European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT
FOR
Myfenax

International Nonproprietary Name:
Mycophenolate mofetil

Procedure No. EMEA/H/C/884

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

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Teva Pharma B.V. submitted on 16 June 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Myfenax, 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).
The applicant Teva Pharma B.V. submitted on 16 June 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Myfenax.

The chosen reference product is:

■ Reference 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
  Cellcept 250 mg Capsules
  Cellcept Powder for oral suspension: 1 g/5 ml
  Cellcept Powder for concentrate for solution for infusion 500mg
- Marketing authorisation holder: **Roche Registration Limited**
- Marketing authorisation granted by:
  - Community
- First authorisation: Date **14-02-1996** Member State: **Community**

■ 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
  Cellcept 250 mg Capsules
- Marketing authorisation holder: : **Roche Registration Limited**
- Date of authorisation: (dd-mm-yyyy): **14-02-1996**
- Marketing authorisation granted by:
  - Community
- (Community) Marketing authorisation number(s): **EU/1/96/005**
- Bioavailability study number(s):

For the 250 mg capsules:
Study No 2006-1164
Study No 2006-1266

For the 500 mg tablets:
Study No 2006-1184
Study No 2006-1267
Study No 2007-1335

The Rapporteur appointed by the CHMP was:

Rapporteur Ian Hudson

Scientific Advice:
The applicant did not seek scientific advice at the CHMP.

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 16 June 2007.
- The procedure started on 20 July 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 October 2007.
- During the meeting 12-15 November 2007, 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 16 November 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 November 2007.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 November 2007.
- During the meeting on 10-13 December 2007, 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 Myfenax on 13 December 2007. The applicant provided the Letter of Undertaking on the follow-up measures to be fulfilled post-authorisation on 11 December 2007.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 21 February 2008.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Myfenax 500 mg film coated tablet and 250 mg capsule is a generic medicinal product containing mycophenolate mofetil as active substance.

The active metabolite of mycophenolate mofetil, mycophenolic acid (MPA), is a selective, non-competitive, 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.

The indication proposed for mycophenolate mofetil is the same as authorized for the reference medicinal product CellCept.

2.2 Quality aspects

Introduction

Myfenax is presented in the form of film coated tablets and hard capsules.

The capsules contain 250 mg of mycophenolate mofetil as active substance. Other ingredients are defined in the SPC section 6.1.
The film coated tablets contain 500 mg of mycophenolate mofetil as active substance. Other ingredients are defined in the SPC section 6.1.

Tablets and capsules are packaged into blisters made of transparent PVC/PVDC/Al.

Active Substance

The chemical name of mycophenolate mofetil is 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. It is a white to off-white, not hygroscopic crystalline powder, practically insoluble in water. It does not show polymorphism. Mycophenolate mofetil is described in Ph Eur.

- Manufacture

The applicant refers to two ASMFs. Drug substance by the second supplier may be manufactured by two different manufacturers.
Mycophenolate mofetil sourced from the first ASMF holder is prepared from mycophenolic methyl ester which is prepared from mycophenolic acid (MPA). MPA used in the manufacture of mycophenolate mofetil is manufactured by fermentation using appropriate and defined fungi strains. Sufficient information on the inoculum media, fermentation media and the purification of MPA is provided. The validation data of the manufacturing process and the specifications for all raw materials and mycophenolate mofetil are provided and considered satisfactory.

Mycophenolate mofetil sourced from the second ASMF holder is obtained from two similar synthetic routes. In brief, mycophenolate mofetil is prepared from mycophenolic acid by condensation with morpholine-2-ethanol in the presence of catalyst to yield crude mycophenolate mofetil which is then purified, recrystallised and dried to yield the active substance. MPA is manufactured by fermentation

using appropriate and defined fungi strains. Sufficient information on the inoculum media, fermentation media and the purification of MPA are provided.
Satisfactory process validation data for batches from both sites are provided. The specification limits for all raw materials and mycophenolate mofetil have been provided and are also considered satisfactory.
In summary, sufficient information has been provided to demonstrate that active substance manufacture from both sources are equivalent in all relevant quality attributes.

- Specification

The drug substance specification as tested by the finished product manufacturer includes tests for Appearance (Visual), Identification (PhEur), Appearance of solution (PhEur), Loss on drying (PhEur), Heavy metals (PhEur), Sulphated ash (Ph.Eur), Related substances (PhEur), Assay (PhEur), Residual solvents (GC), Particle size (laser diffraction). In addition the drug substance sourced from the second supplier is tested for Bulk and Tapped Density.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the active substance.

Batch analysis data of three batches of active substance from each manufacturer are provided. The results are within the specifications and consistent from batch to batch.

- Stability

Long-term and accelerated stability data for three pilot and commercial batches from the first supplier up to 24 months and 18 months respectively in line with ICH guidance were presented. Accelerated data was presented for all batches used in long-term stability studies up to 6 months. All data are within specifications.
The proposed re-test period is justified based on the stability results when the active substance is stored in the original packing material.

Drug substance by the second supplier may be manufactured by two different manufacturers.
Long-term stability data for up to 18 months in line with ICH guidance were presented for seven batches manufactured at the first site. Accelerated data was presented for all batches used in long-term stability studies up to 6 months.
Long-term and accelerated stability data were presented for up to 6 months in line with ICH guidance for three batches manufactured at the second site.
All stability data, including impurities from the two manufacturing sites are well within specifications.
The proposed re-test period is justified based on the stability results when the active substance is stored in the original packing material.

Medicinal Product

Hard capsules

- Pharmaceutical Development

The aim of the development was to obtain immediate release capsules containing qualitatively and quantitatively the same drug substance as the reference product, CellCept 250mg capsules, and exhibit the same bioavailability.

The excipients selected are commonly used for the manufacture of pharmaceutical preparations. These are pregelatinised starch (filler), croscarmellose sodium (disintegrant), povidone (K-90F) (binder) and magnesium stearate (lubricant). A satisfactory declaration that the printing ink complies with the Directive 95/45/EC is provided. Appropriate certificates of suitability were also provided for the gelatin used in the capsules shell.

Comparative dissolution profiles were generated for the reference biobatch (CellCept 250mg capsules) and test biobatch. The chosen dissolution conditions are the most discriminative.

Bioequivalence studies were performed for both the 250 mg strength (capsules) and the 500 mg strength (tablets) under fasting and fed conditions. Plasma concentrations of mycophenolic acid were determined using a validated LCMS method in bioavailability studies. The method is valid with respect to specificity, accuracy, precision, linearity, range, LOD/LOQ and robustness.

The capsule impurity profile of the biobatch is very similar to the reference biobatch. Satisfactory certificates of analysis for the reference biobatch and test biobatch were provided.

The product is intended to be packed in PVC/PVdC/Al blisters. The suitability of the packaging system was determined in the stability studies.

- Manufacture of the Product

The finished product will be manufactured in either of two sites. The manufacturing process is a standard method for capsule manufacture comprising dry mixing, wet granulation, blending and capsule filling. The manufacturing process is identical for both manufacturing sites.

Satisfactory process validation has been conducted on one batch manufactured in the first manufacturing site and two pilot batches manufactured in the other.

- Product Specification

The product specifications include tests by validated methods for Appearance (visual), Identification (Mycophenolate: HPLC/UV, Indigocarmine, Erythrosine, Sunset yellow, Titanium dioxide: TLC), Uniformity of dosage units (PhEur), Dissolution (PhEur), Assay (HPLC), Degradation products (HPLC), Microbial contamination (PhEur).
Degradation products have been evaluated and found to be acceptable from the point of view of safety. The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Satisfactory batch analysis data have been provided for four batches (two from each site). All parameters, including impurities are within specifications. The impurity profile is comparable to the reference product.

- Stability of the Product

Stability data were presented for four batches manufactured at both sites (two from each site).
Data up to 12 months at 25^{o}C/60%RH and 6 months at 40^{o}C/75%RH were presented for two batches for one site. Data up to 9 months stored at 25^{o}C/60%RH and up to 6 months stored at 40^{o}C/75%RH were presented for the other two batches manufactured at the other site. All data, including impurities and degradation products remained well within specification.

Based on the stability studies results the shelf life and storage conditions as defined in the SPC are supported.

<u>Film coated tablets</u>

- Pharmaceutical Development

The aim of the development was to obtain immediate release tablets containing qualitatively and quantitatively the same drug substance as the reference product, CellCept 500mg tablets, and exhibit the same bioavailability.
The excipients selected are commonly used for the manufacture of pharmaceutical preparations. These are microcrystalline cellulose (diluent), croscarmellose sodium (disintegrant), povidone (binder) and

magnesium stearate (lubricant). The coating agent contains hypromellose (film-coating agent), macrogol (plasticiser), talc (lubricant and glidant), titanium dioxide (opacifier), and colourants.

Comparative dissolution profiles were generated for the reference biobatch (CellCept 500mg tablets)) and test biobatch. The chosen dissolution conditions are the most discriminative.
Comparative impurity profiles between the test and innovator biobatches are almost identical

The product is intended to be packed in PVC/PVdC/Al blisters. The suitability of the packaging system was determined in the stability studies.

- Manufacture of the Product

The finished product will be manufactured in either of two sites. The manufacturing process is a standard method for tablet manufacture comprising blending, slugging, milling, compression, coating and packaging.
Satisfactory process validation has been conducted on one batch manufactured in the first manufacturing site and two pilot batches manufactured in the other.

- Product Specification

The product specifications include tests by validated methods for Appearance (visual), Identification (Mycophenolate mofetil: HPLC/UV, Lake of Indigo carmine, Iron oxides: Visual, Titanium oxide: UV), Uniformity of dosage units (PhEur), Dissolution (PhEur), Assay (HPLC), Related substances (HPLC), Microbial contamination (PhEur).
Degradation products have been evaluated and found to be acceptable from the point of view of safety. The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.

Satisfactory batch analysis data have been provided for four batches (two from each site). All parameters, including impurities are within specifications. The impurity profile is comparable to the reference product and there are no unqualified impurities present.

- Stability of the Product

Stability data were presented for four batches manufactured at both sites (two from each site).
Data up to 12 months at 25^{o}C/60%RH and 6 months at 40^{o}C/75%RH were presented for two batches for one site. Data up to 9 months stored at 25^{o}C/60%RH and up to 6 months stored at 40^{o}C/75%RH were presented for the other two batches manufactured at the other site. All data, including impurities and degradation products remained well within specification.

Based on the stability studies results the shelf life and storage conditions as defined in the SPC are supported.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the drug substance and drug product have 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. At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve this as Follow-Up Measures after the opinion, within an agreed timeframe.

2.3 Non Clinical aspects

The proposed products are Myfenax 500 mg film coated tablet and 250 mg capsule claiming to be generic products of CellCept® 500 mg tablets and 250 mg capsules (Roche Registration Ltd), respectively.

Pharmacology

The active substance mycophenolate mofetil is the 2-morpholinoethyl ester of mycophenolic acid (a fermentation product of several *Penicillium* species). Mycophenolic acid is a selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH). Inhibition of IMPDH leads to selective inhibition of B and T lymphocyte cell types. Inhibition of B and T lymphocytes has been used to provide immunosuppression for the prevention of acute rejection in patients receiving allogenic renal, cardiac or hepatic transplants.

The original products are listed as CellCept® 500 mg tablets and 250 mg capsules which were authorised in February 1996 in the EU.

Pharmacokinetics/Toxicology

The pharmacological, pharmacokinetic and toxicological properties of mofetil mycophenolate are well known. As mycophenolate mofetil is a well known active substance, no further studies are required and the applicant has provided none. An overview based on a literature review is thus appropriate.

2.4 Clinical Aspects

Introduction

Mycophenolate mofetil belongs to the immunosuppressant group. Its active metabolite, mycophenolic acid (MPA), is a potent inhibitor 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.

Pharmacodynamics

Mycophenolate mofetil is the 2-morpholinoethyl ester of MPA. MPA is a potent and reversible inhibitor of inosine monophosphate dehydrogenase. T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines whereas other cell types can utilise salvage pathways. For this reason, MPA has more potent cytostatic effects on lymphocytes than on other cells.

Pharmacokinetics

Following oral administration, mycophenolate mofetil undergoes rapid and extensive absorption and complete presystemic metabolism to the active metabolite, MPA (mycophenolic acid). The immunosuppressant activity of mycophenolate mofetil is correlated with MPA concentration. The mean bioavailability of oral mycophenolate mofetil is 94% relative to IV mycophenolate mofetil. Food had no effect on the extent of absorption when administered at doses of 1.5 g BID to renal transplant patients. However, MPA Cmax was decreased by 40 % in the presence of food.
MPA is 97 % bound to plasma albumin.
As a result of enterohepatic recirculation, secondary increases in plasma MPA concentration are observed at approximately 6 – 12 hours post-dose.
MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active.
A negligible amount of drug is excreted as MPA (< 1 % of dose) in the urine. Most (about 87 %) of the administered dose is excreted in the urine as MPAG.

GCP aspects

The applicant has submitted a statement that all clinical bioequivalence studies were performed in compliance with GCP and ethical requirements of Directive 2001/83/EC, including the archiving of essential documents.

Clinical studies

To confirm that the applicant's medicinal products are generic medicinal products of the innovator's tablets and capsules, five bioequivalence studies have been conducted to support this application. Bioequivalence studies were performed for both strengths (250 mg and 500 mg) under fasting and fed conditions:

For the 250 mg capsules:

Study No 2006-1164 (fasting)
Study No 2006-1266 (fed)

For the 500 mg tablets:

Study No 2006-1184 (fasting)
Study No 2006-1267 (fed)
Study No 2007-1335 (fed)

As it has been established that taking mycophenolate mofetil with food reduces the Cmax whilst not affecting the extent of absorption the applicant has conducted the studies under fed as well as fasting condition.

Pharmacokinetics

Study No 2006-1164

A single dose comparative bioavailability study of two formulations of mycophenolate mofetil 250 mg capsules under fasting conditions.

- Methods

STUDY DESIGN

This was an open label, single dose, randomized, two-period, two-sequence, two treatment, crossover study to evaluate the bioavailability of two formulations of mycophenolate mofetil administered orally to healthy subjects under fasting conditions.

Subjects were divided in two groups. In each group, subjects were randomly assigned to one of the two dosing sequences (AB or BA). The randomization scheme was generated by a computer program (SAS®). The study took place in two phases with about 40 subjects in each phase. The decision to continue the second phase was based on the results of the first phase.
Study drugs (one 250 mg capsule) were given after an overnight fast of minimum 10 hours with 240 ml of water followed by at least 4 hours fasting. They were confined to the clinical facility until 36 hours post-dose. Washout period between drug administrations was at least 7 days.
The entire study was conducted according to the protocol except that instead of 40 subjects dosing per group it was 37 in Group I and 43 in Group II.

TEST AND REFERENCE PRODUCTS

Test: Mycophenolate Mofetil Teva 250 mg capsules (Teva Pharmaceuticals Industries Ltd)

Reference: CellCept ® 250 mg capsules (Roche Registration Ltd, UK)

Manufactured by Roche Italy

POPULATION(S) STUDIED

Healthy non-smoking male subjects (18-55 years) and post-menopausal or surgically sterile female subjects were included in the study. All subjects met the inclusion criteria.

Group I: 37 subjects were dosed in period I and 35 completed the study
One subject withdrew from the study due to AE and another subject was withdrawn due to non-compliance.
Group II: 43 subjects were dosed in period I and all completed the study

A total of 78 subjects completed the study and were included in the PK analysis.
Safety analysis consisting of monitoring AE, vital signs and laboratory (haematology, chemistry, urine) analysis was also conducted.

ANALYTICAL METHODS

Concentrations of mycophenolic acid, the active metabolite of mycophenolate mofetil, were measured from plasma samples collected over a 48 hour post dose interval in each period.

Plasma samples were assayed for mycophenolic acid using a validated analytical method. The analytical personnel were blinded from the treatment sequence.

PHARMACOKINETIC VARIABLES

AUCt, AUCinf, Cmax, Tmax, Kel, Thalf of mycophenolic acid were estimated.

STATISTICAL METHODS

Descriptive statistics were calculated by treatments for the PK variables. ANOVA was carried out on log-transformed AUCt, AUCinf and Cmax and on untransformed Tmax, Kel and Thalf. Tmax was analysed by non-parametric approach.

The bioequivalence criteria consisted of 90% CI of the relative mean AUC and Cmax of the test to the reference should be 80-125%, in line with current EMEA guidelines (CHMP/EWP/QWP/1401/98).

- Results

The results of the analysis of mycophenolic acid in 78 subjects is shown below:

Analyte: Mycophenolic acid (N = 78)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (µg*h/mL)	13.3389 13.8149 (27)	13.0392 13.4582 (26)	102.30	99.59 - 105.08	10
AUCinf (µg*h/mL)	14.2036 14.7424 (25)	14.1650 14.4164 (24)	100.27	97.40 - 103.23	10
Cmax (µg/mL)	7.7158 8.5031 (41)	8.0793 8.7586 (38)	95.50	88.74 - 102.78	28
Tmax[a] (h)	0.72 (69)	0.72 (64)	-	-	-
Kel[a] (1/h)	0.0547 (26)	0.0512 (26)	-	-	-
Thalf[a] (h)	13.61 (29)	14.61 (30)	-	-	-
[a]Presented as arithmetic mean (CV%) only.					

No relevant or serious AE were reported in the study. The 90% CI of the relative mean for AUC and Cmax lie between the accepted range of 80-125%.
Plasma levels were below the limit of quantification at the start of period 2 for all subjects, indicating that the washout period was of an adequate duration.
The percentage of $AUC_{0-\infty}$ which was extrapolated was less than 20% for all but 2 observations, 1 subject on the test product and 1 on the reference.

- Conclusion

The test product, Mycophenolate Mofetil Teva 250 mg capsules, is identical in terms of composition both qualitatively and quantitatively to Myfenax 250 mg capsules.
Myfenax 250 mg capsules (Teva Pharmaceuticals Ltd) is bioequivalent to the reference product after single dosing to healthy volunteers under fasting conditions.

Study No 2006-1266

A single dose comparative bioavailability study of two formulations of mycophenolate mofetil 250 mg capsules under fed conditions.

- Methods

STUDY DESIGN

This was an open label, single dose, randomized, two-period, two-sequence, two treatment, crossover study to evaluate the bioavailability of two formulations of mycophenolate mofetil administered orally to healthy subjects under fed conditions.

Subjects were randomly assigned to one of the two dosing sequences (AB or BA) under fed conditions. The randomization scheme was generated by a computer program (SAS®).
Study drugs (one 250 mg capsule) were given after an overnight fast of minimum 10 hour with 240 ml of water and after a high calorie fat breakfast. They were confined to the clinical facility for a minimum of 10.5 hours pre-dosing until the 24 hour post-dose blood sample. Washout period between drug administration was 7 days.
The entire study was conducted according to the protocol.

TEST AND REFERENCE PRODUCTS

Test: Mycophenolate Mofetil Teva 250 mg capsules (Teva Pharmaceuticals Industries Ltd)

Reference: CellCept® 250 mg capsules (Roche Registration Ltd, Italy)

POPULATION(S) STUDIED

Healthy non-smoking male subjects (18-55 years) and post-menopausal or surgically sterile female subjects were included in the study. All subjects met the inclusion criteria.

40 subjects were dosed in period I and 38 completed the study
One subject withdrew from the study for personal reasons prior to period 2 and another subject withdrew prior to period 2 due to AE.
A total of 38 subjects completed the study and were included in the PK analysis.

Safety analysis consisting of monitoring AE, vital signs and laboratory (haematology, chemistry, urine) analysis was also conducted.

ANALYTICAL METHODS

Concentrations of mycophenolic acid, the active metabolite of mycophenolate mofetil, were measured from plasma samples collected over a 72 hour post dose interval in each period.
Plasma samples were assayed for mycophenolic acid using a validated analytical method. The analytical personnel were blinded from the treatment sequence.

PHARMACOKINETIC VARIABLES

AUCt, AUCinf, Cmax, Tmax, Kel, Thalf were estimated on mycophenolic acid.

STATISTICAL METHODS

Descriptive statistics were calculated by treatments for the PK variables. ANOVA was carried out on log-transformed AUCt, AUCinf and Cmax and on untransformed Tmax, Kel and Thalf. Tmax was analysed by non-parametric approach.
The bioequivalence criteria consisted of 90% CI of the relative mean AUC and Cmax of the test to the reference should be 80-125%, in line with current EMEA guidelines (CHMP/EWP/QWP/1401/98).

- Results

The results of the analysis of mycophenolic acid in 38 subjects is shown below:

Analyte: Mycophenolic acid (N = 38)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	15553.6 15941.6 (22)	15023.8 15507.2 (24)	103.53	98.87 - 108.41	12
AUCinf (ng*h/mL)	17066.8 17519.8 (23)	16121.6 16676.5 (24)	105.86	101.25 - 110.69	11
Cmax (ng/mL)	3303.7 3432.8 (28)	3461.7 3646.1 (33)	95.44	85.72 - 106.25	28
Tmax[a] (h)	2.12 (28)	2.03 (30)	-	-	-
Kel[a] (1/h)	0.0448 (34)	0.0492 (37)	-	-	-
Thalf[a] (h)	17.84 (47)	15.96 (36)	-	-	-

[a]Presented as arithmetic mean (CV%) only.

No relevant or serious AE were reported in the study. The 90% CI of the relative mean for AUC and Cmax lie between the accepted range of 80-125%.
There were no subjects for whom the percentage of $AUC_{0-\infty}$ which was extrapolated was greater than 20%. There was 1 subject for whom $AUC_{0-\infty}$ could not be calculated on the reference product and so did not contribute to the analysis of $AUC_{0-\infty}$.
Plasma levels were below the limit of quantification at the start of period 2 for all subjects, indicating that the washout period was of an adequate duration.

- Conclusion

The test product, Mycophenolate Mofetil Teva 250 mg capsules, is identical in terms of composition both qualitatively and quantitatively to Myfenax 250 mg capsules.
Myfenax 250 mg capsules (Teva Pharmaceuticals Ltd) is bioequivalent to the reference product after single dosing to healthy volunteers under fed conditions.

Study No 2006-1184

A single dose comparative bioavailability study of two formulations of mycophenolate mofetil 500 mg tablets under fasting conditions.

- Methods

STUDY DESIGN

This was an open label, single dose, randomized, two-period, two-sequence, two treatment, crossover study to evaluate the bioavailability of two formulations of mycophenolate mofetil administered orally to healthy subjects under fasting conditions.
Subjects were divided in two groups. In each group, subjects were randomly assigned to one of the two dosing sequences (AB or BA). The randomization scheme was generated by a computer program (SAS®). The study took place in two phases with about 40 subjects in each phase. The decision to continue the second phase was based on the results of the first phase.

Study drugs (one 500 mg tablet) were given after an overnight fast of minimum 10 hours with 240 ml of water followed by at least 4 hours fasting. They were confined to the clinical facility until 36 hours post-dose. Washout period between drug administration was at least 7 days.
The entire study was conducted according to the protocol except that instead of 40 subjects dosing per group it was 34 in Group I and 46 in Group II.

TEST AND REFERENCE PRODUCTS

Test: Mycophenolate Mofetil Teva 500 mg tablets (Teva Pharmaceuticals Industries Ltd)

Reference: CellCept® 500 mg tablets (Roche Registration Ltd, UK)

Manufactured by Roche, Italy

POPULATION(S) STUDIED

Healthy adults non-smoking male subjects and post-menopausal or surgically sterile female subjects were included in the study. All subjects met the inclusion criteria.

Group I: 34 subjects were dosed in period I and 32 completed the study
One subject withdrew during period1 from the study due to AE and another subject withdrew during period 2 due to AE.
Group II: 46 subjects were dosed in period I and 45 completed the study
One subject withdrew prior to period 2 due to health reasons.

A total of 77 subjects completed the study and were included in the PK analysis.
Safety analysis consisting of monitoring AE, vital signs and laboratory (haematology, chemistry, urine) analysis was also conducted.

ANALYTICAL METHODS

Concentrations of mycophenolic acid, the active metabolite of mycophenolate mofetil, were measured from plasma samples collected over a 48 hour post dose interval in each period.
Plasma samples were assayed for mycophenolic acid using a validated analytical method. The analytical personnel were blinded from the treatment sequence.

PHARMACOKINETIC VARIABLES

AUCt, AUCinf, Cmax, Tmax, Kel, Thalf of mycophenolic acid were estimated.

STATISTICAL METHODS

Descriptive statistics were calculated by treatments for the PK variables. ANOVA was carried out on log-transformed AUCt, AUCinf and Cmax and on untransformed Tmax, Kel and Thalf. Tmax was analysed by non-parametric approach.
The bioequivalence criteria consisted of 90% CI of the relative mean AUC and Cmax of the test to the reference should be 80-125%, in line with current EMEA guidelines (CHMP/EWP/QWP/1401/98).

- Results

The results of the analysis of mycophenolic acid in 77 subjects is shown below:

Analyte: Mycophenolic Acid (N = 77)					
Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (µg *h/mL)	25.3659 26.2858 (28)	25.8229 26.8275 (29)	98.23	95.47 - 101.7	10
AUCinf (µg *h/mL)	27.5778 28.2125 (29)	28.0102 29.1255 (29)	98.46	95.59 - 101.41	10
Cmax (µg/mL)	11.6002 13.3396 (48)	11.6831 13.2049 (44)	99.29	87.40 - 112.80	49
Tmax[a] (h)	0.81 (77)	0.75 (52)	-	-	-
Kel[a] (1/h)	0.0592 (32)	0.0589 (36)	-	-	-
Thalf[a] (h)	13.30 (44)	13.49 (41)	-	-	-
[a]Presented as arithmetic mean (CV%) only.					

No relevant or serious AE were reported in the study. The 90% CI of the relative mean for AUC and Cmax lie between the accepted range of 80-125%.
Plasma levels were below the limit of quantification at the start of period 2 for all subjects, indicating that the washout period was of an adequate duration.

- Conclusion

The test product, Mycophenolate Mofetil Teva 500 mg tablets, is identical in terms of composition both qualitatively and quantitatively to Myfenax 500 mg tablets.
Myfenax 500 mg tablets (Teva Pharmaceuticals Ltd) is bioequivalent to the reference product after single dosing to healthy volunteers under fasting conditions.

Study No 2006-1267

A single dose comparative bioavailability study of two formulations of mycophenolate mofetil 500 mg tablets under fed conditions.

- Methods

STUDY DESIGN

This was an open label, single dose, randomized, two-period, two-sequence, two treatment, crossover study to evaluate the bioavailability of two formulations of mycophenolate mofetil administered orally to healthy subjects under fed conditions.
Subjects were randomly assigned to one of the two dosing sequences (AB or BA) under fed conditions. The randomization scheme was generated by a computer program (SAS®).
Study drugs (one 500 mg tablet) were given after an overnight fast of minimum 10 hour with 240 ml of water and after a high calorie fat breakfast. They were confined to the clinical facility for a minimum of 10.5 hours pre-dosing until the 24 hour post-dose blood sample. Washout period between drug administration was 7 days.

TEST AND REFERENCE PRODUCTS

Test: Mycophenolate Mofetil Teva 500 mg tablets (Teva Pharmaceuticals Industries Ltd)

Reference: CellCept® 500 mg tablets (Roche Registration Ltd,UK)

POPULATION(S) STUDIED

Healthy adults non-smoking male subjects and post-menopausal or surgically sterile female subjects were included in the study. All subjects met the inclusion criteria.
72 subjects were dosed in period I and 70 completed the study. 2 subjects withdrew prior to period 2 due to personal reasons.
A total of 70 subjects completed the study and were included in the PK analysis.
Safety analysis consisting of monitoring AE, vital signs and laboratory (haematology, chemistry, urine) analysis was also conducted.

ANALYTICAL METHODS

Concentrations of mycophenolic acid, the active metabolite of mycophenolate mofetil, were measured from plasma samples collected over a 72 hour post dose interval in each period.
Plasma samples were assayed for mycophenolic acid using a validated analytical method with a lower limit of quantitation 30 ng/ml. The analytical personnel were blinded from the treatment sequence.

PHARMACOKINETIC VARIABLES

AUCt, AUCinf, Cmax, Tmax, Kel, Thalf were estimated on mycophenolic acid.

STATISTICAL METHODS

Descriptive statistics were calculated by treatments for the PK variables. ANOVA was carried out on log-transformed AUCt, AUCinf and Cmax and on untransformed Tmax, Kel and Thalf. Tmax was analysed by non-parametric approach.
The bioequivalence criteria consisted of 90% CI of the relative mean AUC and Cmax of the test to the reference should be 80-125%, in line with current EMEA guidelines (CHMP/EWP/QWP/1401/98).

- Results

The results of the analysis of mycophenolic acid in 70 subjects is shown below:

Analyte: Mycophenolic acid (N = 70)					
Parameter	**Geometric Means Arithmetic Means (CV%)**		**Ratio of Geometric Means (%)**	**90% Confidence Interval (%)**	**Intra-Subject (CV%)**
	Treatment A	**Treatment B**			
AUCt (ng*h/mL)	28445.2 29362.4 (27)	28632.8 29771.7 (29)	99.34	96.44 – 102.34	11
AUCinf (ng*h/mL)	29800.1 30977.1 (28)	30136.1 30999.0 (30)	98.89	95.93 – 101.94	10
Cmax (ng/mL)	8687.2 9692.1 (49)	9941.6 11163.7 (47)	87.38	77.79 – 98.16	43
Tmax[a] (h)	1.51 (51)	1.30 (60)	-	-	-
Kel[a] (1/h)	0.0461 (29)	0.0467 (29)	-	-	-
Thalf[a] (h)	16.59 (38)	16.25 (37)	-	-	-
[a]Presented as arithmetic mean (CV%) only.					

No relevant or serious AE were reported in the study. The 90% CI of the relative mean for AUC lie between the accepted range of 80-125%. However, for Cmax the results did not fall within the accepted range.
There were no subjects for whom the percentage of $AUC_{0-\infty}$ which was extrapolated was greater than 20%.

Plasma levels were below the limit of quantification at the start of period 2 for all subjects, indicating that the washout period was of an adequate duration.

- Conclusion

The test product, Mycophenolate Mofetil Teva 500 mg tablets, is identical in terms of composition both qualitatively and quantitatively to Myfenax 500 mg tablets.
Myfenax 500 mg tablets (Teva Pharmaceuticals Ltd) is bioequivalent to the reference product in terms of extent of absorption but did not show bioequivalence in terms of rate of absorption after single dosing to healthy volunteers under fed conditions.

Study No 2007-1335

A single dose comparative bioavailability study of two formulations of mycophenolate mofetil 500 mg tablets under fed conditions.

- Methods

STUDY DESIGN

This was an open label, single dose, randomized, two-period, two-sequence, two treatment, crossover study to evaluate the bioavailability of two formulations of mycophenolate mofetil administered orally to healthy subjects under fed conditions.
The trial design was identical to that of study 2006-1267, except for an increase in the number of subjects recruited. The sample size was increased based upon the Cmax variability observed in study 2006-1267 in order to appropriately power the trial.
Subjects were randomly assigned to one of the two dosing sequences (AB or BA) under fed conditions. The randomization scheme was generated by a computer program (SAS®).
Study drugs (one 500 mg tablet) were given after an overnight fast of minimum 10 hour with 240 ml of water and after a high calorie fat breakfast. They were confined to the clinical facility for a minimum of 10.5 hours pre-dosing until the 24 hour post-dose blood sample. Washout period between drug administration was 7 days.

TEST AND REFERENCE PRODUCTS

Test: Mycophenolate Mofetil Teva 500 mg tablets (Teva Pharmaceuticals Industries Ltd)

Reference: CellCept® 500 mg tablets (Roche Registration Ltd, Italy)

POPULATION(S) STUDIED

Healthy adults non-smoking male subjects and post-menopausal or surgically sterile female subjects were included in the study. All subjects met the inclusion criteria.

120 subjects were dosed in period I and 112 completed the study
5 subjects withdrew prior to period 2 (4 subjects had personal reasons and one due to AE). During period 1 two subjects were dismissed (non-compliance, missing blood draws). One subject was dismissed after period 2 dosing due to AE.
A total of 112 subjects completed the study and were included in the PK analysis.
Safety analysis consisting of monitoring AE, vital signs and laboratory (haematology, chemistry, urine) analysis was also conducted.

ANALYTICAL METHODS

Concentrations of mycophenolic acid, the active metabolite of mycophenolate mofetil, were measured from plasma samples collected over a 72 hour post dose interval in each period.
Plasma samples were assayed for mycophenolic acid using a validated analytical method with a lower limit of quantitation 30 ng/ml. The analytical personnel were blinded from the treatment sequence.

PHARMACOKINETIC VARIABLES

AUCt, AUCinf, Cmax, Tmax, Kel, Thalf were estimated on mycophenolic acid.

STATISTICAL METHODS

Descriptive statistics were calculated by treatments for the PK variables. ANOVA was carried out on log-transformed AUCt, AUCinf and Cmax and on untransformed Tmax, Kel and Thalf. Tmax was analysed by non-parametric approach.
The bioequivalence criteria consisted of 90% CI of the relative mean AUC and Cmax of the test to the reference should be 80-125%, in line with current EMEA guidelines (CHMP/EWP/QWP/1401/98).

- Results

The results of the analysis of mycophenolic acid in 112 subjects is shown below:

Analyte: Mycophenolic acid (N = 112)

Parameter	Geometric Means Arithmetic Means (CV%)		Ratio of Geometric Means (%)	90% Confidence Interval (%)	Intra-Subject (CV%)
	Treatment A	Treatment B			
AUCt (ng*h/mL)	28073.3 29064.3 (26)	27812.9 28718.3 (25)	100.94	98.42 - 103.52	11
AUCinf (ng*h/mL)	29355.8 30124.6 (26)	29437.8 30349.6 (26)	99.72	97.49 - 102.00	10
Cmax (ng/mL)	7304.3 7947.2 (41)	7770.9 8638.8 (49)	94.00	86.84 - 101.75	37
Tmax[a] (h)	1.79 (55)	1.49 (58)	-	-	-
Kel[a] (1/h)	0.0441 (28)	0.0435 (27)	-	-	-
Thalf[a] (h)	16.84 (26)	17.12 (28)	-	-	-

[a]Presented as arithmetic mean (CV%) only.

No relevant or serious AE were reported in the study. The 90% CI of the relative mean for AUC and Cmax lie between the accepted range of 80-125%.
There were no subjects for whom the percentage of $AUC_{0-\infty}$ which was extrapolated was greater than 20%.
Plasma levels were below the limit of quantification at the start of period 2 for all but one subject, indicating that the washout period was of an adequate duration. Subject No 42 had pre-dose levels of mycophenoloic acid that represented 0.9% of the corresponding Cmax and therefore subject 42 data were included in the PK analysis.

- Conclusion

The test product, Mycophenolate Mofetil Teva 500 mg tablets, is identical in terms of composition both qualitatively and quantitatively to Myfenax 500 mg tablets.
Myfenax 500 mg tablets (Teva Pharmaceuticals Ltd) is bioequivalent to the reference product after single dosing to healthy volunteers under fed conditions.

Conclusion on studies 2006-1184, 1267 & 2007-1335

The applicant has investigated the relative bioavailability of the test and reference products in both the fed and fasted states.

In the fasted state the single study demonstrated bioequivalence using the conventional criteria.

In the fed state the initial study failed to demonstrate bioequivalence. This prompted the applicant to repeat the study using a larger sample size. The second study produced confidence intervals that were contained within the standard 0.80-1.25 limits.

- ***Overall Conclusions on Bioequivalence studies***

Based on the presented bioequivalence study(ies) Myfenax is considered bioequivalent with CellCept® Roche

Pharmacodynamics

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

Additional data

Not applicable.

Post marketing experience

No post-marketing data are available. These generic medicinal products have not been marketed in any country.

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 for both strengths should follow the PSUR schedule for the reference products. The schedule should be specified before the end of the procedure.

- Description of the Pharmacovigilance system

The applicant has submitted a detailed description of the pharmacovigilance system in place including the responsible person for pharmacovigilance in accordance with "The guideline on monitoring of compliance with Pharmacovigilance regulatory obligations and Pharmacovigilance inspections".

- Risk Management Plan

No description of Risk Management Plan has been provided by the applicant. Since the application concerns a generic with a reference medicinal product for which no safety concern requiring additional risk minimisation activities has been identified this approach is considered acceptable.

Discussion on Clinical aspects

The applicant has submitted clinical bioequivalence studies for both strengths, 250 mg capsules and 500 mg tablets, comparing them with the reference product under fasting and fed conditions. The choice of a single dose study is justified as it is the most sensitive way to compare the bioequivalence of two formulations. The cross-over design minimises variables other than formulation as much as possible.
All studies demonstrated bioequivalence using the conventional criteria, except the initial study for the tablets in the fed state. This prompted the applicant to appropriately repeat the study using a larger sample size. The second study produced confidence intervals that were within the standard 80-125% limits.

Overall, the benefit:risk ratio is favourable.

2.6 Overall conclusions, benefit/risk assessment and recommendation

Overall conclusion and Benefit/risk assessment

The application contains adequate quality, non clinical and the bioequivalence has been shown. 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.

Recommendation

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