EMA/CHMP/451012/2010

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Myclausen

Common name: mycophenolate mofetil

Procedure No. EMEA/H/C/1218

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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Table of contents

Page

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Herbert J. Passauer GmbH & Co. KG submitted on 17 August 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Myclausen, in accordance with the centralised procedure falling within the scope of the Annex to Regulation (EC) 726/2004 under Article 3 (3) – 'Generic of a Centrally authorised product'.

The legal basis for this application refers to Article 10(1) Generic application of Directive 2001/83/EC.

The chosen reference product is:

■ *Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:*

Product name, strength, pharmaceutical form: CellCept 500 mg tablets

Marketing authorisation holder: Roche Registration Limited

Date of authorisation: 14 February 1996

Marketing authorisation granted by:

Community

- Community Marketing authorisation number: EU/1/96/005/002 & 004

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: CellCept 500 mg tablets
- Marketing authorisation holder: Roche Registration Limited

- Date of authorisation: 14 February 1996
- Marketing authorisation granted by:

Community

- Community Marketing authorisation number(s): EU/1/96/005/002 & 004

Bioavailability study number(s): 3668

The Rapporteur appointed by the CHMP was Andrea Laslop

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 20 November 2008. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

- The application was received by the EMEA on 17 August 2009.
- The procedure started on 23 September 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2009.
- During the meeting from 18 – 20 January 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 January 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 February 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 March 2010.
- The summary report of the GCP inspection carried out between 23–26 February 2010 was issued on 8 April 2010.
- During the CHMP meeting from 19-22 April 2010, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 June 2010.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 July 2010.
- During the meeting on 19-22 July 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Myclausen on 22 July 2010.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 7 October 2010.

2. Scientific discussion

2.1. Introduction

Myclausen 500 mg film coated tablet is a generic medicinal product containing mycophenolate mofetil as active substance.
The active metabolite of mycophenolate mofetil, mycophenolic acid (MPA), is a selective, noncompetitive, reversible inhibitor of inosine monophosphate dehydrogenase, resulting in a potent inhibition of guanosine nucleotide synthesis. Due to its potent cytostatic effect on lymphocytes, the indication is in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.
The efficacy and safety of mycophenolate mofetil has been demonstrated in randomised, double-blind comparative studies in patients receiving allogeneic renal, cardiac or hepatic transplants, for prophylaxis of acute transplant rejection. A summary of these studies can be found in the EPAR of CellCept. Since this is a generic application the pivotal basis is the demonstration of bioequivalence with the reference medicinal product.
The indication proposed for mycophenolate mofetil is the same as authorized for the reference medicinal product CellCept.

2.2. Quality aspects

2.2.1. Introduction

Myclausen is presented as immediate release film coated tablets, containing 500 mg of mycophenolate mofetil as the active substance.
Other ingredients are defined in the SPC section 6.1.
The tablets are packaged in PVC/Alu blister packs.

2.2.2. Active Substance

The chemical name of mycophenolate mofetil is 2-(Morpholin-4-yl)ethyl (4E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoate. It is a white to off-white, not hygroscopic crystalline powder, practically insoluble in water. Its apparent partition coefficient in 1-octanol/water (pH 7.4) is 238. Its pKa is reported to be 5.6 for the morpholino group and 8.5 fior the mycophenolate moiety. It does not show polymorphism.
Mycophenolate mofetil is described in Ph Eur.

Manufacture

A Certificate of Suitability (CEP) granted by the EDQM has been presented covering the manufacturing of the active substance

Specification

Mycophenolate mofetil is described in the European Pharmacopoeia (Ph. Eur). The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance, appearance of solution solubility, melting point, identity, assay, related substances, heavy metals, loss on drying, sulphated ash, residual solvents, particle size and microbial contamination.
The drug substance specification of the drug product manufacturer is identical to the Ph. Eur. with additional requirements for residual solvents (Ph. Eur.), particle size (sieving) and microbial contamination (Ph. Eur.).
Analytical test results of three batches of active substance have been presented and all comply with the specifications.

Stability

Mycophenolate mofetil is described in the Ph.Eur. and the provided CEP includes the re-test period. Therefore no further information is required.
The re-test period and storage conditions of the drug substance are accepted.
In accordance with EU GMP guidelines1, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

2.2.3. Medicinal Product

Pharmaceutical Development

The main objective of the formulation development work was to develop a formulation that is comparable in performance to the reference product Cellcept
A discriminatory dissolution method for the determination of the release profile for release and stability purposes was developed.
The active substance particle size has been shown to have no significant effect in dissolution.
Comparative dissolution of two batches of reference products and one batch of Myclausen demonstrated that more than 85% of the drug substance is dissolved in 15 minutes, therefore the dissolution profiles can be considered as similar.
Myclausen 500 mg tablets were manufactured by wet granulation. The process was developed and optimized based on experience gained during manufacturing of pilot and full scale batches. The different choices leading to the final manufacturing process were described.
Comparative impurity profiles between the test and innovator batches are within the specification
All the excipients used in the manufacture of Myclausen are well known and widely used as pharmaceutical excipients. Most of the excipients are described in the Ph. Eur. No formal study of compatibility between the excipients and active substance was conducted but no compatibility issue was observed during stability studies

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

Adventitious agents

There is no BSE/TSE risk associated by any of the materials used since none of them are on animal origin.

Manufacture of the Product

The manufacturing process is a wet granulation process followed by coating of the tablets and packaging.
Prospective process validation was performed by testing three consecutive batches of Myclausen 500 mg film-coated tablets. All relevant and critical steps are controlled and well described.

Product Specification

The release and shelf life specification of Myclausen includes tests and limits for appearance (visually), identification of drug substance (HPLC, UV-at release only), identification of titanium dioxide (chemical reaction-at release only), loss on drying (Ph.Eur.-end of shelf life only) uniformity of dosage units (Ph.Eur.), disintegration (Ph.Eur.-end of shelf life only), dissolution (Ph.Eur.), assay (Ph.Eur.), related substances (Ph.Eur.), residual solvents (Ph.Eur.-at release only) and microbiological contamination (Ph.Eur.).
Full analytical testing as per the proposed drug product specifications was performed on six production scaled batches. All batches comply with the proposed release specifications.

Stability of the Product

Three full scale batches were put on long-term (25±2°C/60±5%RH) intermediate (30±2°C/65±5%RH) and accelerated (40±2°C/75±5%RH) stability testing conditions packaged in the material proposed for the marketed product.
Stability data were presented for up to 18 months under long term and intermediate conditions and up to six months under accelerated. No specific trends or significant changes were observed for any of the tested parameters.
Further supportive data were presented from two batches stored for up to 12 months under long-term and up to six months under accelerated conditions, and from three pilot batches from a different manufacturing site stored for 36 months under long-term conditions.
Photostability testing of Myclausen 500 mg film-coated tablets was accomplished according to the ICH Guidance for Industry, Q1B. Exposed samples and dark controls were tested. No difference was found between them.
In general, the results support the shelf life and storage conditions as defined in the SPC.
In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMEA.

2.2.4. Discussion and Conclusions on chemical, and pharmaceutical aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

2.3. Non-Clinical aspects

No non-clinical data were submitted with this application. The applicant provided an acceptable description of the pharmacological, pharmacokinetic and toxicological properties of mofetil mycophenolate based on published literature obtained through up-to-date literature searches. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. No further studies are required and the applicant has justified why no such data was provided. An overview based on a literature review is thus appropriate.

An Environmental Risk Assessment has been submitted by the applicant. Myclausen is a generic product, which is deemed interchangeable with already marketed products, and is unlikely to increase the combined sales volumes of mycophenolate mofetil-containing products thus not having an adverse effect on the environment.

2.4. Clinical Aspects

2.4.1. Introduction

This is an abridged application for film-coated tablets containing 500 mg mycophenolate mofetil. To support the marketing authorisation application, the applicant has submitted reports on two bioequivalence studies (study no 411-87-06-02-0001, a single dose, randomised, open-label, two-way crossover study under fasting conditions and study no 3668, a single dose, randomised, open-label, 4-period, 2-sequence, replicate crossover study under fasting conditions). The details of this study are summarised in Table 1.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of mycophenolate mofetil based on published literature; this was considered acceptable. The SPC is in line with the SPC of the reference product.

For the clinical assessment the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EPW/QWP/1401/98) in its current version as well as the Questions & Answers on the Bioavailability and Bioequivalence Guidelines (EMEA/CHMP/EWP/40326/2006) are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The CHMP has requested a routine GCP inspection of the clinical and bioanalytical facility of study 3668, which has taken place from 23 – 26 February 2010. The general GCP compliant outcome of the inspection raises no concerns on the reliability of the submitted study data. Trial data are considered as trustworthy and are recommended as acceptable.

Clinical studies

This is an abridged application for film-coated tablets containing 500 mg mycophenolate mofetil. To support the marketing authorisation application, the applicant has submitted reports on two bioequivalence studies (study no 411-87-06-02-0001, a single dose, randomised, open-label, two-way crossover study under fasting conditions and study no 3668, a single dose, randomised, open-label, 4-

period, 2-sequence, replicate crossover study under fasting conditions). The details of this study are summarised in Table 1:

Table 1: Summary of studies

Study identifier	Objective(s) of Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects
Study–No 411-87-06-02-0001	To assess the bioequivalence of an oral test preparation containing 500 mg mycophenolate mofetil (Mycophenolate mofetil film coated tablets 500 mg as compared to a market standard (CellCept 500 mg tablets) under fasting conditions	Monocentric, open, randomized, single-dose, two-period crossover trial	One (test) tablet and One (reference) tablet formulation, 500 mg, Oral	Healthy subjects, 85 enrolled (72 completed)
Study–No 3668	Bioequivalence study: to determine and compare rate and extent of absorption of MMF and MPA from a test formulation of MMF 500 tablets vs. the reference Cellcept 500 mg tablets under fasting conditions	4-period, 2-sequence, randomized, replicate crossover, open-label, single-dose, fasting study	One (test) tablet and One (reference) tablet formulation, 500 mg, Oral	Healthy subjects,44 enrolled (39 completed)

2.4.2. Pharmacokinetics

Study 411-87-06-02-0001

Methods

Study design

The study was a monocentric, open, randomized, single dose, two period crossover trial in healthy volunteers with a wash period of 7 days between the two periods.

Each study period lasted 4 days for each volunteer. Following a 12 hours overnight stay (day 0) and further 12 hours confinement (day 1) in the volunteer unit of the clinical centre, the volunteers reported as out-subjects on day 2 (24 and 36 hours post dose) and day 3 (48 hours post dose) in each study period for the respective blood sampling (pre-dose and 0:15, 0:30, 0:45, 1h, 1:30, 2h, 3h, 4h, 5h, 6h, 8h, 10h, 12h, 24h, 36h, and 48 hours post dose with separation of plasma).

Volunteers swallowed under fasting conditions (at least 10 hours overnight fasting) in the morning on day 1 in each period of the study either 1 film-coated tablet of the test product or 1 film-coated tablet of the reference drug always with 240 ml water. The volunteers fasted from food and beverages other than water, from 9 p.m. on the evening before dosing until lunchtime on the following day, approximately 4 hours post dose. Water was to be provided *ad libitum* until 1 hour before the drug administration on day 1 in each study period. Water was allowed again from 3 hours after drug

administration on day 1 in each study period. The total intake of water on day 1 of dosing later than 3 hours after drug administration was at least 1.5 liters. Concomitant medication was generally not allowed for the duration of the trial.

The wash-out phase between both study periods was 7 days.

The study protocol was signed on 25 June 2008. Final approval from the ethics review committee was received on 08 July 2008. The final study report was dated 24 June 2009.

TEST AND REFERENCE PRODUCTS

Test Product: Mycophenolate mofetil film tablets 500 mg
Manufactured by: Laboratorios Clausen, Montevideo - Uruguay
Batch No.: 00027
Manufacturing date: 02 June 2008
Expiry date: 01 June 2010

Reference Product: CellCept® 500 mg Tablet
Manufactured by: Roche Pharma AG, Germany
Batch No.: M181411
Expiry date: July 2010

POPULATION(S) STUDIED

85 healthy male volunteers were informed about the aim of the study and were asked for their informed consent. 13 volunteers were screened (n=13) but not included in the trial. According to the protocol 72 healthy volunteers were randomized in the present trial. The participants had to be between 18 and 55 years of age, and had to have a body mass index (BMI) within 18 to 29 kg/m2. The mean demographic data for all study completers are presented in Table 2.

Inclusion and exclusion criteria were presented and were acceptable for the product and for this type of study.

Table 2: Summary of Mean Demographic Data (±SD) of study completers (n=72)

(n=72)	Mean ± SD	Min – Max
Age [years]	28.3 ± 7.9	18.0 - 53.0
Height [cm]	174.9 ± 7.4	150.0 - 190.0
Weight [kg]	72.7 ± 9.8	50.0 - 94.0
BMI [kg/m2]	23.7 ± 2.5	18.3 - 28.7
male : female	72 : 0	

Analytical methods

Liquid chromatography with UV detection following liquid-liquid extraction is used as the analytical method.

The method was completely pre-study validated (Aug-Nov-2007) and revalidated immediately prior to the beginning of routine analysis (05-Dec-2008 to 15-Jan- 2009).

Pharmacokinetic Variables

All pharmacokinetic variables were determined in a model-independent way (using SAS Version 9.2). Determination was made for the active metabolite mycophenolic acid only.

AUC was calculated according to the linear trapezoidal method. The highest concentration really measured and the time at which it has been registered after each dose in any given volunteer was regarded as Cmax and tmax respectively. The t½ had to be determined by means of a linear regression using the terminal elimination phase of the drug and a semilogarithmic presentation.

The **primary** endpoints in the present trial were AUC0-tlast and Cmax of mycophenolic acid. These endpoints had to undergo descriptive and comparative statistical evaluation. **Secondary endpoint** was tmax of mycophenolic acid and had to undergo descriptive statistical evaluation together with the **additional endpoints** (AUC0-inf, MRT, and t½ of mycophenolic acid).

Statistical methods

For pharmacokinetic endpoints:

• parametric method (ANOVA-log) for AUC0-tlast and Cmax of mycophenolic acid

• covariates in the model: sequence, treatment, period, volunteer within sequence

• non-parametric method (Hauschke et al. 1990) tmax of mycophenolic acid

• 90% confidence interval for the ratios (test vs. reference) for AUC0-tlast and Cmax of mycophenolic acid

For evaluation of safety:

• descriptive statistical evaluation only.

Bioequivalence:

The 90% confidence intervals of log-transformed values were calculated for the intra-individual ratio test vs. reference for AUC0-tlast and Cmax of mycophenolic acid and then compared to the pre-defined (in study protocol) acceptance limits for AUC0-tlast (80 - 125 %) and for Cmax (80 - 125 %). The 90% confidence interval was calculated for the intra-individual ratio for the difference of tmax (test-reference) and descriptively assessed.

Results

A total number of 72 volunteers completed the trial according to the protocol. The samples of 72 volunteers were analyzed and 72 volunteers were subject to statistical evaluation. There were no drop-outs.

The endpoints of the analysis of mycophenolic acid after an oral single dose of 1 film-coated tablet (=500 mg mycophenolate mofetil) of the test preparation who were subject to pharmacokinetic and statistical evaluation are summarized in Table 3.

Table 3: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median range) for mycophenolic acid (n=72)

Treatment	AUC0-tlast hrs*µg/ml	$AUC_{0-\infty}$ hrs*µg/ml	C_{max} µg/ml	t_{max} hrs	$T_{1/2}$ hrs
Test	24.33 (SD=6.98)	27.38 (SD=8.01)	11.32 (SD=4.84)	0.66 (0.25-6.00)	15.19 (5.98-36.11)
Reference	22.70 (SD=5.79)	25.72 (SD=7.25)	9.93 (SD=4.74)	0.77 (0.25-4.00)	16.02 (5.91-80.72)
***Ratio (90% CI)**	1.0629 (1.0277-1.0992)		1.1855 (1.0431-1.3473)		
ANOVA-log CV (%)	12.16 %		48.61 %		

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC0-tlast area under the plasma concentration-time curve from time zero to 24 hours
C_{max} maximum plasma concentration
T_{max} time for maximum concentration
$T_{1/2}$ half-life

The 90% confidence interval for the ratio test/reference of $AUC_{0-tlast}$ for mycophenolic acid calculated by means of the parametric method (ANOVA-log) was between 1.0277 and 1.0992 and thus within the acceptance limits (80 – 125 % for log-transformed values).

The 90% confidence interval for the ratio test/reference of Cmax for mycophenolic acid calculated by means of the parametric method (ANOVA-log) was between 1.0431 and 1.3473, and thus outside the acceptance range (80 - 125 % for log-transformed values).

Therefore, bioequivalence has not been demonstrated between the reference and test product in this study.

The applicant performed an evaluation of these study results and identified a group of volunteers in which both products performed in an almost identical manner in terms of AUC and Cmax (more than 50 % of the subjects), and another group in which the Cmax of the reference product was registered later and was lower when compared with the test product (43 % of subjects). Since the latter cases were accompanied by a prolonged lag time and by altogether lower drug concentrations, the clinical results and pharmaceutical data were examined and compared for the reference product. The applicant suggested that in volunteers with a later Cmax, tablets or partly dissolved tablet aggregates from one or both formulations reached the duodenum before being completely dissolved. The resulting concentration vs. time curve that would be lower (regarding Cmax) and shifted to the right (regarding Tmax), as the dissolution rate and extent at higher pH values (as observed in the duodenum and small intestine) would be slower and less complete. A further evaluation of the dissolution of both study batches (test and reference) revealed no plausible *in vitro* explanation for the results observed *in vivo*; more than 85% of the drug substance was dissolved within 15 minutes. Also both products had very short disintegration times. Based on this the MAH concluded that no further pharmaceutical development was to be carried out on the test product.

The protocol design for Study 411-87-06-02-0001 had however several shortcomings, which were improved and/or addressed in the protocol design for a new study (Study 3668; see below). The MAH concluded that only the second trial (Study No. 3668) should be regarded as the pivotal and relevant trial for the assessment of the present application.

Study 3668

Methods

Study design

This was a four-period, two-sequence, replicate crossover (reference-test-reference-test), open label, single dose bioequivalence study of Mycophenolate Mofetil 500mg tablets versus CellCept 500mg tablets in healthy, non-smoking male subjects under fasting conditions.

Subjects were admitted to the clinic the day before dosing, and remained until the 24 hour post-dose blood draw of each period, at which time they were allowed to leave the clinic and after which they were required to return for subsequent blood draws. Following an overnight fast, subjects received 1 tablet of the test product or 1 tablet of the reference product on Day 1 of each study period. Water was provided *ad libitum* until 1 hour pre-dose and after 1 hour post-dose. The only fluid intake allowed during this time was 240 mL of ambient temperature dosing water. The subjects fasted overnight for at least 10 hours before drug administration. No food was allowed for at least 4 hours post-dose. At 4.5, 9.5, and 13.5 hours post-dose, standardized meals and beverages were provided to the subjects. All meals and beverages were free of alcohol, grapefruit products, xanthines and caffeine and were identical for all study periods. No concomitant medications were permitted during the study.

During each study period, 21 blood samples were collected from each subject, for pharmacokinetic and statistical analyses. Over the course of the entire study, approximately 544.5 mL of blood was collected from each subject. Blood samples were collected from each subject at the following timepoints: 0 (pre-dose), and at 0.17 (10 minutes), 0.25 (15 minutes), 0.33 (20 minutes), 0.5 (30 minutes), 0.67 (40 minutes), 0.83 (50 minutes), 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 36, and 48 hours post-dose.

There was a 1-week washout period between study treatments.

The clinical part of the study was undertaken between 29 April 2009 and 20 May 2009. The analytical portion of study 3668 was conducted from May 26, 2009 to June 8, 2009.

> The study protocol was signed on 11 March 2009. Final approval from the ethics review committee was received on 06 March 2009. The final study report was dated 05 August 2009.

Test and reference products

Test Product:	Mycophenolate mofetil film tablets 500 mg
Manufactured by:	Laboratorios Clausen, Montevideo - Uruguay
Batch No.:	00027
Manufacturing date:	02 June 2008
Expiry date:	01 June 2010

Reference Product:	CellCept® 500 mg Tablet
Manufactured by:	Roche Pharma AG, Germany
Batch No.:	M9061B01
Expiry date:	July 2011

Population(s) studied

The participants had to be between 18 and 55 years of age, and had to have a body mass index (BMI) within 18.5 to 29.9 kg/m2. Inclusion and exclusion criteria were presented and were acceptable for the product and for this type of study. All subjects met the inclusion criteria. The mean demographic data for all study completers are presented in Table 4.

Table 4: Summary of Mean Demographic Data (±SD) of study completers (n=39)

(n=39)	Mean ± SD	Min – Max
Age [years]	37.7.3 ± 9.6	21.0 - 55.0
Height [cm]	174.0 ± 6.6	161.0 - 185.0
Weight [kg]	77.9 ± 9.7	58.0 - 94.0
BMI [kg/m2]	25.7 ± 2.5	19.8 - 29.8
male : female	39 : 0	

Analytical methods

Mycophenolate mofetil and its metabolite were analysed by HPLC with Electrospray Ionization. The analytes were separated by reverse phase chromatography. The method was adequately validated.

Pharmacokinetic Variables

The pharmacokinetic parameters for mycophenolic acid derived for both treatments using standard, non-compartmental methods (using SAS Version 9.1) were:

Primary parameters:

- AUC0-t = area under the concentration-time curve from time zero to time of last measurable concentration, calculated using the linear trapezoidal rule

- AUC0-inf = area under the concentration-time curve from time zero to infinity

- Cmax = maximum plasma concentration observed after dosing

Secondary parameters:

- Tmax = time occurrence of Cmax

- Kel = first order terminal elimination rate constant

- t½ = terminal half-life

Statistical methods

Descriptive statistics was calculated for plasma concentrations and for all PK parameters (mycophenolate mofetil and mycophenolic acid). Individual and mean plasma concentration versus time curves were plotted on linear and semi-logarithmic scales. Plasma concentration versus time curves were labelled appropriately. Using Mixed procedures in SAS, ANOVA was performed on natural logarithmic (ln) transformed parameters AUC0-t, AUC0-inf, Cmax and on untransformed parameters t½, Kel and Tmax at the significance level of 0.05. The intra-subject coefficient of variation (CV) within test and reference formulation was calculated for AUC0-t, AUC0-inf, and Cmax using the ANOVA

residual error. The ratio (Test/Reference) of geometric LSMs along with the 90% CI was also calculated according to the following comparison: **Test** (Mycophenolate Mofetil 500 mg Tablets) versus **– Reference** (CellCept® 500 mg Tablets).

The bioequivalence assessment was based on the metabolite, mycophenolic acid. The applicant argued that as the parent compound exhibits a high degree of pre-systemic metabolism to the active metabolite, mycophenolic acid, it is unlikely that the pharmacokinetics of the parent compound can be adequately characterized. Bioequivalence was determined if the 90% CI for the ratio (Test/Reference) of geometric LSMs is within the range of 80.00% to 125.00% for the parameters AUC0-t, AUC0-inf and Cmax.

Results

44 healthy male volunteers were dosed in Period I of the study, 39 of whom completed the study. One subject withdrew because of an adverse event (AE; flu), 1 subject was dismissed because the Principal Investigator felt it was in his best interests (hemoglobin level outside of the acceptable range), 1 subject was dismissed because of administrative reasons (positive nicotine screen at Period IV check-in) and 2 subjects withdrew for personal reasons.

The mean pharmacokinetic parameters for mycophenolic acid are summarized in table 5.

Table 5: PHARMACOKINETIC PARAMETERS FOR MYCOPHENOLIC ACID:

Pharmacokinetic Parameters	**Geometric Mean (%CV) Arithmetic Mean ± SD**			
	CellCept® 500 mg Tablets (A)		**Mycophenolate Mofetil 500 mg Tablets (B)**	
	First Administration (n=42)	**Second Administration (n=41)**	**First Administration (n=42)**	**Second Administration (n=41)**
AUC0-t (xx) (µg·hr/mL)	26.83 (32.36) 27.97 ± 9.05	27.12 (27.12) 28.15 ± 7.63	27.10 (25.85) 27.98 ± 7.23	26.35 (27.19) 27.36 ± 7.44
AUC0-inf (µg·hr/mL)	31.65 (30.69) 32.81 ± 10.07 ♠	31.72 (27.15) 33.03 ± 8.97 ♥	32.27 (23.64) 33.04 ± 7.81 ♣	31.67 (27.15) 32.71 ± 8.88 ♦
Cmax (µg/mL)	12.85 (51.35) 14.88 ± 7.64	14.38 (45.65) 16.28 ± 7.43	14.30 (37.75) 15.49 ± 5.85	13.23 (39.33) 14.64 ± 5.76
Tmax (hr)*	0.53 (0.25 – 6.00)	0.52 (0.25 – 2.50)	0.51 (0.25 – 2.00)	0.67 (0.25 – 2.50)
t½ (hr)	12.90 ± 4.81 ♠	13.99 ± 5.88 ♥	13.32 ± 3.31 ♣	13.26 ± 3.77 ♦
Kel (hr-1)	6.11E-02 ± 2.37E-02 ♠	8.19E-02 ± 1.45E-01 ♥	5.52E-02 ± 1.37E-02 ♣	5.77E-02 ± 2.17E-02 ♦

* median (min – max)
♠ n = 30
♣ n = 28
♥ n = 29
♦ n = 25
(xx) AUC0-t**:** Area under the concentration-time curve from time zero to 48h
The relative bioavailability analysis results for AUC0-t, AUC0-inf, and Cmax are summarized in Table 6.

Table 6: ***Relative Bioavailability Analysis of test product (B) versus reference product (A) for Mycophenolic Acid***

Parameter	90% C.I.	Ratio of means	Intra-Subject CV	
			Treatment A	Treatment B
AUC0-t	95.74% to 102.64%	99.13%	16.17%	9.43%
AUC0-inf	98.41% to 111.83%	104.91%	13.11%	7.51%
Cmax	91.93% to 111.05%	101.04%	41.42%	30.87%

Treatment A: CellCept® 500 mg Tablets
Treatment B: Mycophenolate Mofetil 500 mg Tablets

The statistical results indicated that test/reference geometric mean ratios and the 90% confidence intervals for AUC0-t, AUC0-inf, and Cmax of mycophenolic acid were within the 80.00% - 125.00% range.

Therefore, bioequivalence was established between the test formulation and the reference product under single-dose, fasting conditions.

Safety data
Study 411-87-06-02-0001
No serious adverse events were registered in the course of the trial. A total number of three non-serious adverse events were registered in three volunteers. Two adverse events occurred in two subjects after administration of the test product, the other one after exposure to the reference formulation.

All three adverse events were headache. A causal relationship is possible. Headache is a common adverse event of mycophenolate mofetil use.

Study 3668
No serious adverse events were registered in the course of the trial. Nineteen subjects experienced a total of 35 adverse events during the study. The most frequent adverse events are expressed as fractions, relative to the total number of adverse events experienced after each treatment. After treatment with CellCept® 500 mg Tablets, the most frequent adverse event was headache (3/6). After treatment with Mycophenolate Mofetil 500 mg Tablets, the most adverse events were the following: dizziness (2/17) and headache (2/17). At the end-of-study examination, the most frequent adverse events were the following: blood creatinine increased (2/11) and blood urea increased (2/11). No adverse event was reported more than once after the post-study examination (1 adverse event total). Nineteen adverse events were "possibly" related to the study drug. All subjects who experienced adverse events during this study recovered completely.

The observations in healthy volunteers did not differ from the known safety profile of mycophenolate mofetil.

2.4.3. Pharmacodynamics

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

Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.4. Discussion and Conclusion on Clinical aspects

In this dossier, two bioequivalence trials were presented. Mycophenolic acid was the analyte measured in both trials which was considered acceptable by the CHMP. In the first trial, study No. 411-87-06-02-0001, AUC was within the bioequivalence limits (80% to 125%) but not the C_{max}. The second trial, study No. 3668, with a replicate cross-over design showed BE for both AUC and C_{max}. In their responses to the LoOI, the Applicant presented a well researched analysis of possible reasons for the divergent results of the two submitted bioequivalence studies.

The Applicant further investigated if differences in the dissolution profiles and disintegration times for the test and reference products could be responsible for the observed differences in Cmax. This possibility was excluded, and therefore there was no need to reformulate the test product. Protocol design aspects comparing the two trials were discussed in detail. From the comparative analysis it was concluded that the improved design, stricter standardisation and higher number of blood sampling points implemented in the second BE study could have contributed to the convincing demonstration of bioequivalence. It is therefore supported that study 3668 can be regarded as the pivotal trial in this generic application.

Furthermore, as requested by CHMP, the Applicant presented a combined analysis of PK data from both studies. This analysis resulted in 90% confidence intervals for AUC and C_{max} which were contained in the acceptance range of 80%-125%. As there was a significant treatment-by-study interaction, the additional value of these results over the single studies may be regarded as limited. Nevertheless, due to the rationale provided above, it is supported that study 3668 can be regarded as the pivotal trial.

2.5. Pharmacovigilance

PSUR

According to Volume 9-Pharmacovigilance 1.4.2.5.2, less frequent PSURs than customary for new medicinal products are appropriate. The PSUR submission schedule should follow the PSUR schedule for the reference products.

Description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.
The MAH must ensure that the system of pharmacovigilance, as described in version 1.2 presented in Module 1.8.1. of the Marketing Authorisation Application, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The application is based on a reference medicinal product for which no safety concerns requiring specific risk minimization activities have been identified.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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*

2.6. Benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

This application concerns a generic version of mycophenolate mofetil tablets. The reference product Cellcept is indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. No nonclinical studies have been provided for this generic application but an adequate summary of the available nonclinical information for the active substance was presented. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The pivotal basis form bioequivalence studies with a four-period, two-sequence, replicate crossover, open label design (study 3668). The study design was considered adequate; a single dose fasting study was appropriate as there is no food effect on the bioavailability of mycophenolate mofetil. Mycophenolic acid was the analyte for the bioequivalence assessment which was considered acceptable. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Myclausen met the protocol-defined criteria for bioequivalence when compared with the reference product. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.7. Recommendation

Based on the CHMP review of available data, the CHMP considered by consensus that the benefit/risk ratio of Myclausen in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejections in patients receiving allogeneic renal, cardiac or hepatic transplants was favourable and therefore recommended the granting of the marketing authorisation.