mycophenolate mofetil is similar to a 'reference' medicine already authorised in the European Union (EU) called CellCept 250 mg Capsules (Roche Registration Limited, UK).

Mycophenolate mofetil is used to prevent the body rejecting a transplanted kidney, heart or liver. This medicine should be used together with other medicines such as ciclosporin and corticosteroids.

How does Mycophenolate mofetil work?

This medicine contains the active substance, mycophenolate mofetil, which belongs to a group of medicines called immunosuppressants.

How is Mycophenolate mofetil used?

The pharmaceutical form of Mycophenolate mofetil is a hard capsule, which is taken by mouth and should be swallowed whole with a glass of water.

The patient should always take this medicine exactly as his/her doctor or pharmacist has advised. The patient should check with his/her doctor or pharmacist if unsure.

The capsules should not be broken or crushed.

The patient should not take any capsules that have been broken open or split.

The patient should take care not to let any powder from inside a broken capsule get into the eyes or mouth. If this happens, the patient should rinse with plenty of plain water.

The patient should take care not to let any powder from inside a broken capsule get on to the skin. If this happens, the patient should wash the area thoroughly with soap and water.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Mycophenolate mofetil can only be obtained with a prescription.

What benefits of Mycophenolate mofetil have been shown in studies?

As Mycophenolate mofetil is a generic medicine, studies in patients have been limited to tests to determine that Mycophenolate mofetil is bioequivalent to the reference product called CellCept 250 mg Capsules (Roche Registration Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Mycophenolate mofetil?

As Mycophenolate mofetil is a generic medicine of the reference medicine CellCept 250 mg Capsules (Roche Registration Limited, UK), the benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Mycophenolate mofetil (see Section 4 of the package leaflet).

For the full list of restrictions, see the package leaflet.

Why is Mycophenolate mofetil approved?

It was concluded that, in accordance with EU requirements, Mycophenolate mofetil has been shown to have comparable quality and clinical characteristics to the reference product CellCept 250 mg Capsules (Roche Registration Limited, UK). Based on this evaluation, the MHRA concluded that the benefits of Mycophenolate mofetil outweigh the identified risks and recommended Mycophenolate mofetil for approval.

What measures are being taken to ensure the safe and effective use of Mycophenolate mofetil?

A Risk Management Plan has been developed to ensure that Mycophenolate mofetil is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Mycophenolate mofetil, including the appropriate precautions to be followed by healthcare professionals and patients. In addition to the safety information provided in the Mycophenolate mofetil product information, the RMP includes educational materials for healthcare professionals and patients to ensure the safe and effective use of Mycophenolate mofetil.

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

Germany, Spain, France, Croatia, Italy and the UK agreed to a grant Marketing Authorisation for Mycophenolate mofetil on 13 September 2018. A Marketing Authorisation was granted in the UK to Tillomed Laboratories Limited on 10 October 2018.

The full PAR for Mycophenolate mofetil follows this summary.

For more information about treatment with Mycophenolate mofetil, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in November 2018.

SCIENTIFIC DISCUSSION

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Mycophenolate mofetil Tillomed 250 mg Capsules (PL 11311/0591; UK/H/6783/001/DC) could be approved. The product may be referred to as 'Mycophenolate mofetil' or 'Mycophenolate mofetil Capsules' in this scientific discussion.

Mycophenolate mofetil is a Prescription Only Medicine (POM) and is indicated, in combination with ciclosporin and corticosteroids, for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany, Spain, France, Croatia and Italy as Concerned Member States (CMS). The application for Mycophenolate mofetil Capsules was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference medicinal product, CellCept 250mg Capsules (Roche Registration Limited, UK), which was authorised via the centralised procedure (EU/1/96/005/001 & 003) on 14 February 1996.

The active substance, mycophenolate mofetil, belongs to the immunosuppressant group. Following oral administration, mycophenolate mofetil is rapidly absorbed and de-esterified to form the active metabolite mycophenolic acid. Mycophenolic acid (MPA) is a selective, non-competitive, reversible inhibitor of inosine monophosphate dehydrogenase. This inhibition leads to a nucleotide deficiency within cells that slows proliferative rate. In lymphocytes, a slow proliferation rate and changes to the surface glycosylation of adherence molecules render the lymphocytes less effective in recognising and eliminating allografts and organ transplants.

A bioequivalence study was submitted to support the application comparing the applicant's test product Mycophenolate Mofetil 250 mg Capsules with the reference product CellCept 250 mg Capsules (Roche Registration Limited, UK), under fasting conditions. The applicant has stated that the bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on a being generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considered that the application could be approved at the end of procedure on 13 September 2018 (Day 210). After a subsequent national phase, a Marketing Authorisation was granted in the UK to Tillomed Laboratories Limited on 10 October 2018.

II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a size '1', two-piece, hard gelatin capsule, with a blue opaque cap and a brown opaque body with "EM" printed in black on the capsule cap and "250" printed in black on the capsule body, filled with white to off-white granular powder.

Each capsule contains 250 mg of mycophenolate mofetil, as the active substance. The product also contains pharmaceutical excipients in the capsule, capsule shell and printing ink namely, pregelatinised starch, croscarmellose sodium, povidone (K 90), magnesium stearate, gelatin, indigo carmine (E132), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172) and printing ink (which contains shellac, black iron oxide (E172) and potassium hydroxide). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in polyvinylchloride white opaque/aluminium foil perforated unit dose blisters, in pack sizes of 100 x 1 or 300 x 1 capsules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

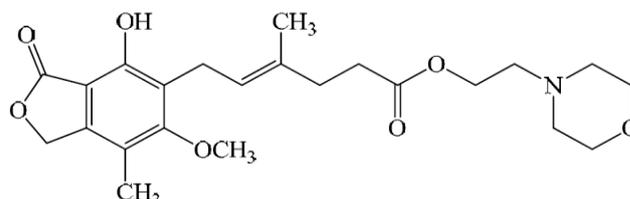
II.2 DRUG SUBSTANCE

Mycophenolate mofetil

INN: Mycophenolate mofetil

Chemical name: 2-(Morpholin-4-yl)ethyl (4E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate

Structure



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

M_r : 433.5

Appearance: White or almost white crystalline powder.

Solubility: Mycophenolate mofetil is practically insoluble in water, freely soluble in acetone, sparingly soluble in anhydrous ethanol

Chirality: Mycophenolate mofetil does not exhibit optical isomerism, as it does not contain asymmetric carbon atoms.

Polymorphism: Polymorphism is not reported in the literature for mycophenolate mofetil

Mycophenolate mofetil is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data, complying with the proposed specifications, are provided.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate safe, efficacious, stable, hard capsules, each containing 250 mg of mycophenolate mofetil, which were comparable in performance to CellCept 250 mg Capsules (Roche Registration Limited, UK). Suitable pharmaceutical development data have been provided for this application.

Comparative *in vitro* dissolution profiles have been provided for this product and the reference product. The dissolution profiles have been accepted.

With the exception of iron oxide red (E172), iron oxide yellow (E172), indigo carmine (E132) and the constituents of the printing ink (shellac, black iron oxide (E172) and potassium hydroxide), all the excipients comply with their respective European Pharmacopoeia monographs. Iron oxide red (E172), iron oxide yellow (E172) and indigo carmine (E132) are controlled to their respective in-house specifications. Shellac and black iron oxide (E172) are in compliance with their National Formulary specifications; potassium hydroxide is controlled to its United States Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. 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).

This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with full production-scale batches that have shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on future full-scale production batches.

Control of Finished Product

The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data complying with the release specifications have been provided. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf life of 2 years, with the special storage instructions 'Do not store above 30°C. Store in the original package in order to protect from moisture.' has been approved.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

Bioequivalence/Bioavailability

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.

II.4 Discussion on chemical, pharmaceutical and biological aspects

It is recommended that a Marketing Authorisation is granted for this application, from a quality point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of mycophenolate mofetil are well known, no new non-clinical studies are required and none have been provided.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology for mycophenolate mofetil.

Pharmacology

No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

III.2 Pharmacokinetics

No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

III.3 Toxicology

No new data have been submitted and none are required for this type of application. Refer to Section III.1, Introduction, above.

III.4 Ecotoxicity/Environmental Risk Assessment (ERA)

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. Since Mycophenolate mofetil Capsules are intended for generic substitution, it is not anticipated to lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.5 Discussion of the non-clinical aspects

It is recommended that a Marketing Authorisation is granted, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction.

The clinical pharmacology of mycophenolate mofetil is well-known. No new clinical pharmacokinetic data is provided or required for this application.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

In accordance with the regulatory requirements CPMP/EWP/QWP/1401/98 Rev 1/Corr**, Guideline on the Investigation of Bioequivalence, the Marketing Authorisation Holder submitted a bioequivalence study under fasting conditions to support the application. With the exception of data from the bioequivalence study detailed in Section IV.2, Pharmacokinetics below, no new pharmacodynamic or pharmacokinetic data are provided and none are required for this type of application.

IV.2 Pharmacokinetics

The pharmacokinetic (PK) profile of mycophenolate mofetil is well known. No new clinical pharmacokinetic data is provided or required for this application.

In support of the application, a bioequivalence study was submitted. Details of the study are provided below.

An open-label, randomised, two-treatment, two-period, two-sequence, single dose, crossover study comparing the applicant's test product Mycophenolate Mofetil 250 mg Capsules and the reference product CellCept 250 mg Capsules (Roche Registration Limited, UK) in healthy male subjects, under fasting conditions.

Subjects were dosed with either treatment after at least a 10-hour fast. Blood sampling was performed pre- and up to 72 hours post dose in each treatment period. The washout period between the treatment arms was 9 days. Plasma samples were analysed for mycophenolic acid the active metabolite of mycophenolic acid.

A summary of the pharmacokinetic results for mycophenolic acid are presented below:

Table 1: Bioequivalence evaluation of Mycophenolic Acid

Parameters (Units)	Geometric Least Squares Means and it's ratio (N = 49)			Intra subject %CV	90% Confidence Interval	Power (%)
	Test Product (T)	Reference Product (R)	(T/R)%			
C_{max} (ng/mL)	8280.727	7500.484	110.40	32.50	99.16% - 122.93%	96.14
AUC_{0-t} (hr*ng/mL)	10707.484	10288.208	104.08	13.20	99.54% - 108.82%	100.00
AUC_{0-inf} (hr*ng/mL)	12105.522	11304.350	107.09	14.73	101.90% - 112.54%	100.00

C_{max} maximum plasma concentration

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours

AUC_{0-inf} area under the plasma concentration-time curve from time zero to infinity

%CV Coefficient of variation

No pre-dose levels of mycophenolic acid were detected. Concentration was zero at time 0.00 for all subjects. T_{max} was not observed at the first sample time in any subject. C_{max} was within the validated range of the analytical test for all subjects.

Conclusion

In line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the 90% confidence intervals of the test/reference ratio for C_{max} and AUC values for lie within the acceptable limits (80.00% to 125.00%) for the primary evaluation – the active metabolite, MPA. Thus, the data support the claim that the applicant's test product, is bioequivalent to the reference product, CellCept 250 mg Capsules (Roche Registration Limited, UK), under fasting conditions.

IV.3 Pharmacodynamics

The clinical pharmacodynamics properties of mycophenolate mofetil are well-known. No new pharmacodynamic data were submitted and none are required for this type of application.

IV.4 Clinical Efficacy

The clinical efficacy of mycophenolate mofetil is well-known. No new efficacy data are presented or are required for this type of application.

IV.5 Clinical Safety

No new safety data were submitted and none are required for this type of application. The safety profile of mycophenolate mofetil is well-known. No new or unexpected safety issues arose from this application

IV.6 Risk Management Plan

The MAH has submitted a Risk Management Plan (RMP), 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.

A summary of safety concerns is listed in the table below:

Table 2: Summary of safety concerns

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Hypersensitivity • Teratogenic effects (spontaneous abortion and congenital malformations) • Serious infections including viral reactivation • Bone marrow suppression (leukopenia, thrombocytopenia, anaemia, pancytopenia), and associated haemorrhage/bleeding • Pure red cell aplasia (PRCA) • Bronchiectasis • Hypogammaglobulinaemia • Digestive system adverse events, including gastrointestinal tract ulceration, haemorrhage and perforation • Drug interactions with drugs when mycophenolate mofetil is concomitantly administered with drugs that interfere with enterohepatic recirculation • Convulsions • Hepatitis • Renal impairment • Toxicity in renal transplant patients with severe chronic renal impairment • Pancreatitis
Important potential risks	<ul style="list-style-type: none"> • Lymphomas and other malignancies, particularly of the skin • Exacerbations of rare hereditary deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT) • Risk of infection with live vaccines • Reduced effectiveness of vaccines • Potentially reduced mycophenolate mofetil efficacy when mycophenolate mofetil is concomitantly administered with rifampicin • Interstitial lung disease and pulmonary fibrosis • Increased risk of certain infections, possibly

	gastrointestinal haemorrhage and pulmonary oedema in elderly population
Missing information	<ul style="list-style-type: none"> • Use in cardiac or hepatic transplant patients with severe chronic renal impairment • Use in cardiac transplant patients with severe hepatic parenchymal disease • Use in paediatric cardiac or hepatic transplant patients • Use in paediatric population < 2 years in renal transplant • Treatment with mycophenolate mofetil during hepatic transplant rejection

Routine pharmacovigilance and risk minimisation activities are planned for all safety concern .Beyond the Product Information, routine risk minimisation measures concerns the legal status of the product, which is subject to restricted medical prescription (treatment should be initiated and maintained by appropriately qualified transplant specialists).

Consistent with the reference product CellCept (as per Pharmacovigilance Risk Assessment Committee (PRAC) recommendations), the MAH has proposed additional risks minimisation measures for the safety concern 'Teratogenic effects (spontaneous abortions and congenital malformations)' to educate physicians and patients to understand the risk of spontaneous abortion and congenital malformations associated with exposure to mycophenolate during pregnancy, as well as detail the measures that should be taken to mitigate the safety concern.

Educational material for the risk of spontaneous abortion and congenital malformations is proposed in the form of:

- Patient guide
- Guide for healthcare professionals

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted, from a clinical point of view.

V. USER CONSULTATION

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with mycophenolate mofetil is considered to have demonstrated the therapeutic value of the compound.

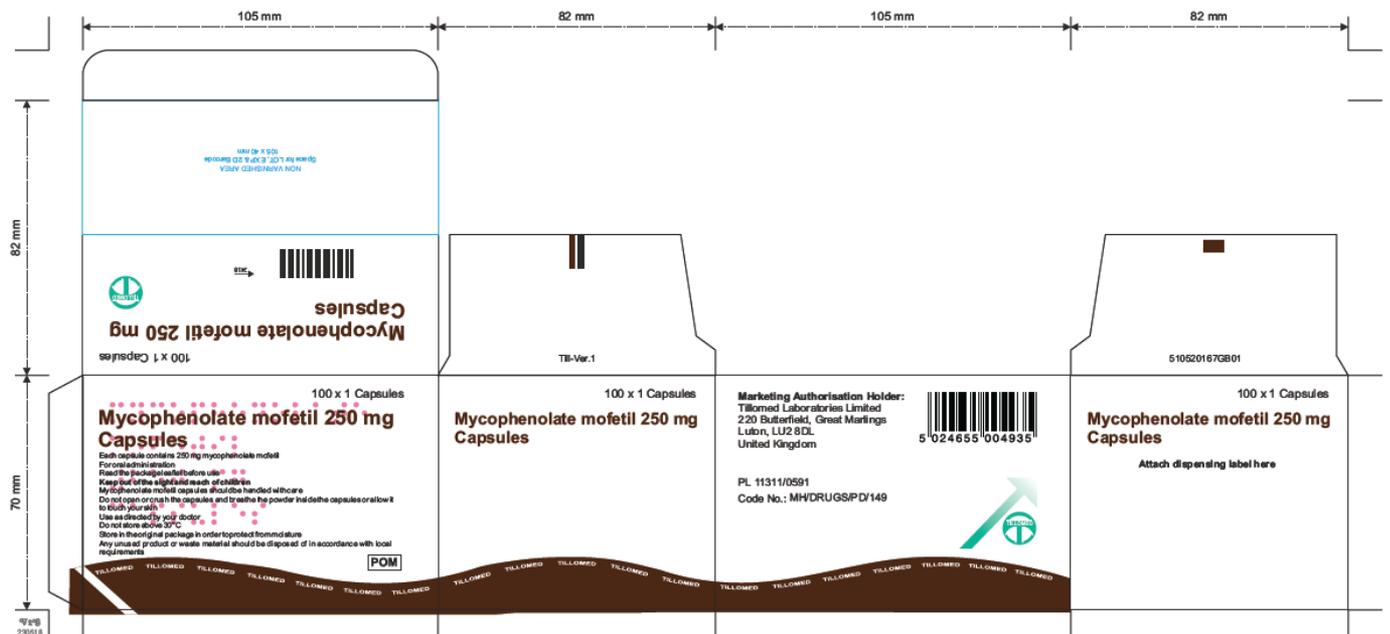
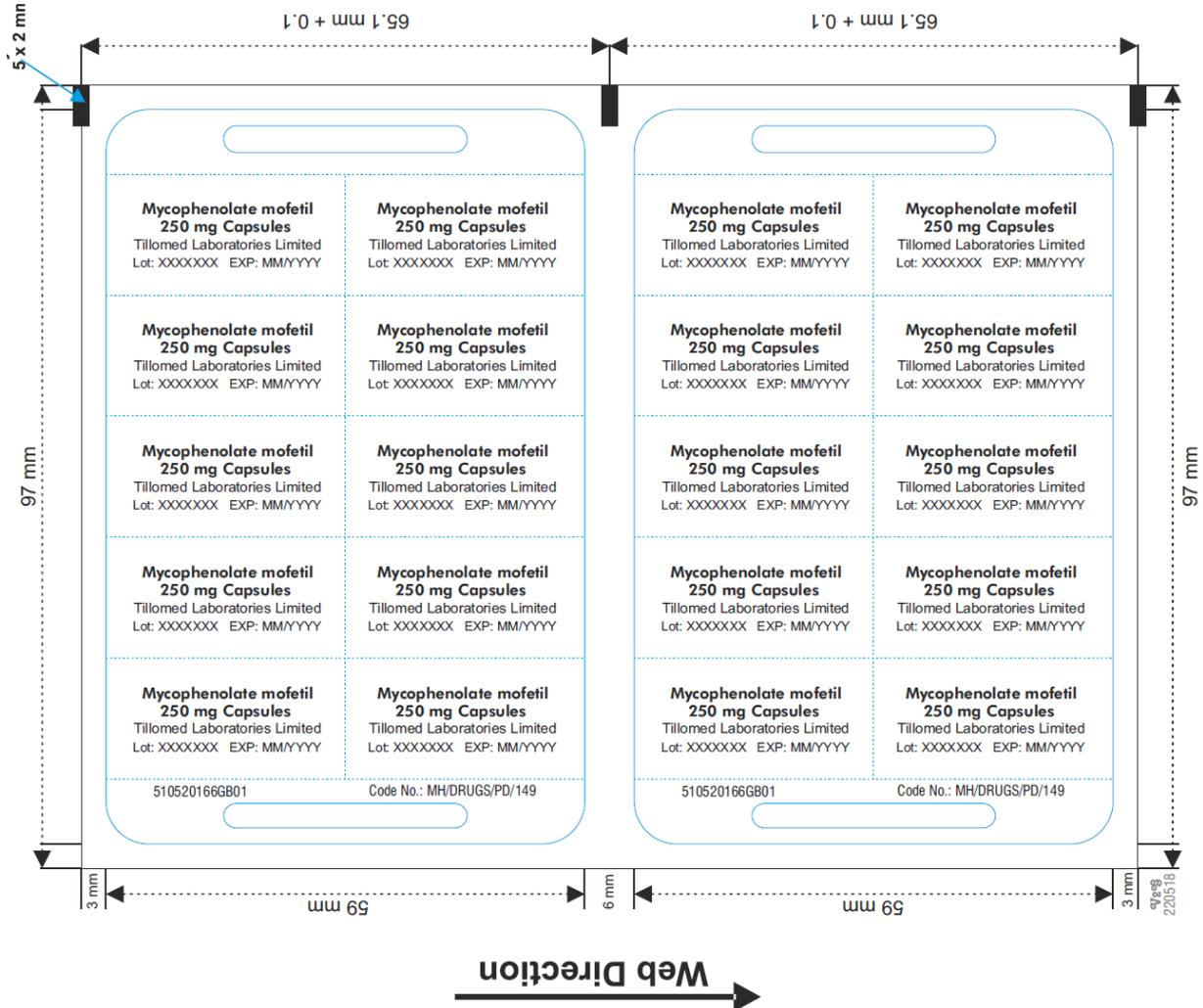
The clinical overview is adequate and bioequivalence has been demonstrated between the applicant's product, Mycophenolate mofetil 250 mg Capsules, and the reference product, CellCept 250 mg Capsules (Roche Registration Limited, UK). The benefit-risk of the applicant's Mycophenolate mofetil 250 mg Capsules is deemed to be comparable to that of the reference product, CellCept 250 mg Capsules (Roche Registration Limited, UK).

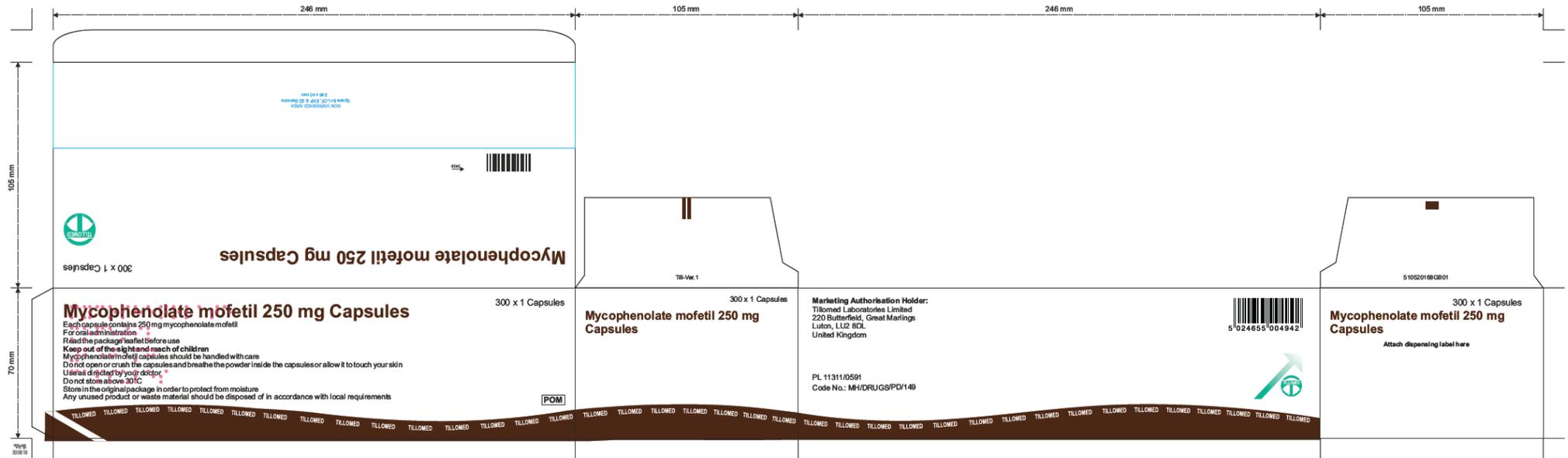
The benefit/risk assessment is, therefore, considered to be positive.

The grant of a Marketing Authorisation is recommended.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
 The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL is available on the MHRA website. The current labelling is presented below:





Moda - Showdesign s.r.l. Padova

Annex 1 - Table of content of the PAR update for MRP and DCP**Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report**

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)