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APPLICATION NUMBER

50-791

**Clinical Pharmacology and Biopharmaceutics
Review**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 50-791	Submission Date(s): 04/30/03, 9/2/03, 1/12/04
Brand Name	Myfortic®
Generic Name	Mycophenolate sodium (formerly ERL080)
Reviewer	Jang-Ik Lee, Pharm.D., Ph.D.
Pharmacometrics Reviewer	Jenny J. Zheng, Ph.D.
Team Leader	Philip Colangelo, Pharm.D., Ph.D.
OCPB Division	DPE III (HFD-880)
OND Division	ODE IV DSPIDP (HFD-590)
Sponsor	Novartis Pharmaceuticals Corp.
Relevant IND(s)	57,005
Submission Type; Code	Original, [505(b)(2)]
Formulation; Strength(s)	Delayed-release tablets; 180 mg, 360 mg
Indication	Prophylaxis of organ rejection in patients receiving allogeneic renal transplants
Dosage and Administration	720 mg twice daily in combination with cyclosporine and corticosteroids

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I. EXECUTIVE SUMMARY

Mycophenolic acid (MPA) is a reversible inhibitor of inosine monophosphate dehydrogenase and, therefore, exhibits immunosuppressive activity by inhibiting lymphocyte proliferation. Myfortic[®] delayed release tablets contain 180 mg or 360 mg of MPA, which is the same active moiety that CellCept[®] (mycophenolate mofetil, MMF) produces; only MPA in Myfortic[®] is formulated as the sodium salt (MPS). CellCept[®] was developed by Roche Laboratories and approved as a capsule formulation in 1995 (N50-722). It contains an MPA prodrug, the morpholinoethyl ester of MPA (MMF), that is rapidly and completely converted by gastrointestinal and liver esterases into the active moiety MPA. Myfortic[®] tablets are enteric coated and are designed not to release MPA in the stomach to minimize gastrointestinal irritation. This 505(b)(2) application contains less extensive clinical pharmacology and biopharmaceutics (CPB) information than would be expected with a new molecular entity because existing data are available for MPA in the CellCept[®] NDA and medical literature. This review is mostly based on eleven CPB studies submitted by the sponsor, with the exclusion of the food effect study with inadequate blood sampling (W154). Dr. Jenny J. Zheng, Pharmacometrics Reviewer, reviewed four literature articles submitted that contain MPA exposure-response relationship data.

A. Recommendation

The CPB information in this application is acceptable. However, the CPB review does not recommend the interchangeable use of Myfortic[®] and CellCept[®] proposed by the sponsor. In the CPB substudies of the pivotal phase III clinical studies (B301 and B302), the rate of MPA absorption from Myfortic[®] 720 mg was not equivalent to that from CellCept[®] 1000 mg (i.e., a near equimolar dose). In Study B301 conducted in *de novo* renal transplant patients, the maximum concentration (C_{max}) and area under the concentration-time curve determined within a dosing interval (AUC_τ) for MPA were larger by 11% (least squares mean [LSM] ratio, 1.11; 90% confidence interval [CI], 0.82 – 1.50) and 22% (LSM ratio, 1.22; 90% CI, 1.04 – 1.43), respectively, following a steady state oral dose of Myfortic[®] 720 mg than CellCept[®] 1000 mg, when compared in a parallel manner. In Study B302 conducted in stable renal transplant patients, the AUC was comparable (the 90% CI of LSM ratio within 0.8 – 1.25), but the C_{max} was lower by 11% (LSM ratio, 0.89; 90% CI, 0.70 – 1.13) and the C_{min} greater by 34% (LSM ratio, 1.34; 90% CI, not calculated) following the administration of Myfortic[®] 720 mg than CellCept[®] 1000 mg, when compared in a crossover manner. Both Studies B301 and B302 showed a longer median time to maximum concentration (T_{max}) of MPA by 1.2 hr and 0.6 hr following the administration of Myfortic[®] 720 mg than CellCept[®] 1000 mg, respectively.

The CPB review recommends administering Myfortic[®] on an empty stomach to avoid the variability in MPA absorption between doses due to a marked food effect. In Study 0109, the respective median lag time of the absorption (T_{lag}) and T_{max} of MPA determined following the administration of Myfortic[®] 720 mg under fed conditions were longer by 3.5 hr and 5 hr than those determined under fasted conditions. The administration under fed conditions also resulted in a 33% decrease (LSM ratio, 0.67; 90% CI, 0.52 – 0.86) in MPA C_{max} with a larger variability of the T_{max} in the range of 2 - 23 hours. Note that Myfortic[®] was administered on an empty stomach in the pivotal clinical studies.

The reviewer recommends granting a biowaiver for the 180-mg strength based on the proportionality in ingredients in essence, the similarity in dissolution profile, and the absence of limiting factors (solubility, permeability) in MPA absorption after dissolution at the pH range in the intestine.

B. Phase IV Commitments

There is no Phase IV commitment recommended by the CPB reviewer.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Basic Pharmacokinetic Parameters: Table 1 presents the basic pharmacokinetic parameters of MPA and its major metabolite (7-O-MPA glucuronide, MPAG) determined following single and steady state (for 6 consecutive days) oral doses of Myfortic[®] 720 mg twice daily to stable renal transplant patients. The respective accumulation ratios of MPA were 1.4 and 1.6 based on the geometric means of C_{max} and AUC_{12hr} of MPA determined following the single and steady state oral doses. The respective ratios for MPAG were 2.7 and 3.1. The pharmacokinetics of MPA and MPAG were near linear at the single and steady state doses: the geometric mean ratio for the AUC_{12hr} of MPA following the steady state dose to the AUC_∞ following the single dose was 1.11. The ratio for MPAG was 1.12. The pharmacokinetics of MPA and MPAG were also proportional to the dose of Myfortic[®] administered as a single dose to stable renal transplant patients over the dose range of 360 mg to 2160 mg. After an intravenous dose of MPA 360 mg, the mean ± SD clearance (CL) of MPA was 8.4 ± 1.8 L/hr, the respective mean volume of distribution of MPA at steady state (V_{ss}) and elimination phase (V_z) were 54.3 ± 25.2 L and 112 ± 48 L, and the mean t_{1/2} was 9.7 ± 4.7 hr.

Table 1. Pharmacokinetic parameters of MPA and MPAG determined in 12 stable renal transplant patients following single and steady state (for 6 consecutive days) oral doses of Myfortic[®] 720 mg twice daily.

Pharmacokinetic Parameter	MPA		MPAG	
	Single Dose	Steady State Dose	Single Dose	Steady State Dose
Tlag* (hr)	1 (0 - 1.5)		1 (0.5 - 2)	
Tmax* (hr)	2 (1 - 2.5)	2 (1.5 - 3.0) [§]	3 (2 - 12)	3 (0 - 4)
Cmin [°] (µg/mL)		1.53 ± 0.60 [§]		68.7 ± 25.1
Cmax [°] (µg/mL)	26.6 ± 9.7	37.0 ± 13.3 [§]	59.5 ± 17.0	151 ± 44
AUC _{12hr} [°] (µg-hr/mL)	42.9 ± 12.2	67.9 ± 20.3 [§]	405 ± 114	1235 ± 376
AUC _∞ [°] (µg-hr/mL)	59.8 ± 18.9		1113 ± 446	
CL/F [°] (L/hr)	13.4 ± 5.2 [#]	12.4 ± 6.3 [§]		
Vz/F [°] (L)	222 ± 85 [#]	227 ± 97 [^]		
t _{1/2} [°] (hr)	12.5 ± 5.3 [#]	16.3 ± 9.9 [^]	16.0 ± 4.7	

* median (range), [°] mean ± SD, [§] n = 10, [#] n = 9, [^] n = 8

Absorption: There was a lag time of the absorption (Tlag) before a rapid rise in the plasma concentration of MPA toward a C_{max} following an oral dose of Myfortic[®] to stable renal transplant patients. After the C_{max}, the concentration declined rapidly up to 4 hours but gradually at 4 hours to 48 hours post dose. The mean gastrointestinal absorption of MPA was

0.93 based on the comparison of MPAG AUC following the same oral and intravenous doses of MPA (360 mg each). The mean absolute bioavailability (F) of MPA was 0.72.

Distribution: As stated above, MPA is widely distributed: the V_{ss} is approximately $\frac{3}{4}$ of total body water. The unbound fraction of MPA determined following a steady state oral dose of Myfortic[®] 720 mg ranged between 1.2% and 1.5%. When ¹⁴C-MPA was added to human whole blood *in vitro* over the concentration from 0.1 µg/mL to 100 µg/mL, the fraction of MPA in plasma ranged between 0.82 and 0.87 and the ratio of blood to plasma concentrations ranged between 0.67 and 0.72.

Metabolism: Given that the mofetil ester of MPA (MMF) is cleaved into the active moiety MPA before reaching the systemic circulation, MPA shares the same metabolic pathways with MMF after the initial cleavage of the ester. MPAG and MPA acyl glucuronide were formed from MPA by human liver, kidney, and intestinal microsomes *in vitro*. A variety of recombinant UDP glucuronosyltransferases originating from liver, kidney, esophagus, stomach, bile duct epithelium, colon, and pancreas were all capable of metabolizing MPA to MPAG. MPAG was virtually inactive in inhibition of purine biosynthesis. The acyl glucuronide has pharmacological activity comparable to MPA. The relative AUC ratio for MPA, MPAG, and MPA acyl glucuronide was 1:24:0.28 following Myfortic[®] 720 mg. The enterohepatic recirculation of MPAG has been reported in the literature. After an intravenous dose of MPA 360 mg (Study 0104), the mean CL of MPA was 8.4 ± 1.8 L/hr and the mean t_{1/2} 9.7 ± 4.7 hr.

Excretion: Following a single oral dose of Myfortic[®] 720 mg to stable renal transplant patients, the amount (% dose administered) of MPA excreted in the urine for 48 hr post dose (A_{e48hr}) was $3.1 \pm 2.5\%$. The A_{e48hr} of MPAG accounted for most of the excretion with a mean value of $62.8 \pm 13.7\%$ of the dose administered. The total A_{e48hr} excreted as MPA and MPAG was $65.9 \pm 13.9\%$ of the dose administered.

Variability in MPA Pharmacokinetics: The inter-subject variability (coefficient of variation, CV) in the C_{max} and AUC_τ of MPA determined following a steady state oral dose of Myfortic[®] 720 mg to stable renal transplant patients were approximately 40% and 25%, respectively. MPA exposure increased over time following the administration of Myfortic[®] 720 mg twice daily to *de novo* renal transplant patients. The mean C_{max} of MPA increased from 15.0 ± 10.7 µg/mL at Week 2 to 26.2 ± 12.7 µg/mL at Month 3. Similarly, the mean AUC_τ of MPA increased from 28.6 ± 11.5 µg-hr/mL at Week 2 to 52.3 ± 17.4 µg-hr/mL at Month 3. In consistence with the change in the AUC_τ, the mean apparent CL (CL/F) of MPA decreased from 29.9 ± 14.4 L/hr at Week 2 to 15.3 ± 5.4 L/hr at Month 3. There was no further change in MPA pharmacokinetics from Month 3 to Month 6.

Pediatrics: The respective mean C_{max} and AUC_∞ of MPA determined in older pediatric (11 to 16 years old) stable renal transplant patients following a single oral dose of Myfortic[®] 450 mg/m² body surface area (BSA) were greater by 24% and 11% than those determined in adult stable renal transplant patients following Myfortic[®] 720 mg (equivalent to 416 mg/m² for adult patients with a BSA of 1.73 m²). The difference in MPA exposure was even greater in a younger pediatric cohort (5 to 10 years old): higher by 42% and 30% in the respective C_{max} and AUC_∞. The respective mean apparent clearance (CL/F) and t_{1/2} of MPA were greater by 10% and shorter

by approximately 4 hours in both pediatric cohorts. The T_{max} values were not meaningfully different.

In Vitro Evidence of Drug-Drug Interactions: There is no *in vitro* evidence to suspect any *in vivo* drug-drug interactions involving CYP enzymes. Incubation of MPA with human liver microsomes in the presence of NADPH (absence of UDPGA) resulted in very low levels of CYP-dependent metabolism. In a CYP inhibition study using human liver microsomes, MPA did not significantly inhibit the metabolism of midazolam, a marker substrate for CYP3A, or phenacetin, a marker substrate for CYP1A2. There was no significant inhibition of the metabolism of other CYP marker substrates by MPA at concentrations of up to 500 μM.

Myfortic[®]-Antacid Interaction: The administration Myfortic[®] 720 mg in combination with Maalox[®] 30 mL four times daily resulted in the reduction of the C_{max} and AUC of MPA by 25% and 37%, respectively. Therefore, Myfortic[®] and Maalox[®] should not be administered simultaneously.

Myfortic[®]-Neoral[®] Interaction: Myfortic[®] coadministration had no effect on cyclosporine pharmacokinetics. It is reported in the medical literature that cyclosporine potentially blocks the enterohepatic recirculation of MPA.

MPA Solubility: The highest strength of Myfortic[®] tablet (360 mg) is soluble in _____ (_____) of water, _____ buffer pH _____ but not soluble in 0.1 N hydrochloric acid. Therefore, strictly speaking, Myfortic[®] is not a high solubility drug product from a biopharmaceutics classification system (BCS) perspective.

MPA Permeability: The apical-to-basolateral permeability of MPA across Caco-2 cell monolayer was 158×10^{-5} cm/min, which was similar to the basolateral-to-apical permeability. MPA was 4 times more permeable than propranolol that has shown > 90% of absorption in human studies. In addition, the ratio of MPAG AUC (i.e., MPAG AUC after oral Myfortic dose / MPAG AUC after intravenous MPA dose) was 0.93. Therefore, MPA is a highly permeable drug from a BCS perspective.

Food Effect on MPA Absorption: The respective median T_{lag} and T_{max} of MPA determined following the administration of Myfortic[®] 720 mg under fed conditions were longer by 3.5 hr and 5 hr than those determined under fasted conditions. The administration under fed conditions also resulted in a 33% decrease (LSM ratio, 0.67; 90% CI, 0.52 – 0.86) in the C_{max} of MPA with a larger variability of the T_{max} ranging between 2 and 23 hours. However, the extent of MPA absorption (AUC_t) was comparable (LSM ratio, 0.91; 90% CI, 0.82 – 1.01) under fed versus fasted conditions. Overall, Myfortic should be administered on an empty stomach to avoid dose-to-dose variability in the rate of MPA absorption.

Relative Bioavailability of Myfortic[®] Tablets to CellCept[®] Capsules: In Study B301 conducted in *de novo* renal transplant patients, the C_{max} and AUC_t of MPA were larger by 11% (LSM ratio, 1.11; 90% CI, 0.82 – 1.50) and 22% (LSM ratio, 1.22; 90% CI, 1.04 – 1.43), respectively, following a steady state oral dose of Myfortic[®] 720 mg than CellCept[®] 1000 mg when compared in a parallel manner. In Study B302 conducted in stable renal transplant patients, the AUC was

comparable (the 90% CI of LSM ratio within 0.8 – 1.25), but the Cmax was lower by 11% (LSM ratio, 0.89; 90% CI, 0.70 – 1.13) and the Cmin was greater 34% (LSM ratio, 1.34; 90% CI, not calculated) following the administration of Myfortic® 720 mg than CellCept® 1000 mg, when compared in a crossover manner. Both Studies B301 and B302 showed a longer median Tmax of MPA by 1.2 hr and 0.6 hr, respectively, following the administration of Myfortic® 720 mg than CellCept® 1000 mg. Thus, the absorption profile of MPA following the administration Myfortic® 720 mg is not equivalent to that following CellCept® 1000 mg although the two release near equimolar amounts of MPA.

Dissolution Method and Specification: Dissolution testing was performed using USP apparatus 2 (paddle) at 50 ± 2 rpm at 37 ± 0.5 °C. Test medium 1 was 0.1N of hydrochloric acid (pH 1.2). After 120 min testing in test medium 1, 0.1N NaHCO₃ was added resulting in a pH of 7.2 (test medium 2). Gastro-resistance was demonstrated by the intactness of the enteric coating under the acidic condition where no amount of dissolved drug substance from six individual tablets exceeds 5%. The media change to the neutral condition initiated drug release. After 180 min (i.e., after 60 min in the neutral condition), nearly complete drug release was achieved. Thus, the dissolution specification of 75% for 120 min in medium 1 and then Q = 75% (no less than, NLT 75%) within 60 min in medium 2 is acceptable.

Comparison of Dissolution Profiles between Myfortic® 180 mg and 360 mg Tablets: The calculated similarity factor F2 was 58 between the two strengths at the paddle rotation speed of 50 rpm, which is the proposed and acceptable dissolution test method for Myfortic® tablets. Thus the dissolution profiles of Myfortic® 180-mg and 360-mg tablets are comparable.

/S/

Date: _____

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CPB Briefing Date: February 11, 2004

Attendees: Marc Cavaille Coll, Dakshina Chilukuri, Philip Colangelo, John Hunt, Seong Jang, Jenny Zheng, Gerlie De Los Reyes, Arzu Selen, Ramesh Sood,

II. QUESTION-BASED REVIEW

A. General Attributes

1. *What regulatory background or history information contribute to the assessment of the clinical pharmacology and biopharmaceutics of this drug?*

This application is based on the following features that would support an NDA filing under the section 505(b)(2) of the Federal Food Drug and Cosmetic Act.

- Both Myfortic[®] and CellCept[®] release the same active moiety (MPA) to the systemic circulation.
- Myfortic[®] 720 mg and CellCept[®] 1000 mg deliver near equimolar amounts of MPA (only 2.6% higher with CellCept[®]) and produce comparable exposure (AUC).
- The disposition of MPA (distribution, metabolism, and elimination) has already been described in the CellCept[®] NDA and medical literature.

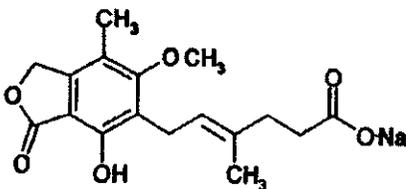
Therefore, the sponsor did not conduct dose finding studies for Myfortic[®] supporting entry into Phase III. However, given that Myfortic[®] is a different molecular entity and a different formulation compared to CellCept[®], the sponsor conducted limited studies characterizing the absorption phase of Myfortic[®].

2. *What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?*

a. *Chemical Name:*

(E)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methyl-hex-4-enoic acid sodium salt

b. *Structure*



c. *Molecular Weight:*

342.32 (C₁₇H₁₉O₆Na)

d. *Physicochemical Properties:*

MPS is white to off-white crystalline powder. The pKa values of MPA are 4.9 (pKa1) and 8.3 (pKa2). Myfortic[®] has been formulated as enteric coated delayed release tablets containing MPS (180 mg or 360 mg as MPA).

3. *What are the proposed mechanism of drug action and therapeutic indication?*

a. *Indication*

The proposed indication of Myfortic® is the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

b. *Mechanism of Action*

MPA is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) and, therefore, inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T- and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effect on lymphocytes. Thus the mode of action is complementary to calcineurin inhibitors which interfere with cytokine transcription and resting T-lymphocytes.

4. *What is the proposed dosage and route of administration?*

The proposed dose for Myfortic® is 720 mg (two 360 mg tablets) orally administered twice daily (1.44 g total daily dose). The proposed dose is based on the following:

- The recommended dose of CellCept® is an oral or intravenous dose of 1000 mg administered twice daily for renal transplant patients. Two Myfortic® 360 mg tablets (total, 720 mg as MPA) and four CellCept® 250 mg capsules (total, 739 mg as MPA) contain near equimolar amounts of active drug (only 2.6% higher in CellCept®) and deliver the same active moiety MPA to the systemic circulation.
- Myfortic® administered at a dose of 720 mg twice daily was therapeutic equivalent to CellCept® administered at a dose of 1000 mg twice daily in *de novo* (Study B301) and stable (Study 302) renal transplant patients (see Clinical Review).

Patients are to be instructed that Myfortic® tablets should not be crushed, chewed, or cut prior to ingesting but should be swallowed whole in order to maintain the integrity of the enteric coating. The sponsor proposed to take Myfortic® consistently with or without food but the CPB reviewer recommends taking Myfortic® on an empty stomach to reduce the dose-to-dose variability in MPA absorption (see section II. B. 3. *food effect*). The current CellCept® package insert recommends CellCept® administration on an empty stomach but allows CellCept® administration with food to stable renal transplant patients. Even though, the sponsor proposed interchangeable uses of Myfortic® 720 mg and CellCept® 1000 mg, the CPB reviewer does not agree with the sponsor because their rates of MPA absorption are not equivalent (see section II. E. 7.).

B. **General Clinical Pharmacology**

1. *What are the design features of the pivotal clinical trials?*

The sponsor conducted two pivotal Phase III clinical trials (Studies B301 and B302). Study B301 was a double-blind, double-dummy, randomized, multicenter, parallel-group study. The study was conducted to assess the therapeutic equivalence of 2 x Myfortic[®] 360 mg tablets compared to 4 x CellCept[®] 250 mg capsules as measured by the incidence of biopsy-proven acute rejection, graft loss, death, or loss to follow-up in the first 6 months of treatment in *de novo* renal transplant recipients. In this study, Myfortic[®] or CellCept[®] was administered as a part of triple immunosuppressive therapy utilizing Neoral[®] and prednisone. The pharmacokinetics of MPA and MPAG were compared in a parallel manner at Week 2, Month 3, and Month 6 during twice daily administration of Myfortic[®] and CellCept[®].

Study B302 was a one year, randomized, double-blind, double-dummy, multicenter, parallel-group study. The study was conducted to evaluate the incidence and severity of gastrointestinal adverse events and neutropenia at 3 months after administration of Myfortic[®] 760 mg or CellCept[®] 1000 mg to stable renal transplant patients. In this study, Myfortic[®] and CellCept[®] were administered as a part of triple immunosuppressive therapy with Neoral[®], with or without steroids. However, MPA exposure was compared between the treatments of Myfortic[®] and CellCept[®] in a crossover manner.

2. *What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?*

Clinical endpoints were chosen to determine the therapeutic equivalence of Myfortic[®] in comparison to CellCept[®] with respect to the efficacy and safety outcomes of immunosuppression in renal transplant patients. The primary efficacy endpoint was the incidence of the composite variable (biopsy-proven acute rejection, graft loss, death, or lost to follow-up) at 6 and 12 months. The primary safety endpoints were adverse events including infections and gastrointestinal adverse events.

3. *Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Yes to assess pharmacokinetic parameters, refer to II. F, Analytical Section.

4. *Exposure-response*

a. *What are the characteristics of the exposure-response relationships for efficacy and safety? If relevant, indicate the time to onset of the pharmacological response or clinical endpoint.*

The exposure-response relationships in Myfortic[®] are expected to be comparable to those in CellCept[®] because Myfortic[®] delivers nearly the same molar amount of the same active moiety as CellCept[®] does. Therefore, in this 505(b)(2) application, the sponsor did not determine but instead submitted copies of four published articles addressing the relationships in MMF. Dr. Jenny J. Zheng, Pharmacometrics Reviewer, summarized the relationships as follows (see her pharmacometrics review attached in Appendix IV. C.):

1. The rate of renal allograft rejection may be reduced from the background rate by administration of mycophenolate mofetil. The extent of this effect is significantly related to mycophenolic acid AUC.

2. Individualization of mycophenolate mofetil dose based on mycophenolic acid AUC may have merit.
3. For renal transplantation:
 - a. An MPA AUC value $>30 \mu\text{g}\cdot\text{h/mL}$ (determined via HPLC assay) and predose plasma MPA concentration of $>2.0 \mu\text{g/mL}$ (determined via EMIT assay) may be appropriate.
 - b. The upper limit of the MPA concentration range for clinical efficacy cannot be determined.
4. For cardiac transplantation:
 - a. MPA AUC values as measured by HPLC may be the best predictor of clinical efficacy, with values of $42.8 \mu\text{g}\cdot\text{h/mL}$ associated with a lack of rejection.
 - b. The optimal range of MPA pre-dose concentrations and AUC values are yet to be determined.

b. *Does this drug prolong the QT or QTc interval?*

MPA is not known to affect the QT interval.

c. *Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

Not applicable.

5. *What are the pharmacokinetic characteristics of the drug and its metabolite?*

a. *What are the single dose and multiple dose pharmacokinetic parameters?*

Table 2 presents a comparison of the pharmacokinetic parameters of MPA determined following single (first) and steady state (2-day washout period followed by 6 consecutive dosing days) oral doses of Myfortic[®] 720 mg twice daily to stable renal transplant patients (Study 0102). There was no difference in median Tmax. The accumulation ratios were 1.4 and 1.6 based on the geometric means of Cmax and AUC_{12hr}, respectively. MPA pharmacokinetics were near linear at the study conditions: the geometric mean ratio of MPA AUC_{12hr} following the steady state dose to MPA AUC_∞ following the first dose was 1.11 (range, 0.79 to 1.70; n = 8).

Table 2. Pharmacokinetic parameters (mean ± SD) of MPA determined in 12 stable renal transplant patients following single and steady state oral doses of Myfortic[®] 720 mg twice daily (Study 0102).

PK Parameters	Single Dose	Steady State Dose	Geometric Mean Ratio (Range)
Tlag* (hr)	1 (0 – 1.5)		
Tmax* (hr)	2 (1 – 2.5)	2 (1.5 – 3.0) ^o	
Cmin (μg/mL)		1.53 ± 0.60 ^o	
Cmax (μg/mL)	26.6 ± 9.7	37.0 ± 13.3 ^o	1.43 (0.68 – 3.51) ^o
AUC _{12hr} (μg-hr/mL)	42.9 ± 12.2	67.9 ± 20.3 ^o	1.64 (1.15 – 2.22) ^o
AUCt (μg-hr/mL)	56.5 ± 17.1		
AUC _∞ (μg-hr/mL)	59.8 ± 18.9		
CL/F (L/hr)	13.4 ± 5.2 [#]	11.5 ± 3.3 ^o	
Vz/F (L)	222 ± 85 [#]	227 ± 97 [^]	
t _{1/2} (hr)	12.5 ± 5.3 [#]	16.3 ± 9.9 [^]	

* median (range), ^o n = 10 (excluded two extreme outliers), [#] n = 9, [^] n = 8

After an intravenous dose of MPA 360 mg (Study 0104), the mean CL of MPA was 8.4 ± 1.8 L/hr, the respective mean volume of distribution of MPA at steady state (V_{ss}) and elimination phase (V_z) 54.3 ± 25.2 L and 112 ± 48 L, and the mean $t_{1/2}$ 9.7 ± 4.7 hr.

Table 3 presents a comparison of the pharmacokinetic parameters for MPAG determined following the single and steady state oral doses of Myfortic® 720 mg (Study A0102). There was no difference in median T_{max} . The accumulation ratios were 2.7 and 3.1 based on the geometric means of C_{max} and AUC_{12hr} , respectively. MPAG pharmacokinetics were near linear at the study conditions: the geometric mean ratio of the MPAG AUC_{12hr} following the steady state dose to the MPAG AUC_{∞} following the first dose was 1.12 (range, 0.90 to 1.36; $n = 9$).

Table 3. Pharmacokinetic parameters (mean \pm SD) of MPAG determined in 12 stable renal transplant patients following single and steady state oral doses of Myfortic® 720 mg twice daily (Study 0102).

PK Parameters	Single Dose	Steady State Dose	Geometric Mean Ratio (Range)
T_{lag}^* (hr)	1 (0.5 – 2)		
T_{max}^* (hr)	3 (2 – 12)	3 (0 – 4)	
C_{min} ($\mu\text{g/mL}$)		68.7 ± 25.1	
C_{max} ($\mu\text{g/mL}$)	59.5 ± 17.0	151 ± 44	2.68 (1.66 – 5.16) [#]
AUC_{12hr} ($\mu\text{g-hr/mL}$)	405 ± 114	1235 ± 376	3.12 (2.20 – 5.58) [#]
AUC_t ($\mu\text{g-hr/mL}$)	945 ± 346		
AUC_{∞} ($\mu\text{g-hr/mL}$)	1113 ± 446		
$t_{1/2}$ (hr)	16.0 ± 4.7		

* median (range), [#] $n = 9$

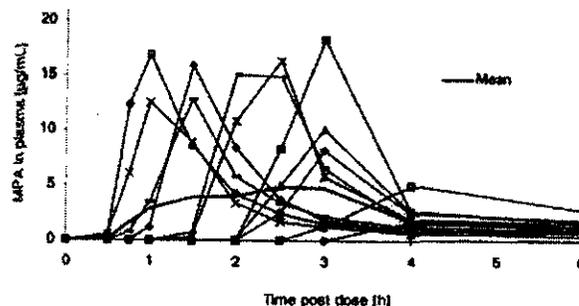
b. How does the pharmacokinetics of the drug and its major active metabolites in healthy volunteers compare to that in patients?

For this application, the sponsor conducted no pharmacokinetic study in normal healthy subjects with Myfortic® administration. Therefore, the pharmacokinetics of MPA and its metabolites cannot be compared between healthy subjects and transplant patients.

c. What are the characteristics of drug absorption?

In the concentration-time profiles of MPA following a single oral dose of Myfortic® 360 mg to stable renal transplant patients (Study 0104, Figure 1), there was a lag period of absorption (median, 1.25 hr; range, 0 to 4.1 hr) before a rapid rise in MPA plasma concentration. Median (range) T_{max} was 2.75 hr (1.0 hr to 12.0 hr). After reaching a C_{max} , MPA concentrations declined rapidly up to 4 hr but then gradually from 4 to 48 hr post dose. The mean absolute bioavailability (F) of MPA following an early oral formulation of Myfortic® to 12 stable renal

Figure 1. Plasma concentration-time profiles of MPA following a single oral dose of Myfortic 360 mg to 12 stable renal transplant patients ($n = 12$, Study A0104).



transplant patients was 0.72 ± 0.20 , i.e., as compared to the same 360-mg dose of intravenous MPA. However, the ratio of MPAG AUC (i.e., MPAG AUC after oral Myfortic dose / MPAG AUC after intravenous MPA dose) was 0.93, which indirectly shows a high permeability of MPA following an oral dose.

d. What are the characteristics of drug distribution?

As shown above, MPA is widely distributed: the V_{ss} is approximately $\frac{1}{4}$ of total body water. The unbound fraction of MPA determined 2 hr and 12 hr after a steady state oral dose of Myfortic[®] 720 mg or CellCept[®] 1000 mg to 40 stable renal transplant patients (Study 2302) ranged between 1.2 and 1.5%.

When ¹⁴C-MPA was added to human whole blood *in vitro* over the concentration range of 0.1 to 100 $\mu\text{g/mL}$, ¹⁴C-MPA was extensively distributed into the plasma compartment: the fraction in plasma was in the range of 0.82 to 0.87 and the ratio of blood to plasma concentration was 0.67 to 0.72. The distribution was concentration-independent except at 100 $\mu\text{g/mL}$, where there was a slight decrease (approx. 15%) in the plasma fraction. This slight decrease is unlikely to be of clinical significance at a dose of Myfortic[®] 720 mg because the C_{max} of MPA at this dose is much less than 100 $\mu\text{g/mL}$.

e. Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was conducted for this application.

f. What are the characteristics of drug metabolism?

In vitro, MPAG and MPA acyl glucuronide were formed from MPA by microsomes isolated from human liver, kidney, and intestine. A variety of recombinant UDP glucuronosyltransferases originating from liver, kidney, esophagus, stomach, bile duct epithelium, colon, and pancreas were all capable of metabolizing MPA to MPAG. Whereas MPAG is virtually inactive in the inhibition of purine biosynthesis, MPAG acyl glucuronide has activity comparable to that of MPA. Incubation of MPA with human liver microsomes resulted in only very low levels of CYP enzyme-dependent metabolism.

In humans, the predominant metabolic pathway is the conjugation of MPA *via* glucuronyl transferase to MPAG. The enterohepatic recirculation of MPAG has been reported in which MPAG in the bile is de-glucuronidated by gut flora to yield MPA which is then reabsorbed in the intestine into the systemic circulation. The enterohepatic recirculation accounts for approximately 30% of the systemic exposure of MPA. The recirculation can produce a secondary concentration peak several hours after the absorption peak (C_{max}).

Given that the mofetil ester of MPA (MMF) is cleaved into the active moiety MPA before reaching the systemic circulation, MPA shares the same metabolic pathways with MMF after the initial cleavage of the ester. In addition to the similar exposure to MPA (see question G.7.), the exposures to MPAG and MPA acyl glucuronide were similar following steady state doses of Myfortic[®] 720 mg and CellCept[®] 1000 mg to 40 stable renal transplant patients (Study 2302,

Table 4). The relative AUC ratio of MPA, MPAG, and MPA acyl glucuronide at steady state was 1:24:0.28 and 1:23:0.31 following Myfortic[®] and CellCept[®] doses, respectively.

Table 4. Comparison of pharmacokinetic parameters of MPAG and MPA acyl glucuronide following steady state doses of Myfortic[®] 720 mg and CellCept[®] 1000 mg to 40 stable renal transplant patients (Study 2302).

PK Parameters	MPAG			MPA Acyl Glucuronide		
	Myfortic [®] 720 mg (test)	CellCept [®] 1000 mg (reference)	Geometric Mean Ratio (90% CI)	Myfortic [®] 720 mg (test)	CellCept [®] 1000 mg (reference)	Geometric Mean Ratio (90% CI)
T _{max,ss} (hr)*	4.0 (0.25-8.0)	2.5 (—)		3.0 (—)	1.0 (—)	
C _{max} (µg/mL)	224 ± 72	185 ± 65	1.22 (1.10-1.34)	4.1 ± 1.9	3.9 ± 1.4	1.04 (0.96-1.12)
C _{min} (µg/mL)	84 ± 39	64 ± 28		0.7 ± 0.4	0.6 ± 0.4	
AUC _t (µg-hr/mL)	1724 ± 569	1413 ± 495	1.22 (1.13-1.30)	19.6 ± 9.4	18.8 ± 8.8	1.02 (0.91-1.14)

* median (range), ^ mean ± SD

g. What are the characteristics of drug excretion?

The majority of Myfortic[®] dose administered was excreted in the urine as MPAG; only a small percentage was excreted as unchanged MPA. Following a single oral of Myfortic[®] 720 mg to 18 stable renal transplant patients (Study 0109), the amount (% dose administered) of MPA excreted in the urine for 48 hr post dose (A_{e48hr}) was only 3.1 ± 2.5%. The mean renal clearance (CL_r) of MPA was 9.8 ± 7.6 mL/min. The A_{e48hr} of MPAG accounted for most of the excretion with a mean of 62.8 ± 13.7% of dose administered. The mean CL_r of MPAG were 15.5 ± 5.9 mL/min. The total A_{e48hr} excreted as MPA and MPAG was 65.9 ± 13.9% of dose administered.

h. Based on pharmacokinetic parameters, what is the degree of linearity in the dose-concentration relationship?

The pharmacokinetics of MPA and its metabolite MPAG were proportional to the dose of Myfortic[®] administered over the range of 360 mg – 2160 mg. Table 5 presents a comparison of the MPA pharmacokinetic parameters determined following single oral doses of Myfortic[®] in the range of 180 to 2160 mg to 16 stable renal transplant patients (Study 0105). Both mean C_{max} and AUC_t were proportional to Myfortic[®] dose except at the lowest dose of 180 mg. Median T_{lag} was relatively consistent across the dose range (range, 1.0 hr - 1.5 hr). Median T_{max} was also independent of dose (range, 2.2 hr - 2.5 hr). Even though AUC_∞ was not reliably calculated for all study patients, the extrapolation from AUC_t to AUC_∞ was < 10% for patients whose AUC_∞ was adequately calculated. Therefore, the AUC_t rather than AUC_∞ was used in the comparison.

Table 5. Comparison between MPA pharmacokinetic parameters determined following each single dose of Myfortic® to 16 stable renal transplant patients (Study 0105).

Parameter	Statistics	Myfortic® Dose			
		180 mg	360 mg	720 mg	2160 mg
Tlag (hr)	Median (Range)	1.5 —	1.25 —	1.0 —	1.0 —
Tmax (hr)	Median (Range)	2.5 (—	2.2 —	2.5 —	2.5 —
Cmax (µg/mL)	Mean ± SD	5.3 ± 1.9	9.0 ± 3.4	16.7 ± 8.0	40.1 ± 16.0
	Geometric Mean Ratio	0.59	1	1.86	4.46
AUCt (µg-hr/mL)	Mean ± SD	8.9 ± 3.4	20.2 ± 5.4	42.4 ± 10.4	121 ± 29
	Geometric Mean Ratio	0.44	1	2.10	5.99

Table 6 presents a summary of statistical analyses to determine the dose proportionality of Myfortic®. The Cmax and AUCt (or AUC∞) were analyzed for both MPA and MPAG using a power model (i.e., $AUC = a \times \text{Dose}^b$). All parameters tested met dose-proportionality criteria: the 90% CI for the exponent parameter in the power model is contained in the interval of 0.68 - 1.32. Based on the linear regression analysis, the Cmax and AUC of MPA and MPAG were proportional to dose: correlation coefficients (r^2) for the relationship between the parameter and Myfortic® dose were > 0.975. However, MPA pharmacokinetics were not quite dose-proportional at the Myfortic® doses of 180 mg to 360 mg. When the dose normalized values were compared between the two dose levels, the geometric mean ratios (90% CI) were 0.88 (0.63 - 1.22) and 1.17 (1.01 - 1.37) for the Cmax and AUCt of MPA, respectively. The Cmax and AUCt of MPAG showed no such disproportionality: 0.93 (0.80 - 1.08) and 0.94 (0.87 - 1.02), respectively.

Table 6. Summary of statistical analyses for the dose proportionality of Myfortic® (Study 0105).

	PK Parameter	Exponent Parameter of Power Model		Linear Regression Coefficient (r^2)
		Estimate	90% Confidence Interval	
MPA	AUCt (µg-hr/mL)	1.06	1.00 - 1.11	0.999
	Cmax (µg/mL)	0.81	0.68 - 0.94	0.975
MPAG	AUC∞ (µg-hr/mL)	0.95	0.92 - 0.98	0.999
	Cmax (µg/mL)	0.92	0.87 - 0.97	0.991

i. How do the pharmacokinetic parameters change with time following chronic dosing?

MPA exposure increased over time at the earlier phase following *de novo* renal transplant. Table 7 presents a comparison of the pharmacokinetic parameters of MPA at Week 2, Month 3, and Month 6 following the administration of Myfortic® 720 mg or CellCept® 1000 mg twice daily (Study B301). For patients taking Myfortic®, the mean Cmax of MPA increased from 15.0 ± 10.7 µg/mL at Week 2 to 26.2 ± 12.7 µg/mL at Month 3, the mean Cmin increased from 0.52 ± 0.22 µg/mL to 1.26 ± 0.48 µg/mL, and the mean AUCτ increased from 28.6 ± 11.5 µg-hr/mL to 52.3 ± 17.4 µg-hr/mL. Consistently with the change in AUCτ, the mean CL/F of MPA decreased from 29.9 ± 14.4 L/hr at Week 2 to 15.3 ± 5.4 L/hr at Month 3. However, the results at Months 3 and 6 were comparable. The MPA exposure was numerically higher following Myfortic® than CellCept® administration but this is not reliable because of the nature of parallel

comparison: no difference in MPA exposure was observed in a crossover comparison (Study B302).

Table 7. Changes in MPA pharmacokinetics over time following the administration of Myfortic® and CellCept® in *de novo* renal transplant patients (Study B301).

Statistics	Myfortic® 720 mg (Test)			CellCept® 1000 mg (Reference)		
	Week 2	Month 3	Month 6	Week 2	Month 3	Month 6
N	12	12	12	16	16	16
Tmax (hr)	1.8 (—)	2 —	2 —	0.6 —	0.5 —	0.8 (—)
Cmax (µg/mL)	15.0 ± 10.7	26.2 ± 12.7	24.1 ± 9.6	12.6 ± 6.6	18.3 ± 8.0	19.8 ± 9.4
Cmin (µg/mL)	0.52 ± 0.22	1.26 ± 0.48	1.30 ± 0.58	0.42 ± 0.20	0.89 ± 0.38	0.85 ± 0.26
AUC _τ (µg-hr/mL)	28.6 ± 11.5	52.3 ± 17.4	57.2 ± 15.3	24.8 ± 6.9	38.8 ± 10.5	39.3 ± 11.7
CL/F (L/hr)	29.9 ± 14.4	15.3 ± 5.4	13.6 ± 4.3	31.9 ± 12.5	20.2 ± 7.0	20.0 ± 6.2

j. *What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?*

There was no remarkable difference in the inter-subject variability of MPA pharmacokinetics between Myfortic® and CellCept® when compared following their administrations in 18 stable renal transplant patients (Study B302, Table 8): the CVs in the Cmax and AUC_τ of MPA were approximately 40% and 25%, respectively. The intra-subject variability was not reliably determined in this submission. MPA pharmacokinetics were not studied in healthy subjects in this application.

Table 8. Comparison between MPA pharmacokinetic parameters determined following steady state doses of Myfortic® 720 mg and CellCept® 1000 mg to stable renal transplant patients in a crossover manner (n = 18, Study B302).

PK Parameter	Myfortic® 720 mg (Test)	CellCept® 1000 mg (Reference)	Difference (Range)	LS Mean Ratio (90% CI)
Tmax (hr)*	1.5 (—)	0.75 (—)	0.6 —	
Cmax (µg/mL)#	18.9 ± 7.9 (42)	21.3 ± 9.1 (43)		0.89 (0.70 – 1.13)
Cmin (µg/mL)#, ^	2.0 ± 0.7 (34)	1.5 ± 0.7 (44)		1.34 (not reported)
AUC _τ (µg-hr/mL)#	57.4 ± 15.0 (26)	58.4 ± 14.1 (24)		0.98 (0.87 - 1.11)
CL/F (mL/min)#	13.6 ± 4.2 (31)	13.4 ± 5.0 (37)		1.02 (not reported)

LS, least squares; * median (range); # mean ± SD (CV %); ^ n = 16

C. Intrinsic Factors

1. *What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?*

a. Elderly

No studies were conducted to determine MPA pharmacokinetics in elderly patients (≥ 65 years old). However, in a population pharmacokinetic analysis using the data from 24 stable renal transplant patients pooled from Studies A0102 and B301, the mean AUC and C_{max} values of MPA in older adults (45 – 67 years old) were 26.7 $\mu\text{g}/\text{mL}$ and 59.6 $\mu\text{g}\cdot\text{hr}/\text{mL}$, respectively. In contrast, the values in younger adults (23 – 44 years old) were 30.4 $\mu\text{g}/\text{mL}$ and 61.6 $\mu\text{g}\cdot\text{hr}/\text{mL}$, respectively. Thus, the MPA exposure was not different between younger and older adults.

b. Pediatric Patients

The MPA exposure determined in pediatric patients was greater than the exposure determined in adult patients following the similar dose administered based on BSA. The respective mean C_{max} and AUC ∞ of MPA determined in older pediatric (11 – 16 years old) stable renal transplant patients following a single oral dose of Myfortic[®] 450 mg/m² BSA (Study 0106, Table 9) were greater by 24% and 11% than those determined in 12 adult stable renal transplant patients following Myfortic[®] 720 mg (416 mg/m² for adult patients with a BSA of 1.73 m², Study 0102, Table 2). The respective mean CL/F and t_{1/2} were greater by 10% and shorter by 3.6 hours in the older cohort. The median T_{max} values were not meaningfully different. The difference in MPA exposure was even greater in younger cohort (5 – 10 years old) than the adult patients: by 42% and 30% for the C_{max} and AUC ∞ , respectively. In the younger cohort, the respective mean CL/F and t_{1/2} were greater by 10% and shorter by 4.4 hours but the median T_{max} values were not meaningfully different.

Table 9. Pharmacokinetic parameters of MPA determined following a single oral dose of Myfortic[®] 450 mg/m² body surface area to stable pediatric renal transplant patients (Study 0106).

Parameter	Cohort I (n = 11)	Cohort II (n = 13)	All (n = 24)
Age (yr)*	8 (5 – 10)	14 (11 – 16)	11 (5 – 16)
Body Surface Area (m ²)*	1.02 (0.72 – 1.27)	1.47 (0.84 – 1.98)	1.18 (0.72 – 1.98)
Tlag (hr)*	1.0 (—)	0.5 (—)	0.75 (—)
Tmax (hr)*	2.5 (—)	2.5 (—)	2.5 (—)
Cmax ($\mu\text{g}/\text{mL}$) [^]	40.2 \pm 24.9	33.0 \pm 17.2	36.3 \pm 21.1
Cmax/Dose ($\mu\text{g}/\text{mL}/\text{mg}$) [^]	0.09 \pm 0.05	0.05 \pm 0.03	0.07 \pm 0.04
AUC ∞ ($\mu\text{g}\cdot\text{hr}/\text{mL}$) [^]	82.2 \pm 27.9 [#]	66.4 \pm 13.9 [#]	74.3 \pm 22.3 ^{**}
AUC ∞ /Dose ($\mu\text{g}\cdot\text{hr}/\text{mL}/\text{mg}$) [^]	0.18 \pm 0.06 [#]	0.12 \pm 0.05 [#]	0.15 \pm 0.06 ^{**}
CL/F (L/hr) [^]	6.2 \pm 2.3 [#]	9.2 \pm 3.9 [#]	7.7 \pm 3.4 ^{**}
CL/F/BW (L/hr/kg) [^]	0.21 \pm 0.12 [#]	0.21 \pm 0.04 [#]	0.21 \pm 0.08 ^{**}
t _{1/2} (hr) [^]	8.1 \pm 4.1 [#]	8.9 \pm 3.1 [#]	8.5 \pm 3.5 ^{**}

* median (range), [^] mean \pm SD (CV %), [#] n = 5, ^{**} n = 10

There was no apparent correlation between patient's age and the pharmacokinetic parameters of MPA ($p > 0.05$). However, the dose-normalized C_{max} of MPA were negatively correlated with patient's body weight ($r = 0.622$, $p = 0.001$) and body surface area ($r = 0.630$, $p = 0.001$) with statistical significance. The dose-normalized AUC ∞ of MPA were negatively correlated with

patient's body weight ($r = 0.594$, $p = 0.070$) and body surface area ($r = 0.626$, $p = 0.053$) with borderline statistical significance. The CL/F of MPA was significantly positively correlated with patient's body weight ($r = 0.753$, $p = 0.012$) and body surface area ($r = 0.673$, $p = 0.033$). The trend was very similar for the parameters of MPAG.

c. Gender

Gender does not appear to affect on MPA pharmacokinetics in a clinically significant degree. In a pharmacokinetic analysis using the data from 21 stable renal transplant patients pooled from Studies 0102 and B301, the mean AUC and C_{max} values of MPA in females were 29.2 µg/mL and 70.0 µg-hr/mL, respectively. In contrast, the values in males were 28.7 µg/mL and 56.1 µg-hr/mL, respectively. In a mixed effects analysis including age and weight, the mean AUC value in females were higher by 22% than the value in males but the difference was not statistically significant ($p > 0.05$).

d. Race

The effect of ethnic difference on MPA pharmacokinetics was not reliably determined. Most patients enrolled in CPB studies for Myfortic[®] were Caucasians and, therefore, the number of black and Asian patients enrolled was very small. In the food effect study (0109) following a single oral dose of Myfortic[®] 720 mg, there were 3 blacks and 1 Asian among 18 study patients. The mean AUC values of MPA in blacks and all patients were 35.9 µg-hr/mL and 40.4 µg-hr/mL, respectively. In Study 2302, following a steady state dose of Myfortic[®] 720 mg, there were 3 blacks and 1 Asian among 40 study patients. The mean AUC values of MPA in blacks and all patients were 75.5 µg-hr/mL and 74.7 µg-hr/mL, respectively. In the pediatric study (0106), there was only 1 black. In Studies 0109 and 2302, the mean of MPA AUC for the 3 black patients was similar to that for all patients.

e. Renal Impairment

The sponsor did not conduct a specific clinical or clinical pharmacology study to determine the effect of renal insufficiency on MPA pharmacokinetics but seeks a labeling claim based on a medical literature review. Note that most articles provided by the sponsor to support the claim on the effect of renal insufficiency on MPA pharmacokinetics report the results determined using MMF. The articles are acceptable for review because Myfortic[®] delivers the same active moiety (MPA) to the systemic circulation and, therefore, the disposition of MPA following Myfortic[®] administration would not be appreciably different from the disposition following MMF administration. Based on the published articles, the sponsor summarized the following features of MPA pharmacokinetics in renal insufficiency:

- MPA exposure (AUC) is not appreciably different over the range of renal function from normal to severe impairment. Given the fact that MPA is extensively metabolized *via* glucuronidation to MPAG, it would not be expected that renal failure results in an increase in MPA exposure.
- MPAG exposure increases as renal function decreases because MPAG is predominantly renally cleared.

- A 2- to 3-fold increase in free MPA concentration was observed in a setting of severe renal insufficiency because MPA is highly bound to plasma proteins, in particular, albumin (>95%), and high concentrations of both MPAG and BUN compete with MPA for plasma protein binding sites.
- Dialysis is not an effective method of clearing MPA because of the high protein binding characteristics of MPA.

The CellCept® package insert reported 75% and 33% increase in MPA AUC following a single dose of CellCept® 1000 mg in severe (GFR < 25 mL/min) and mild (GFR, 50 mL/min to 80 mL/min) renal impairment, respectively, compared to healthy control (GFR > 80 mL/min). The MPAG AUC was 3- to 6-fold higher in severe renal impairment.

f. Hepatic impairment

The sponsor did not conduct a clinical or clinical pharmacology study to determine the effect of hepatic impairment on MPA pharmacokinetics but seeks a labeling claim based on a medical literature review. Note that most articles provided by the sponsor to support the claim report results determined using MMF. The articles are acceptable as reasoned in the previous section for renal impairment. Based on the published articles, the sponsor concluded as follows:

The predominant metabolic pathway for MPA is the conjugation *via* glucuronyl transferase to MPAG. It is known that glucuronyl transferase is unaffected by hepatic disease. This is due to hepatic glucuronidation being a high capacity system which maintains activity even in the face of decreased hepatic function. Therefore, MPA pharmacokinetics are not effected by the level of hepatic function.

2. Based upon what is known about exposure-response relationships and their variability, and the groups studied; what dosage regimen adjustments are recommended for each of these subgroups?

a. Elderly

No dosage adjustment is recommended for elderly patients.

b. Pediatric patients

The sponsor conducted no clinical study to determine pediatric doses, and proposed no pediatric indications and thus no dosage recommendations for pediatric patients at this time. Incidentally, the mean AUC in pediatric patients following a nominal dose of 450 mg/m² BSA (Study 0106) was greater by 24% than that of adults following a dose of 416 mg/m² BSA (Study 0102, see section II. C. b. *Pediatric patients*). Adjusting the 8.2% higher dose administered to pediatric patients, the mean AUC appears to be greater by 16% in pediatric patients compared to that in adult patients. At a nominal dose of 400 mg/m² BSA, the AUC would be greater by 5% in pediatric patients. In the absence of safety and efficacy data for Myfortic® determined in children, the nominal dose of 400 mg/m² BSA would be a reasonable dose for Myfortic® based on available pharmacokinetic data. However, since only two tablet strengths (180 mg and 360 mg) are available in Myfortic®, the actual pediatric dose would be 360 mg, 540 mg, or 720 mg

that is rounded up or down from the nominal dose. For younger children whose BSA ranges from 0.90 m² to 1.35 m², the rounding would be up to 20%, whereas the rounding would be up to 14% for older children whose BSA ranges from 1.35 m² to 1.80 m². Therefore, a lower cut-off of BSA for Myfortic[®] dosing was recommended to be 1.19 m² not to exceed the rounding more than 14%. Thus, Myfortic[®] tablets are not recommended for younger children (BSA < 1.19 m²) because the tablet strengths do not allow an accurate dosing based on BSA. For CellCept[®], a nominal dose of 600 mg/m² BSA is recommended in the labeling for pediatric use. CellCept[®] is available as oral solution in addition to solid dosage forms.

c. Gender

No dosage adjustment is recommended based on gender.

d. Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

No dosage adjustment is recommended based on race.

e. Renal impairment

The sponsor did not propose Myfortic[®] dose adjustment based on patient's renal function. The sponsor proposed the same dose for patients experiencing delayed renal graft function post-operatively. However, the sponsor recommends a careful follow-up for patients with severe chronic renal impairment (GFR < 25 mL/min/1.73 m²) because MPAG may be accumulated. In CellCept[®] labeling, no more than CellCept[®] 1000 mg is recommended for severe renal impairment.

f. Hepatic impairment

No dose adjustment is recommended for renal transplant patients with hepatic impairment.

g. What pregnancy and lactation use information is there in the application?

No adequate and well-controlled studies were conducted for Myfortic[®] in pregnant women and it is not known whether MPA is excreted in human milk. The sponsor proposed Pregnancy Category C for Myfortic[®] as proposed for CellCept[®]. Therefore, Myfortic[®] should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus. It is recommended that Myfortic[®] therapy should not be initiated until a negative pregnancy test has been obtained. Effective contraception must be used before beginning Myfortic[®] therapy, during therapy, and for six weeks following discontinuation of therapy. It is recommended that a decision be made whether to discontinue the drug or to discontinue nursing while on treatment or within 6 weeks after stopping therapy.

D. Extrinsic Factors

1. What extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Some drugs when administered concomitantly are likely to affect MPA exposure (see section D.3. *Drug-Drug Interactions*). No extrinsic factors other than coadministered drugs are reported to influence MPA exposure.

2. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments do you recommend for each of these factors?

Not applicable.

3. Drug-Drug Interactions

a. Is there an *in vitro* basis to suspect *in vivo* drug-drug interaction?

There is no *in vitro* evidence to suspect *in vivo* drug-drug interaction involving CYP enzymes. Incubation of MPA with human liver microsomes in the presence of NADPH (absence of UDPGA) resulted in very low levels of CYP-dependent metabolism. In a CYP inhibition study using human liver microsomes, the ratio of free C_{max} to inhibition constant (K_i) of MPA for the inhibition of midazolam metabolism (CYP3A4/5 marker substrate) was 0.0080 (Table 10). Similarly, the ratio for phenacetin (CYP1A2 marker substrate) was 0.0047. The free C_{max} of MPA was estimated from total $C_{max} = 31.2 \pm 18.1 \mu\text{g/mL}$ ($32.6 \pm 18.9 \mu\text{M}$) and $f_u = 1.4 \pm 0.4\%$ determined in Study 2302 following a steady state dose of Myfortic[®] 720 mg. Therefore, the inhibitory effect of MPA on CYP3A4/5 or CYP1A2 substrate metabolism appears to be negligible *in vivo*. There was no significant inhibition of the metabolism of other CYP marker substrates by MPA at the concentration of up to 500 μM .

Table 10. Inhibition of the metabolism of human CYP enzyme marker substrates by MPA.

CYP Enzyme	Specific Enzymatic Activity	Inhibition Constant for MPA (K_i)	Inhibition Type	free MPA C_{max}^A / K_i
CYP1A2	Phenacetin O-deethylation	$98 \pm 9 \mu\text{M}$	competitive	0.0047
CYP2A6	Coumarin 7-hydroxylation	no inhibition*		
CYP2C8	Paclitaxel 6 α -hydroxylation	70% relative activity*		
CYP2C9	S-Warfarin 7-hydroxylation	no inhibition*		
CYP2C19	S-Mephenytoin 4-hydroxylation	no inhibition*		
CYP2D6	Bufuralol 1'-hydroxylation	no inhibition*		
CYP2E1	Chlorzoxazone 6-hydroxylation	85% relative activity*		
CYP3A4/5	Midazolam 1'/4-hydroxylation	$57 \pm 6 \mu\text{M}$	competitive	0.008

^A from total $C_{max} = 31.2 \pm 18.1 \mu\text{g/mL}$ ($32.6 \pm 18.9 \mu\text{M}$) and $f_u = 1.4 \pm 0.4\%$ (Study A2302), * up to MPA 500 μM

b. *Is the drug a substrate of CYP enzymes?*

MPA is not a good substrate of CYP enzymes. Incubation of MPA with human liver microsomes resulted in very low levels of CYP-dependent metabolism.

c. *Is the drug an inhibitor and/or an inducer of CYP enzymes?*

MPA is a poor CYP1A2 and 3A4/5 inhibitor as mentioned in section D.3.a. MPA is not known to be a CYP inducer.

d. *Is the drug an inhibitor and/or an inducer of P-glycoprotein transport processes?*

MPA does not appear to be a P-glycoprotein substrate based on *in vitro* permeability study using Caco-2 cell monolayers (see section E.1.b, *Permeability*). It is not known whether MPA is an inhibitor or inducer of P-glycoprotein transport processes.

e. *Are there metabolic/transporter pathways that may be important?*

There is no known metabolic/transporter pathway that may be important for a pharmacokinetic interaction between MPA and other potential comedications. The involvement of transport systems other than P-glycoprotein in the inhibition of MPA enterohepatic circulation has not been ruled out.

f. *Does the label specify co-administration of another drug and has the interaction potential between these drugs been evaluated?*

The labeling addresses the drug-drug interaction potential of Myfortic[®] with cyclosporine and antacids based on the studies conducted by the sponsor (see section III. DETAILED LABELING RECOMMENDATIONS). The label also addresses the potential, as shown in the CellCept[®] package insert and/or based on the medical literature review, when Myfortic[®] is administered concomitantly with acyclovir, ganciclovir, azathioprine, MMF, cholestyramine and bile acid binders, oral contraceptives, and live vaccines.

g. *What other co-medications are likely to be administered to the target patient population?*

Myfortic[®] has been administered in combination with the following agents other than stated in the previous question in clinical trials: antilymphocyte/thymocyte immunoglobulin, Simulect (basiliximab), Zenapax (daclizumab), Orthoclone OKT3 (muromonab), and corticosteroids. The efficacy and safety of the use of Myfortic[®] with other immunosuppressive agents than cyclosporine and corticosteroids have not been studied.

h. *Are there any in vivo drug-drug interaction studies that indicate the exposure-response relationships are different when drugs are co-administered?*

Effect of Antacid on MPA Pharmacokinetics

Myfortic® administration with the antacid containing magnesium and aluminum ions resulted in a reduction of the extent of MPA absorption. Table 11 presents the pharmacokinetic parameters of MPA determined in stable renal transplant patients following a single oral dose of Myfortic® 720 mg with and without the four times daily administration of Maalox Regular Strength 30 mL containing aluminum hydroxide 225 mg and magnesium hydroxide 200 mg per each 5 mL (Study 0101). The reductions in Cmax and AUC of MPA absorption with Maalox® coadministration were approximately 25% and 37%, respectively. However, the respective median (range) delays in Tlag and Tmax of MPA absorption were only 0.25 (—) hr and 0.3 (—) hr. The AUC∞ and t1/2 of MPA were not compared because they were not reliably determined for the majority of study patients. Similarly, Myfortic® administration with Maalox® resulted in a reduction of the Cmax and AUCt of MPAG by approximately 16% and 24%, respectively. The median (range) delays in Tlag and Tmax of MPAG appearance were only 0.3 (—) hr and 0 (—) hr, respectively.

Table 11. Comparison between pharmacokinetic parameters of MPA following a single oral dose of Myfortic® 720 mg without and with a coadministration of Maalox® 30 mL to 12 stable renal transplant patients (Study 0101).

	Tlag (hr)*	Tmax (hr)*	Cmax (µg/mL) [^]	AUC _{0-t} (µg-hr/mL) ^{^#}
With Maalox®	0.75 (—)	2 (—)	17.4 ± 10.0	34.2 ± 11.8
Without Maalox®	0.25 (—)	2 (—)	18.6 ± 5.2	52.4 ± 10.2
Difference	0.25 (—)	0.3 (—)		
Geometric Mean Ratio			0.75 (0.47 – 1.19)	0.63 (0.51 – 0.79)

* median (range), [^] mean ± SD, [#] n = 11

The decreases in the Cmax and AUC of MPA and MPAG are possibly due to the chelation of MPA by magnesium and/or aluminum ions containing in the antacid. An effect on gastric emptying is not likely because the median changes in Tlag and Tmax were negligible. Therefore, it appears to be prudent to avoid taking Myfortic® simultaneously with magnesium / aluminum-containing antacids. Similar findings have been reported with CellCept®.

Effect of Myfortic® on Cyclosporine Pharmacokinetics

Myfortic® coadministration had no effect on cyclosporine pharmacokinetics. Table 12 presents a comparison between the cyclosporine pharmacokinetic parameters determined in stable renal transplant patients on day 1 without Myfortic® coadministration and day 10 with a steady state Myfortic® dose (Study 0102). The geometric mean ratios of Neoral® with Myfortic® to Neoral® alone for the Cmin, Cmax, and AUCt of cyclosporine were 1.06 (range, —), 0.96 (90% CI, 0.86 – 1.07) and 1.05 (90% CI, 0.99 – 1.12), respectively. These were all close to 1 and indicate no effect of Myfortic® on cyclosporine pharmacokinetics. Moreover, the difference in median Tmax was only 0.25 hr.

Table 12. Comparison between cyclosporine pharmacokinetic parameters determined in 12 stable renal transplant patients on day 1 without Myfortic[®] and day 10 with a steady state dose of Myfortic[®] 720 mg (Study 0102).

PK Parameter	Neoral [®] alone (Day 1)	Neoral [®] with Myfortic [®] (Day 10)	Geometric Mean Ratio	90% Confidence Interval
Neoral [®] Dose (mg, b.i.d.)	117 ± 18 [#]	117 ± 18 [#]		
Tmax* (hr)	1 —	1.25 —		
Cmin [^] (µg/mL)	90.6 ± 0.57	96.9 ± 22.7	1.06	
Cmax [^] (µg/mL)	1143 ± 265	1090 ± 219	0.96	0.86 – 1.07
AUC _{12hr} [^] (µg-hr/mL)	3491 ± 621	3668 ± 579	1.05	0.99 – 1.12
CL/F [^] (L/hr)	35.7 ± 6.4 [#]	33.5 ± 5.1 [#]		
Vz/F [^] (L)	364 ± 119 [#]	267 ± 60 [#]		

* median (range), ^ mean ± SD, # N = 9

Effect of Cyclosporine on Myfortic[®] Pharmacokinetics

Cyclosporine potentially blocks the entero-hepatic recirculation of MPA. The literature reported that rats administered cyclosporine and MMF do not exhibit the secondary peaks in MPA plasma concentration-time profiles. This phenomenon appears to be due to the inhibition of MPAG secretion from liver cells into bile and hence an interruption of enterohepatic recycling. The net results were lower levels of MPA but higher levels of MPAG than expected when compared to MMF monotherapy. The same net outcome has been observed in patients as well. The mechanism for the interruption of secretion is not known.

Other *In Vivo* Drug Interactions

The sponsor conducted no other drug-drug interaction studies than mentioned above for this application. Instead, the sponsor provided the information on drug-drug interactions reported in the literature and/or studied for CellCept[®].

i. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

Myfortic[®] is to be coadministered with other immunosuppressive drugs such as steroids, cyclosporine / tacrolimus, basiliximab / daclizumab, and muromonab in transplant patients. Therefore, an over-immunosuppression may occur in the coadministration and lead to infections or lymphomas.

j. Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

MPA binding to plasma proteins, in particular albumin, was high. In *in vitro* studies, the unbound fraction was <7% and was independent of MPA concentration over the range of 0.1 µg/mL to 100 µg/mL. The bound fraction varies according to albumin concentration. In cases of hypoalbuminemia, the free fraction may increase.

In the medical literature, MPA bioavailability after the administration of MMF determined in stable renal transplant patients receiving chronic cyclosporine doses was lower than that determined in healthy subjects. The lower MPA concentrations, higher MPA excretion in the urine, and higher renal MPA clearance have also been reported in the literature for renal transplant patients on cyclosporine. The mechanism and clinical significance of the finding is not clearly known. The finding may be due to higher BUN and lower albumin present in the patients compared to normal healthy subjects. Both of these biochemistry features would tend to increase the free MPA concentrations available for renal filtration. A decrease in Myfortic[®] bioavailability by cyclosporine was also speculated based on the comparison between the Myfortic[®] absolute bioavailability determined in stable renal transplant patients (72%, Study 0104) and healthy subjects (> 90%, []).

4. What issues related to dose, dosing regimens, or administration are unresolved, and represent significant omissions?

No additional issues are recognized at this time.

E. General Biopharmaceutics

1. Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility and permeability data support this classification?

a. Solubility

At 37°C after 24 hours equilibration, MPS was soluble in water (— mg/mL) and simulated intestinal fluid of [] buffer pH (— mg/mL), and practically insoluble in simulated gastric fluid of 0.1 N hydrochloric acid (— mg/mL). At 25°C after 24 hours equilibration, MPS was soluble in — (— mg/mL) and — buffer pH — mg/mL), slightly soluble in water (— mg/mL) and — (— mg/mL), and practically insoluble in 0.1 N hydrochloric acid (— mg/mL). Thus, the highest strength of Myfortic[®] 360-mg tablet is soluble in — mL ([] of water, [] and — buffer pH [] but not soluble in 0.1 N hydrochloric acid. Therefore, strictly speaking, Myfortic[®] is not a high solubility drug product from a BCS perspective.

b. Permeability

In the determination of the permeability profile of MPA, human intestinal cell line Caco-2 grown on a permeable filter support was used. The apical-to-basolateral permeability of MPA was 158×10^{-5} cm/min (Table 13). The basolateral-to-apical permeability was comparable to the apical-to-basolateral permeability. When compared with the permeability of propranolol that has shown > 90% absorption in human studies, MPA was four times more permeable. Therefore, MPA is a highly permeability drug from a BCS perspective. In addition, the ratio of MPAG AUC (i.e., MPAG AUC after oral Myfortic dose / MPAG AUC after intravenous MPA dose) was 0.93, which indirectly show a high permeability of MPA following an oral dose.

Table 13. Permeability coefficients of P_{app} (mean \pm SD) across Caco-2 cell monolayers.

Compound	Conc (μ M)	Apical to Basolateral		Basolateral to Apical	
		P_{app} (10^{-5} cm/min)	% Recovery	P_{app} (10^{-5} cm/min)	% Recovery
MPA	5	158 \pm 14	109	152 \pm 3	113
Mannitol	0.01	2.2 \pm 0.3	98		
Propranolol	0.01	41.4 \pm 1.8	48		

2. What is the *in vivo* relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

Both to-be-marketed and clinical trial formulations of Myfortic[®] 360-mg strength tablets were used in pivotal clinical trials (B301 and B302). The *in vivo* relationship of the proposed to-be-marketed to pivotal clinical trial formulation was not determined.

a. What data support a waiver of *in vivo* bioequivalence data (BCS classification system, formulation ingredient information, dissolution profiles)?

The clinical formulations differ in minor manufacturing process, shape, color, and imprint from the to-be-marketed formulation (see Chemistry Review). Those changes do not appear to require an *in vivo* bioequivalence study. Furthermore, the proposed to-be-marketed formulation was predominantly used in the clinical pivotal trials.

b. What are the safety or efficacy issues for bioequivalence studies that fail to meet the 90% CI using bioequivalence limits of 80 - 125%?

Not applicable.

c. If the formulations do not meet the standard criteria for bioequivalence, what clinical pharmacology and/or clinical safety and efficacy data support the approval of the to-be-marketed product?

Not applicable.

d. If the formulations are not bioequivalent, what dosing recommendations should be made that would allow approval of the to-be-marketed formulation?

Not applicable.

3. What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A high fat meal delayed the rate of MPA absorption and MPAG formation following an oral Myfortic[®] administration: the Tlag and Tmax of MPA and MPAG were prolonged and the Cmax values were decreased. A high fat meal also increased the variability of the rate of MPA

absorption and MPAG formation. However, high fat meal had no effect on the extent (AUC) of MPA and MPAG exposure.

Following a single oral dose of Myfortic[®] 720 mg to 18 stable renal transplant patients with FDA-recommended high fat meal, the Tlag and Tmax of MPA were apparently much more variable than those following the dose under fasted conditions (Figure 2, Study 0109). In many subjects, there appeared to be two MPA concentration peaks. The magnitudes of the peaks under fed conditions were apparently lower than those under fasted conditions.

Figure 2. Combined individual concentration-time profiles of MPA following a single oral dose of Myfortic[®] 720 mg to 18 stable renal transplant patients under fed and fasted conditions (Study 0109) (Note that the scales of Y-axis in figures A and B are not the same.)

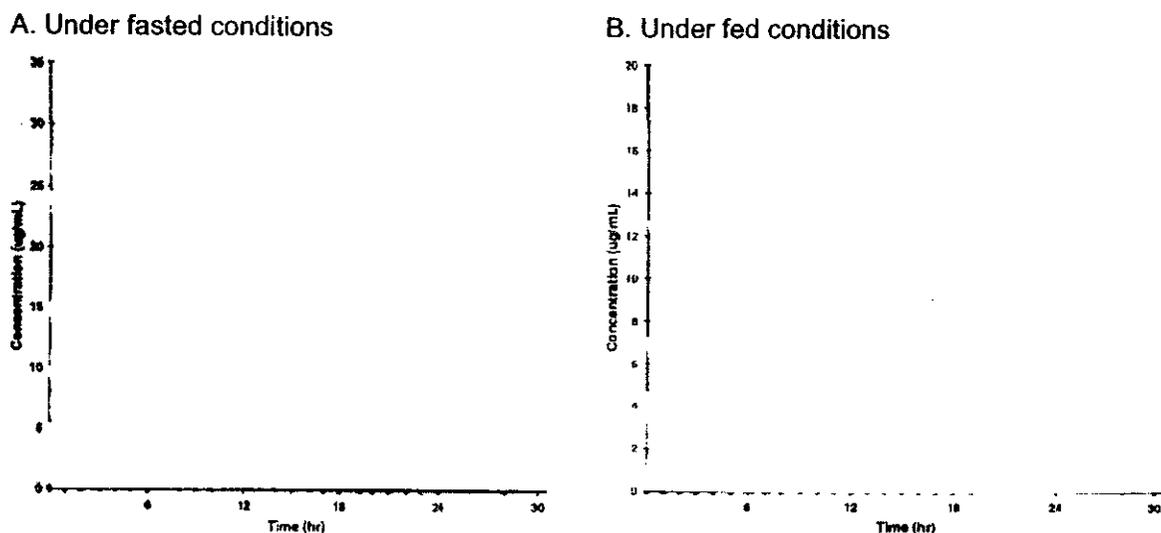


Table 14 presents a comparison between MPA pharmacokinetic parameters determined under fed and fasted conditions in the food effect study (0109). The administration of Myfortic[®] under fed conditions resulted in a marked delay and variability in MPA absorption. The median Tlag and Tmax of MPA determined under fed conditions were longer by 3.5 hr (range, []) and 5 hr [], respectively, than those determined under fasted conditions. Whereas the respective ranges of the Tlag and Tmax were 0 hr to 6 hr and 1 hr to 12 hr under fasted conditions, those were 0 hr to 10 hr and 2 hr to 23 hr under fasted conditions. The administration under fed conditions also resulted in a 33% decrease in MPA Cmax. However, the extent of MPA absorption (AUCt) was comparable (LSM ratio, 0.91; 90% CI, 0.82 – 1.01). The amount of MPA excreted in urine and the renal clearance were also comparable. The AUC[∞] and t_{1/2} of MPA were not compared because those were not reliably determined.

Table 14. Comparison between MPA pharmacokinetic parameters determined following a single oral dose of Myfortic 720 mg to 18 stable renal transplant patients under fed and fasted conditions (Study 0109).

PK Parameter	Fed (Test)	Fasted (Reference)	Difference (Range)	LSM Ratio [^] (90% CI)
Tlag (hr) [*]	4	1	3.5	
Tmax (hr) [*]	7	2	5	
Cmax (µg/mL) [#]	10.7 ± 5.1	15.6 ± 7.2		0.67 (0.52 - 0.86)
AUCt (µg-hr/mL) [#]	36.2 ± 9.8	40.4 ± 15.4		0.91 (0.82 - 1.01)
Ae _{48hr} (% dose) [#]	3.0 ± 1.4	3.1 ± 2.5		
CLr (mL/min) [#]	11.2 ± 6.8	9.8 ± 7.6		1.14

* median (range), # mean ± SD (CV %), ^ least squares mean ratio

The overall effect of high fat meal on MPAG pharmacokinetics was similar to that on MPA pharmacokinetics. The respective median (range) Tlag and Tmax of MPAG determined under fed conditions were longer by 4 hr ([3]) and 5 hr ([3]). However, the Cmax, AUCt, and AUC_∞ of MPAG were not meaningfully different between fed and fasted conditions: all LSM ratios and corresponding 90% CI were within the range of 0.8 – 1.25. The mean t_{1/2} values were also comparable between the two conditions (13.4 hr versus 14.0 hr).

Given that Myfortic[®] formulation is designed to not release MPA in the stomach, the food effect appears to be due to increase in gastric emptying time under fed conditions. Another food effect study conducted (W154) was not reviewed because the blood sampling points as designed did not capture the full MPA exposure at later time points due to marked delay in MPA absorption.

Based on the food effect described above, the CPB reviewer recommends administering Myfortic[®] tablets on an empty stomach to minimize a potential variation in MPA exposure between doses. Particularly, MPA absorption can occur in the next rather than current dosing interval if Myfortic[®] tablets are administered under fed conditions. The pivotal phase II clinical trials were conducted with the administration of Myfortic[®] or CellCept[®] one hour before or two hours after meals (see Clinical Review).

4. When would a fed bioequivalence study be appropriate and was one conducted?

For a future consideration of Myfortic[®] administration with food, this reviewer recommends conducting an additional relative bioavailability study to compare the absorption profile of MPA following a steady state administration of Myfortic[®] 720 mg and CellCept[®] 1000 mg under fed conditions. Because the pivotal Phase III clinical studies submitted currently by the sponsor were conducted following the administration of Myfortic[®] and CellCept[®] on an empty stomach, a relative comparison of food effect on the MPA absorption, safety, and efficacy between Myfortic[®] and CellCept[®] is not possible at this time. It is speculated that the relative absorption profile of MPA compared under fed conditions would not be exactly the same as that compared under fasted conditions. However, the relative profile under fed conditions may allow Myfortic[®] to be administered with food to stable renal transplant patients. According to the current CellCept[®] labeling, CellCept[®] may be administered with food to stable renal transplant patients if necessary.

5. How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The sponsor proposed the following dissolution methods and specifications based on their dissolution studies:

Principle: Ph. Eur. 2.9.3, Dissolution Test for Solid Dosage Forms
 USP <724>, Delayed-release Forms

Apparatus: USP apparatus II (paddle)

Rotation Speed: 50 ± 2 rpm

Test Medium 1: 0.1 N hydrochloric acid for the first 120 min

Test Medium 2: buffer solution (After 120 min,
 is added to Test Medium 1. The pH of the
 mixture is adjusted to using
 or concentrated hydrochloric acid solution if
 necessary.)

Temperature: 37.0 ± 0.5 °C

Units tested: not less than 6 tablets (1 per vessel)

Analysis: UV absorbance at

Specifications: , for 120 min in Test Medium 1

Level 1: $Q = \%$ (not less than, NLT $\%$) within 60 min in Test Medium 2 using 6 units

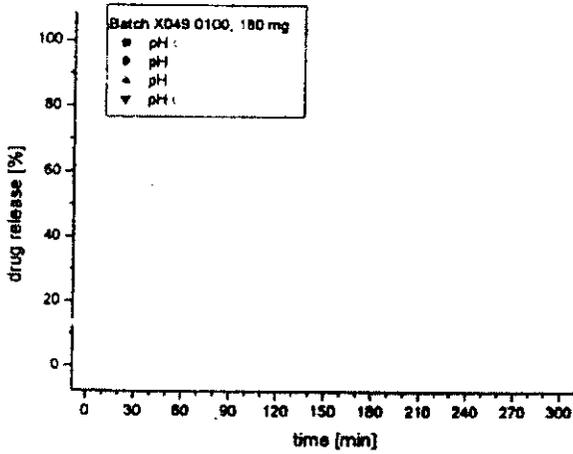
Level 2: mean $Q = \%$ with no unit $< \%$ ($Q - \%$) using 6 units in Level 1 plus 6 new units

As shown in Figure 3, the enteric coating remained intact during the 120 min in 0.1 N hydrochloric acid: the amount of drug substance dissolved from six individual tablets did not exceed . The profiles demonstrate that at pH the hypromellose phthalate polymer contained in the film coating starts to dissolve and release the drug substance. At this pH, release of drug substance was very slow. As the pH increased, dissolution of the drug substance increased.

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Figure 3. Dissolution profiles of Myfortic® tablets at different pH.

A. 180 mg tablets (n = 6)



B. 360 mg tablets (n = 6)

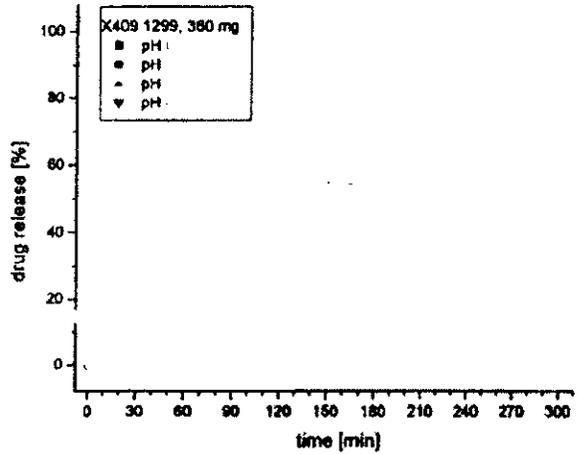
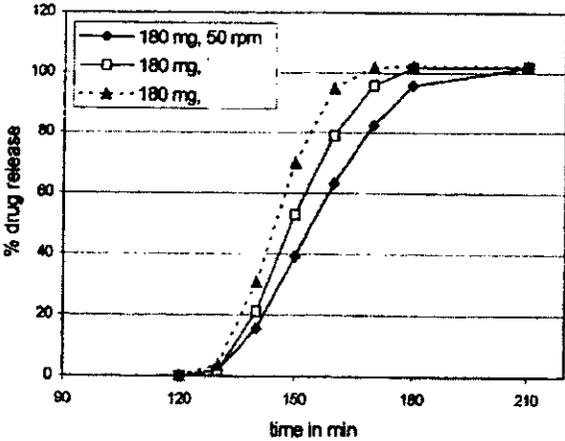


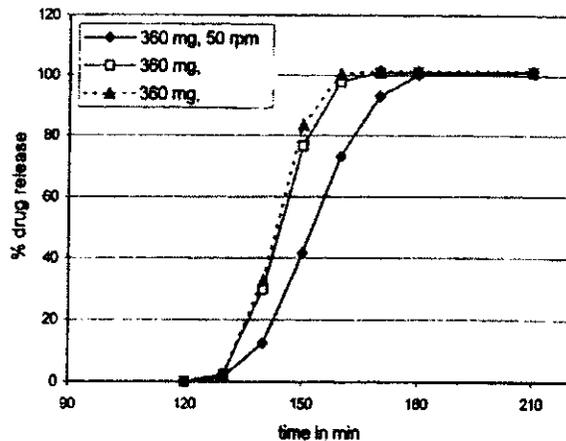
Figure 4 displays the mean dissolution profiles of Myfortic® tablets 180 mg and 360 mg at different paddle rotation speeds. The release rates decreased with decreasing rotation speeds. For the 50 rpm, the slowest dissolution profile was obtained. The dissolution profile for 360 mg strength at 5 rpm was very close to the profile obtained at 10 rpm, whereas the profiles at 15 and 20 rpm were clearly pronounced for 180-mg strength.

Figure 4. Dissolution profiles of Myfortic® tablets using the proposed method (12 units each profile)

A. 180 mg tablets



B. 360 mg tablets



As shown in Table 15, mean dissolution (%) was $96 \pm 4\%$ and $100 \pm 1\%$ for 180 mg and 360 mg strengths, respectively, at the speed of 50 rpm in 60 min at neutral pH (180 min after start of dissolution testing). Thus, the sponsor's proposed dissolution specifications are acceptable.

Table 15. Dissolution profiles of Myfortic® tablets using the proposed method (n = 12 each).

Rotation Speed	Strength	Parameter	Time (min)						
			120	130	140	150	160	170	180
50 rpm	180 mg (Test)	Mean % Release	0	1.7	15.4	39.1	63.1	82.5	95.8
		% Coeff. of Variation	-	38	26	14	10	7	4
	360 mg (Reference)	Mean % Release	0	1.3	12.4	41.5	73.2	93.0	100.0
		% Coeff. of Variation	-	13	38	19	10	4	1
rpm	180 mg (Test)	Mean % Release	0	1.6	21.2	52.9	79.0	95.8	-
		% Coeff. of Variation	-	20	26	13	7	4	-
	360 mg (Reference)	Mean % Release	0	1.7	25.8	73.3	96.9	100.9	-
		% Coeff. of Variation	-	37	56	17	4	1	-
rpm	180 mg (Test)	Mean % Release	0	3.7	30.8	70.0	94.9	-	-
		% Coeff. of Variation	-	39	27	14	6	-	-
	360 mg (Reference)	Mean % Release	0	1.8	29.4	82.7	100.2	-	-
		% Coeff. of Variation	-	123	29	7	2	-	-

6. What CPB and other information support the approval of the other strength of the to-be-marketed product that was not tested in clinical safety and efficacy studies?

The two pivotal safety and efficacy studies (B301 and B302) used Myfortic® 360-mg strength tablet. Myfortic® 180-mg strength tablet was used in dose proportionality (0105) and pediatric (0106) studies only. Therefore, the sponsor is seeking the approval of the 180-mg strength with a biowaiver based on the claims listed below. This reviewer added his comments after each claim.

① Myfortic® tablets are a BCS Class I drug products (high permeability and high solubility).

The BCS class of Myfortic® tablets was not adequately determined. MPA was highly permeable through Caco-2 cell monolayers (see section E.1.b. *Permeability*). Whereas MPA was highly soluble at a neutral pH range (see section E.1.a. *Solubility*), MPA was not highly soluble at strongly acidic pH and the sponsor did not determine the solubility at $\text{pH} = \text{pKa} - 1$ (pH). Therefore, the biowaiver request cannot be granted based on the properties of MPA in BCS. Furthermore, a biowaiver cannot be granted based on the BCS data for non-immediate release formulations such as Myfortic® (see current BCS Guidance). Nevertheless, a biowaiver can be considered based on other relevant claims.

② Both 180-mg and the 360-mg strengths share an identical ratio of drug substance and excipients.

Whereas the ratio of inactive ingredients in tablet core is proportional to the active ingredient as shown in Table 16, the amount of enteric coating agent (hypromellose phthalate) is not proportional. However, the two strengths may have a similar release mechanism because the amount of hypromellose phthalate is proportional with respect to tablet surface area (see Chemistry Review).

Table 16. Composition (mg) in Myfortic® tablets.

Ingredient	180 mg Strength	360 mg Strength	Function	Reference to standards
Core				
Mycophenolate sodium	(180)*	(360)*	drug substance	Novartis monograph
Lactose, anhydrous				Ph. Eur., NF
Crospovidone				Ph. Eur., NF
Povidone (K-30)				Ph. Eur., USP
Starch				Ph. Eur., NF
Colloidal silicon dioxide				Ph. Eur., NF
Magnesium stearate				Ph. Eur., NF
				Novartis monograph
Targeted core weight				
Film Coating				
Hypromellose phthalate			enteric coating	Ph. Eur., NF
Titanium dioxide			coloring agent	Ph. Eur., NF, 21CFR
Iron oxide yellow			coloring agent	95/45/EEC, NF, 21CFR
Indigotine			coloring agent	95/45/EEC, 21CFR
Iron oxide red			coloring agent	95/45/EEC, NF, 21CFR
				Novartis monograph
				Ph. Eur., USP
				Ph. Eur., NF
Targeted total weight	355.0	690.0		

③ Both strengths are manufactured by the same manufacturer and at the same production site.

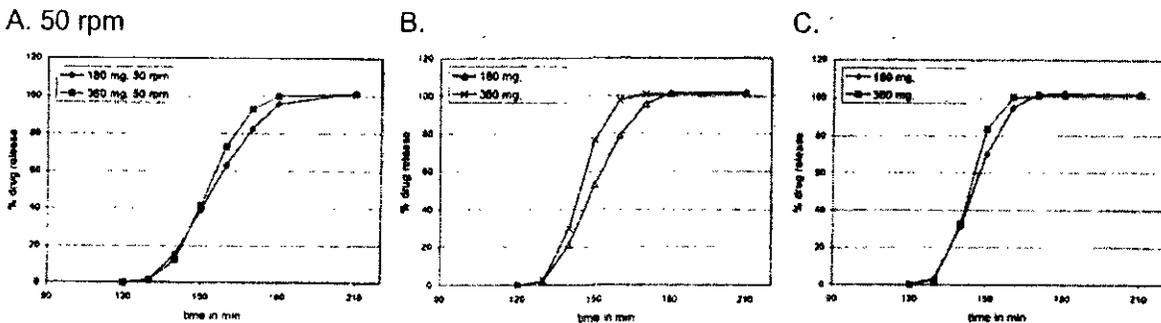
This statement does not necessarily mean the same manufacturing process. However, the manufacturing processes are slightly different in coating methods, which is not likely to cause a noticeable difference *in vivo* performance (see Chemistry Review).

④ The dissolution behaviors of the 180-mg and 360-mg strengths were comparable.

Using the data presented in Table 15, the calculated similarity factor F2 was 58 between the two strengths at the paddle rotation speed of 50 rpm. However, the CVs at the early sampling time points were higher than the values recommended in the Agency's Guidance. At 100 rpm, the intra-batch variability was outside the criteria recommended in the Agency's Guidance and, furthermore, the calculated F2 factor was only 47. Variability at the early time points of 130 to 150 minutes was extremely high. The sponsor explained the variability

which might cause the difference in the dissolution profile. At 100 rpm, the variability at the early time point of 130 minutes was high especially for the 360-mg tablets. The F2 was 60. Figure 5 graphically demonstrates the comparisons of dissolution profiles between 180-mg and 360-mg strength tablets at different paddle rotation speeds.

Figure 5. Comparison of dissolution profiles between 180-mg and 360-mg strengths of Myfortic® tablets at different paddle rotation speeds.



Because the within batch variation was higher than that in the Agency's Guidance, the sponsor applied the Weibull-model dependent approach using 90% CIs in the dissolution data analysis. At all paddle rotation speeds studied, the 90% CIs of the mean time parameter τ and the mean shape parameter β were within the range of τ ± 1 for dissolution similarity in comparison between the reference batch of 360-mg strength and three test batches of 180-mg strength.

- ⑤ A dose proportionality study (0105) showed that MPA pharmacokinetics were dose-proportional over the dose range of 180 mg to 2160 mg.

The C_{max} and AUC of MPA at the doses of 180 mg and 360 mg were not dose proportional when determined comparing their dose-normalized values using bioequivalence criteria: the respective LSM ratios (90% CI) for the C_{max}/Dose and AUC_t/Dose were 0.88 (0.63 - 1.22) and 1.17 (1.01 - 1.37, see section II. B. 5. h.).

- ⑥ The MPA release characteristics and MPA AUCs observed in a pediatric study (0106) using 180-mg strength were identical to those observed in adult studies using 360-mg strength.

This claim is not acceptable because no statistical test was performed and, in reality, the MPA exposure determined in pediatric patients was higher than the exposure determined in adult patients following a similar dose administered based on BSA (see section II.C.1.b. *Pediatric Patients*).

Overall, even though the sponsor's claims for the biowaiver request are not completely accurate, the CPB reviewer recommends granting the biowaiver for the 180-mg strength based on the proportionality in ingredients in essence, the similarity in dissolution profile, and the absence of limiting factors (solubility, permeability) in MPA absorption after dissolution at the pH range in the intestine.

7. If the NDA is for a modified release formulation of an approved immediate product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

This NDA is a 505(b)(2) application based on the comparable bioavailability and/or therapeutic equivalence of Myfortic® tablets (delayed release) to the previously approved CellCept® capsules (immediate release) providing the same active drug (MPA) upon absorption. Therefore, the

sponsor conducted clinical and clinical pharmacology studies (B301 and B302) to compare Myfortic® 720 mg (2 x 360 tablets, total 720 mg as MPA) and CellCept® 1000 mg (4 x 250 mg capsules, total 739 mg as MPA). As a result, the rate of MPA absorption following the administration of Myfortic® 720 mg was not equivalent to the rate following the administration of CellCept® 1000 mg although the two dosage forms contain near equimolar amounts of MPA.

In Study B301, not only the C_{max} but also AUC_τ of MPA were larger by 11% (LSM ratio, 1.11; 90% CI, 0.82 – 1.50) and 22% (LSM ratio, 1.22; 90% CI, 1.04 – 1.43), respectively, following Myfortic® (n = 12) than CellCept® (n = 16) administration when compared in a parallel manner based on the pooled values observed from *de novo* renal transplant patients completed all Week 2, month 3, and Month 6 study visits.

In Study B302, when the MPA pharmacokinetics were compared in a crossover manner in 18 evaluable stable renal transplant patients, the extent (AUC) of MPA absorption was comparable between steady state doses of Myfortic® 720 mg and CellCept® 1000 mg administered twice daily under fasted conditions. However, the rate of MPA absorption was more variable and delayed with lower C_{max} following Myfortic® than CellCept® administration.

Figure 6 displays a comparison of the combined individual concentration-time profiles of MPA determined in Study B302. The T_{lag} and T_{max} of MPA absorption are apparently longer and more variable following Myfortic® than CellCept® administration. For some patients, the absorption of previous dose appeared to be still ongoing at the time of Myfortic® test dose administration.

Figure 6. Combined individual concentration-time profiles of MPA determined following steady-state doses of Myfortic® and CellCept® to stable renal transplant patients in a crossover manner (n = 18, Study B302).

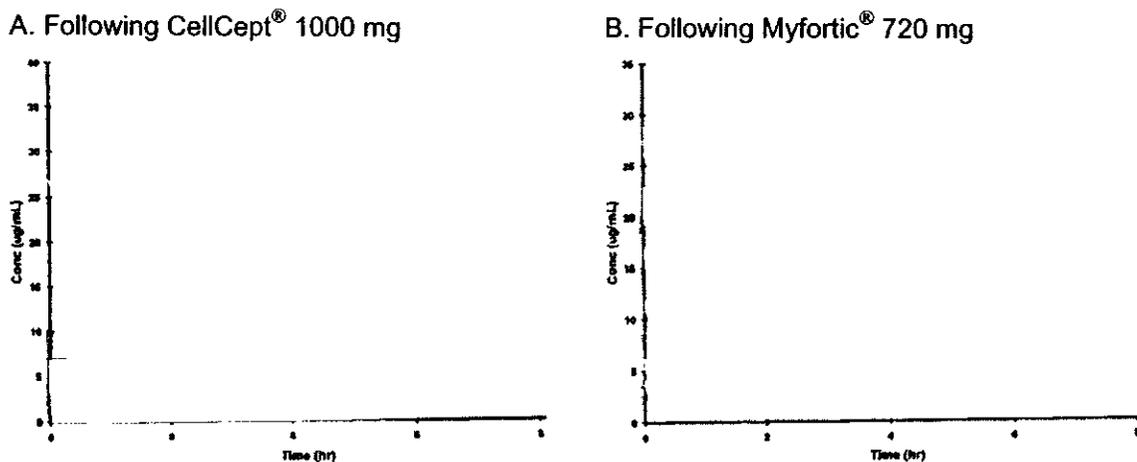


Table 17 presents a comparison of the pharmacokinetic parameters of MPA between Myfortic® and CellCept® administration in Study B302. Following Myfortic® than CellCept® administration, The median T_{max} of MPA was longer by 0.6 hr (range, 0.5 – 1.1), the C_{max} was lower by 11% (LSM ratio, 0.89; 90% CI, 0.70 – 1.13), but the C_{min} was higher by 34% (LSM ratio, 1.34; 90% CI, 0.70 – 1.13). The variability in T_{max} was larger in Myfortic® (range, 0.5 – 1.1) than CellCept® (range, 0.5 – 1.1), administration. However, the AUC_τ (LSM

ratio, 0.98; 90% CI, 0.87 – 1.11) and CL/F (LSM ratio, 1.02) were comparable. The variabilities in the C_{max}, C_{min}, AUC_τ, and CL/F was also comparable between the two products. The difference in MPA pharmacokinetics between the two products does not seem to be due to MPA-cyclosporine interaction because cyclosporine trough concentrations were also comparable at each study visit window (data not shown).

Table 17. Comparison between MPA pharmacokinetic parameters determined following a steady-state doses of Myfortic[®] 720 mg and CellCept[®] 1000 mg to stable renal transplant patients in a crossover manner (n = 18, Study B302).

PK Parameter	Myfortic [®] 720 mg (Test)	CellCept [®] 1000 mg (Reference)	Difference (Range)	Least Squares Mean Ratio (90% CI)
T _{max} (hr)*	1.5 —	0.8 —	0.6 —	
C _{max} (µg/mL)#	18.9 ± 7.9	21.3 ± 9.1		0.89 (0.70 – 1.13)
C _{min} (µg/mL)*, ^	2.0 ± 0.7	1.5 ± 0.7		1.34 (not reported)
AUC _τ (µg-hr/mL)#	57.4 ± 15.0	58.4 ± 14.1		0.98 (0.87 - 1.11)
CL/F (mL/min)#	13.6 ± 4.2	13.4 ± 5.0		1.02 (not reported)

* median (range), # mean ± SD (CV %), ^ n = 16

Studies W151 and W152 showed similar results to Study B302. However, Study 2302 showed an opposite trend that the respective C_{max} and AUC of MPA following a steady state dose of Myfortic[®] 720 mg were larger by 16% (LSM ratio, 1.16; 90% CI, 0.94 - 1.42) and 18% (LSM ratio, 1.18; 90% CI, 1.08 - 1.29) than the dose of CellCept[®] 1000 mg in an intent-to-treat analysis. The opposite results seem to be due to a delayed absorption of the Myfortic[®] dose administered a night before the pharmacokinetic study. The ratios were markedly reduced when analyzed after excluding subjects with high MPA carry-over.

Thus, Myfortic[®] 720 mg did not show a comparable MPA absorption profile (rate of absorption) to the near equimolar dose of CellCept[®] 1000 mg. Therefore, Myfortic[®] and CellCept[®] should not be used interchangeably.

8. If unapproved products or altered approved products were used as active controls, how is bioequivalence to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate bioequivalence?

Not applicable. The bioavailability / therapeutic equivalence studies conducted for this submission used approved CellCept[®] capsules as an active control.

9. What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

No other issues are recognized until now.

10. If replicate design studies were conducted and individual bioequivalence was analyzed, what were the outcomes with respect to variability and subject-by-formulation interactions?

Not applicable.

F. Analytical

1. How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

See Section F.4. below.

2. Which metabolites have been selected for analysis and why?

MPAG has been selected for analysis in most CPB studies. This is appropriate because MPAG is the major metabolite accounting for approximately 96% of the plasma AUC of the total moieties (parent and metabolites). MPA acyl glucuronide accounting for approximately 1% of the AUC was measured for metabolite profiling purpose only (Study 2302).

3. For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total (bound and unbound) plasma concentrations were measured for MPA and MPAG, which is appropriate. Because MPA and MPAG are highly bound to plasma proteins, the total concentrations would not be meaningfully different from bound concentrations. Unbound concentrations have no additional value for the purpose of this application but are technically difficult to measure compared to the total concentrations, and therefore unbound concentrations were measured for protein binding studies only.

4. What bioanalytical methods are used to assess concentrations?

MPA concentrations (unchanged MPA) in plasma were determined directly using high performance liquid chromatographic (HPLC) methods with UV detection in most CPB studies. Total MPA concentrations in plasma were determined after enzymatic hydrolysis of the MPAG using the HPLC methods. MPAG (conjugated MPA) concentrations in plasma were calculated by [total - unchanged MPA concentrations]. In Study B302 only, the commercial enzyme immunoassay EMIT () was used for the determination of MPA concentrations. In Study 2302 MPA, free MPA and MPA acyl glucuronide concentrations were determined using an HPLC method () the lower limit of quantitation (LOQ) were \sim ng/mL and \sim μ g/mL, respectively.

Unchanged MPA Assay using HPLC Methods

In an initial validation, the HPLC method for the determination of unchanged MPA consisted of plasma protein precipitation with acetonitrile and direct injection of supernatant in an HPLC system coupled to an UV detector at \sim n. The retention time of MPA ranged between \sim and \sim min. The LOQ was \sim μ g/mL. The calibration curves from \sim ng/mL to \sim ng/mL were fitted with a quadratic least square equation ($y = a + bx + cx^2$) and the correlation coefficients (r^2) were > 0.999 over three days. The quality controls (QC) consisted of \sim ng/mL, \sim ng/mL, and \sim ng/mL. The absolute recoveries of the QCs were () respectively. The intra-day precision (CV %) and accuracy (bias %) ranged from () ()

and from [] ng/mL) to [] ng/mL), respectively. The inter-day precision and accuracy ranged from [] and from [] respectively. Blank human plasma samples showed no interference in the chromatograms at the elution time of MPA. The in-process performance of the MPA assay is summarized in Table 18.

Table 18. In-process performance of the analytical methods used to measure the concentrations of MPA, MPAG, and cyclosporine.

Study	Sample	Site	Method	Analyte	QC (µg/mL)	Accuracy (mean bias %)	Precision (CV %)	Calibration Range (µg/mL)	LOQ (µg/mL)
0101	Plasma	BAPK-CH	HPLC	MPA, Total MPA		-6.6	9.8		
						-0.9	5.6		
						4.1	4.7		
0102	Plasma	BAPK-CH	HPLC	MPA, Total MPA		-5.9	8.4		
						2.1	6.8		
						2.2	3.2		
	Whole Blood	BAPK-CH	Immuno-assay	Cyclosporine		0.3	8.2		
						1.2	12.5		
					-2.4	7.6			
0104	Plasma	BAPK-CH	HPLC	MPA, Total MPA		-7.5	12.9		
						0.9	7.8		
						0.9	5.2		
0105	Plasma	BAPK-CH	HPLC	MPA, Total MPA		5.8	7.3		
						3.0	4.5		
						1.8	4.5		
						1.3	4.7		
0106	Plasma	BAPK-F	HPLC	MPA		3	7		
						-1.1	6		
				Total MPA		1	5		
						-1.5	9		
						1	6		
					2	7			
0109	Plasma	BAPK-CH	HPLC	MPA		5.6	8.4		
						6.2	4.3		
				Total MPA		6.5	5.3		
						6.6	4.7		
	Urine	BAPK-CH	HPLC	MPA		-7.0	6.0		
						-2.5	5.0		
				Total MPA		-2.1	3.1		
						1.1	2.5		
					5.1	4.5			
2302	Plasma	BAPK-F	HPLC	MPA		-6.0	5.0		
						-9.3	6.9		
						-6.0	8.5		
				Total MPA		-4.3	18.1		
						-8.0	4.6		
						7.7	3.6		
B301	Plasma	BAPK-CH	HPLC	MPA		2.8	8.4		
						2.5	5.0		
						1.8	4.1		
B302	Plasma	Charite Hospital, Berlin	EMIT	MPA		5	11.3		
						-0.1	8.3		
						0.2	9.3		
W151	Plasma	BAPK-CH	HPLC	MPA		8.9	11.9		
						-9.7	7.8		
						-5.1	5.6		
						1.4	9.7		

W152	Plasma	BAPK-CH	HPLC	MPA	-4.7	9.6		
					-2.5	5.4		
					0.6	2.6		
					0.0	2.1		
W154	Plasma	EAPK-CH	HPLC	MPA, Total MPA	-2.9	8.3		
					3.3	6.4		
					0.4	4.2		

BAPK-CH and BAPK-F Novartis Bioanalytics and Pharmacokinetics in Basel, Switzerland and in Rueil-Maison, France, respectively;

MPA was stable in spiked plasma samples at room temperature over 3 days: the bias determined on the third day ranged from [] MPA was stable in spiked plasma samples after successive freeze-thaw cycles: the recovery after the third cycle ranged from [] Processed QC samples were stable for 24 hours at 4°C and at room temperature: recovery values ranged from [] and from [] respectively. MPA was also stable in a long term storage: the bias between [] old samples and freshly prepared calibrators ranged from []

Unchanged MPA Assay using EMIT

EMIT utilizes the homogeneous enzyme immunoassay technology. The assay is based on competition for MPA antibody binding sites. MPA in the sample competes with MPA labeled with the enzyme glucose-6-phosphate dehydrogenase (Enzym Reagent 2). Active (unbound) enzyme converts the oxidized nicotinamide adenine dinucleotide (NAD) (Antibody Reagent I) to NADH, resulting in a kinetic absorbance change that can be measured spectrophotometrically. Enzyme activity decreases upon binding to the antibody, allowing the MPA concentration in the sample to be measured in terms of enzyme activity. The estimation was performed without sample preparation. The LOQ was [] µg/mL and the standard curves were constructed in the range of [] µg/mL. In a pre-study validation, the respective intra- and inter-assay precision ranged from [] and from [] by testing of three QCs ([] µg/mL, [] µg/mL, and [] µg/mL). The relationship between the HPLC and EMIT assays was: $EMIT = [] HPLC + []$ The correlation coefficient was 0.987. MPAG showed no interference. The in-process performance of this assay is summarized in Table 18.

Total MPA Assay using HPLC Methods

Total (unchanged and conjugated) MPA concentrations were measured after an enzymatic hydrolysis of MPAG using an HPLC method. The assay was started four hours after the incubation of triplicated samples with 12.5-fold dilution in the presence of 500 units of β-glucuronidase at 37°C. Due to the absence of MPAG as reference compound, completeness of the enzyme reaction and consequent absolute MPAG concentration could not be quantitatively determined. A conversion factor [molecular weight of MPAG / molecular weight of MPA = 1.55] was applied. The LOQ for MPA and MPAG was [] µg/mL and [] µg/mL, respectively. The calibration curves in the range from [] µg/mL had $r^2 > 0.999$ over three days. The QC consisted of [] ng/mL, [] ng/mL, and [] µg/mL. The intra-day precision and accuracy ranged from [] and from [] respectively. Plasma samples from Study W151 were reanalyzed for the determination of unchanged MPA concentrations after storage at -20°C and the recovery ranged from [] compared to week 1 values. The in-process performance of this assay is summarized in Table 18.

Cyclosporine Assay

Cyclosporine concentrations were measured locally using an immunoassay or HPLC method according to individual study center's routine transplant patient care in most CPB studies. In Study 0102, for an accurate determination of Myfortic®-Neoral® interaction, a commercial immunoassay ζ \mathcal{J} , was used centrally. The assay performance is summarized in Table 18.

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

IV. APPENDICES

A. Package Insert (proposed and annotated)

Attached separately.

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

C. Consult Review

PHARMACOMETRIC REVIEW

NDA number:	50-791
Submission date:	April 30, 2003
Product:	180 mg and 360 mg delayed release tablet
Brand name:	MYFORTIC (ERL080)
Generic name:	mycophenolate sodium
Sponsor:	Novartis Pharmaceuticals Corp.
Type of submission:	PM consult
Primary Reviewer:	Jang-Ik Lee, Pharm.D., Ph.D.
PM reviewer:	Jenny J Zheng, Ph.D.

SUMMARY:

MYFORTIC is an enteric-coated delayed release tablet formulation of mycophenolate sodium. CellCept, an approved product containing mycophenolate mofetil ester (MMF), is currently indicated for prophylaxis of acute rejection in patients receiving allogeneic kidney, heart, and liver transplants in combination with cyclosporine and corticosteroids. MYFORTIC and CellCept both produce the same active species in the systemic circulation following their administrations, mycophenolic acid (MPA).

The sponsor submitted four literature articles to address the exposure response relationship of mycophenolate mofetil (MMF) to support the NDA filing of MYFORTIC under section 505(b)(2) of the Federal Food Drug and Cosmetic Act.

1. M Hale et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. *Clinical Pharmacology Therapeutics*, 64:672-83, 1998.
2. Van Gelder T, et al. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 1999; 68(2):261-266.
3. V. Cox and MH Ensom. Mycophenolate mofetil for solid organ transplantation: does the evidence support the need for clinical pharmacokinetic monitoring? *Therapeutic drug Monitoring*, 25:137-157, 2003.
4. Shaw LM et al. Monitoring of mycophenolic acid in clinical transplantation. *Therapeutic Drug Monitoring* 2002; 24(1):68-73.

Articles 1 and 2 provided the results from the same trial and articles 3 and 4 are the review article.

The general conclusions drawn from the four articles are as follows:

5. The rate of renal allograft rejection may be reduced from the background rate by administration of mycophenolate mofetil. The extent of this effect is significantly related to mycophenolic acid AUC.
6. Individualization of mycophenolate mofetil dose based on mycophenolic acid AUC may have merit.
7. For renal transplantation:
 - a. An MPA AUC value $>30 \mu\text{g}\cdot\text{h}/\text{mL}$ (determined via HPLC assay) and predose plasma MPA concentration of $>2.0 \mu\text{g}/\text{mL}$ (determined via EMIT assay) may be appropriate.
 - b. The upper limit of the MPA concentration range for clinical efficacy cannot be determined.
8. For cardiac transplantation:

- a. MPA AUC values as measured by HPLC may be the best predictor of clinical efficacy, with values of 42.8 $\mu\text{g}\cdot\text{h}/\text{mL}$ associated with a lack of rejection.
- b. The optimal range of MPA pre-dose concentrations and AUC values are yet to be determined.

COMMENTS:

1. The trial described in the articles by Hale et al and Van Gelder et al was prospectively designed and was the first randomized blinded concentration controlled study reported for transplantation. The authors concluded that the rate of renal allograft rejection may be reduced from the background rate by administration of mycophenolate mofetil. The extent of this effect is significantly related to mycophenolic acid (MPA) AUC. However, no specific range of MPA AUC was proposed by the authors.
2. Most of the studies included in the review article are retrospective, not prospective, studies. The proposed targeted MPA AUC recommended from these articles needs to be interpreted with caution.

RECOMMENDATION:

The literature information provided by the sponsor for mycophenolate mofetil (MMF) suggested that the incidence of rejection is associated with mycophenolic acid exposure (AUC). However, it appears that no relationship has been established between clinical toxicity and mycophenolic acid exposure.

/S/

Jenny J Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

/S/

RD/FT initialed by P. Colangelo, Ph.D., Pharm.D., Team Leader _____

Review of Articles 1 and 2:

1. M Hale et al. The pharmacokinetic-pharmacodynamic relationship for mycophenolate mofetil in renal transplantation. *Clinical Pharmacology Therapeutics*, 64:672-83, 1998.
2. Van Gelder T, et al. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* 1999; 68(2):261-266.

Trial Design: The trial described in articles 1 and 2 was designed as multi-center, double-blind, randomized parallel-group study of 24 weeks duration in renal allograft recipients after first or second cadaveric transplantation. The planned enrollment was 156 patients, randomly assigned to treatment groups designated low, intermediate, or high mycophenolic acid. The target AUCs were 16.1, 32.2, and 60.6 $\mu\text{g}\cdot\text{h}/\text{mL}$ for low, intermediate, and high groups, respectively.

Pharmacokinetics (PK): Full 12 hour pharmacokinetic profiles were collected after an overnight fast on days 3,7, and 11 after the start of mycophenolate mofetil administration. On days 21, and 28 and then at 4-week intervals until week 20, a truncated pharmacokinetic samples schedule was followed that involved blood draws before dosing and at 20, 40, 75, and 120 minutes after dosing. After PK measurement, the incremental change of mycophenolate mofetil dose was limited to no more than 100, 200, and 300 mg per dose for the low, intermediate, and high groups, respectively. The dose adjustment was based on the assumption that mycophenolic acid oral clearance was constant over the time course of the study.

Efficacy End Point: Patients who experienced biopsy-proven rejection were classified as end point failure. The rejection was based on both clinical ground and histological evidence. Patients who completed the 24 weeks without rejection or treatment of rejection or death were classified as success. Comparison of those 2 groups constituted the primary evaluation of pharmacokinetics and pharmacodynamics.

Adverse Event: The following adverse events were selected for examination: nausea, diarrhea, leucopenia, cytomegalovirus infection, urinary tract infection, and abdominal pain. For each of the selected adverse events, the value "1" was assigned to the classification variable if the patient reported the adverse event at any time during the course of the study and the value "0" was assigned if the patient completed the 24 week period of observation without experiencing that adverse event.

PK/PD Analysis: Univariate logistic regression was used to examine the relationship between each of the explanatory variables including median value of mycophenolic acid AUC, C_{max} , C_{predose} , and cyclosporine pre-dose concentration obtained throughout the 24 week duration of the study and efficacy. Bivariate logistic regression was performed to assess their additional contribution to the explanation of the efficacy outcome, once account had been taken of AUC.

Results:

1. Mycophenolic acid AUC estimated from samples obtained during the first 2 hours after administration showed good agreement with the AUC estimated from samples over the 12 hour inter-dosing interval. Eighty percent of the truncated profile estimates fell within 20% of the values estimated from full 12 hour data.
2. The AUC targets were systematically exceeded (Figure 1).
3. The median apparent mycophenolic acid clearance declined over time (Figure 2), and therefore the assumption of constant clearance was incorrect, which explained in part why the observed AUC estimates exceeded the targeted AUC values.
4. A total of 20 patients (13%) experienced biopsy-proven rejection during the study.
5. The 4-parameter logistic regression (Emax model) was statistically indistinguishable from 1 and 0.

6. The 2-parameter logistic analysis yielded a pharmacokinetic-pharmacodynamic relationship that was highly statistically significant ($p < 0.001$, Table 1 and Figure 3). It showed that the reduction in probability of rejection as mycophenolic acid AUC increases, with 50% of maximal efficacy occurring for an AUC of $15 \mu\text{g}\cdot\text{h}/\text{mL}$.
7. The mean daily MMF dose and the mean MPA AUC values in the three target MPA AUC groups at several time points after transplantation was shown in Table 2.
8. Except median mycophenolic acid AUC, C_{max} , C_{predose} , and cyclosporine C_{predose} were also associated with probability of rejection. But, mycophenolate mofetil dose was not statistically significantly associated with the probability of rejection.
9. Bivariate logistic regression as shown in Table 3 showed that mycophenolic acid AUC remains statistically significant when tested with other parameters. The mycophenolic acid C_{max} , and C_{predose} are not statistically significant. However, the cyclosporine C_{predose} is statistically significant.
10. A total of 42 (28%) patients withdrew from the study before 24 weeks; these comprised 6, 11, and 25 patients in the low, intermediate, and high mycophenolic acid AUC groups, respectively.
11. No pharmacokinetic parameters were found to be statistically significantly associated with adverse events such as diarrhea, nausea, leucopenia, cytomegalovirus infection, urinary tract infection, and abdominal pain. However, the risk of diarrhea was significantly related to mean mycophenolate mofetil dose.

Conclusions:

1. This is the first randomized blinded concentration controlled study reported for transplantation.
2. The rate of renal allograft rejection may be reduced from the background rate by administration of mycophenolate mofetil. The extent of this effect is highly significantly related to mycophenolic acid AUC.
3. Individualization of mycophenolate mofetil dose based on mycophenolic acid AUC may have merit.
4. The decline in mycophenolic acid oral clearance observed in this study should be considered when further studies are to be conducted.
5. The risk of rejection was actually higher at the early time after the transplantation. However, this analysis considered the integrated risk of rejection over a period of 24 weeks after transplantation. No attempt was made to model or describe the changing risk over the course of 24 weeks. More sophisticated models that account for the time course of risk of rejection should be considered.

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Figure 1. Time course of mycophenolic acid area under the concentration-time curve after renal transplantation (median 25th and 75th percentiles). Data are provided for high, intermediate, and low target groups: target AUC values were 60.6, 32.2 and 16.1 $\mu\text{g}\cdot\text{h}/\text{mL}$, respectively.

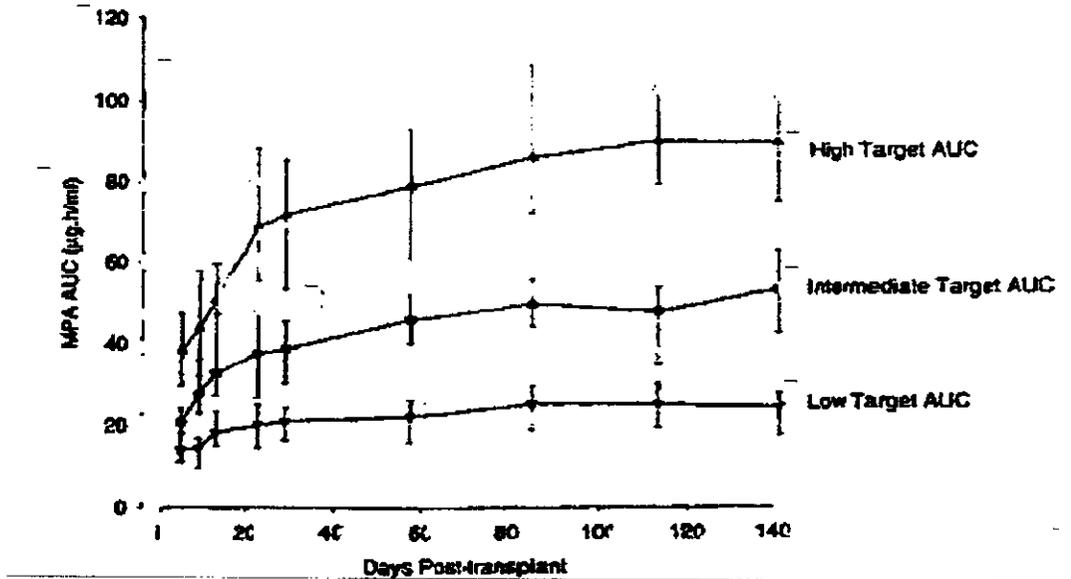


Figure 2. Time course of apparent oral clearance of mycophenolic acid, MMF, mycophenolate mofetil; MPA, mycophenolic acid

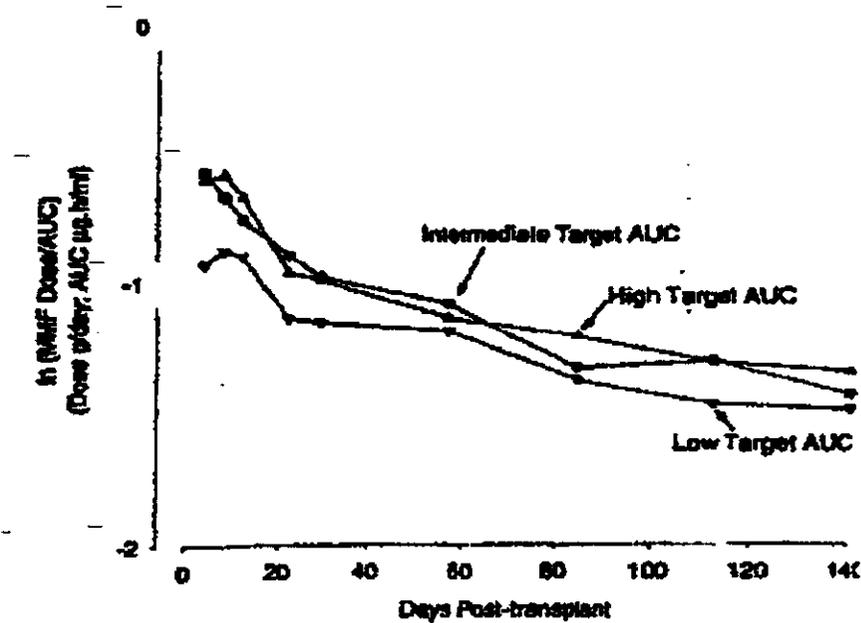


Figure 3. Sigmoid logistic regression relationship for MPA AUC and likelihood of rejection together with median ln MPA AUC for patients who experienced rejection and patients who did not experience rejection

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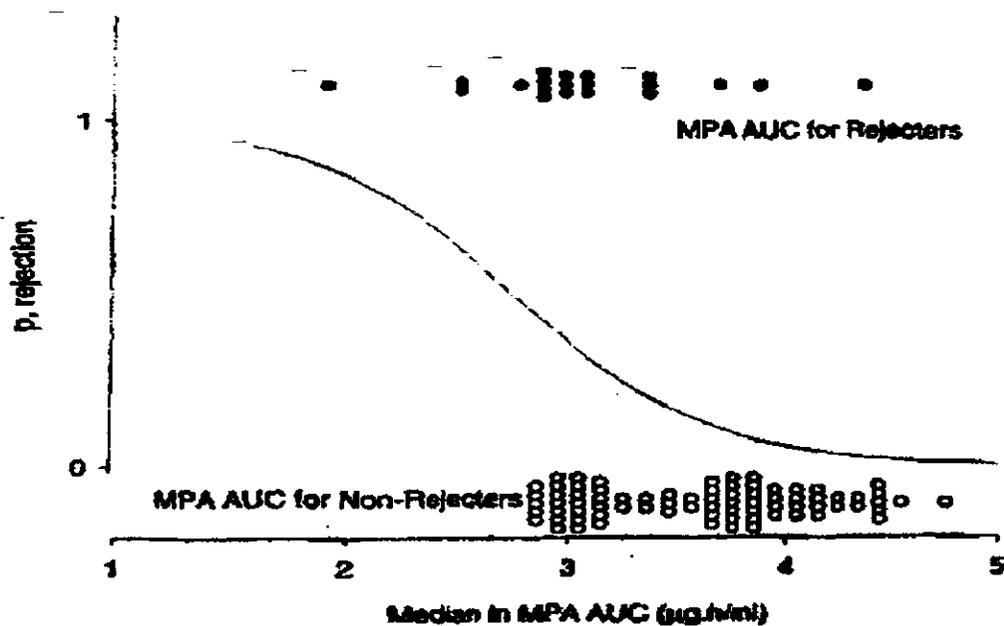


Table 1. P values for univariate logistic regression

	<i>BPR</i> versus successful completion	<i>BPR + PR</i> versus successful completion
Mycophenolic acid AUC	<.0001	.0001
Mycophenolic acid C_{max}	.0008	.0003
Mycophenolic acid $C_{predose}$.0049	.0396
cyclosporine $C_{predose}$.0071	.0021
Mycophenolate mofetil dose	.0918	.3584

BPR, Biopsy-proved rejection; *PR*, presumed rejection; *AUC*, area under the concentration-time curve; C_{max} , maximum observed plasma concentration; $C_{predose}$, predose plasma concentration.

Table 2. The mean daily MMF dose (g/day) and MPA AUC levels in the three target MPA AUC groups at several time points after transplantation

	Low group (16.1 µg·h/mL)		Intermediate (32.2 µg·h/mL)		High (60.6 µg·h/mL)	
	Daily dose	AUC	Daily dose	AUC	Daily dose	AUC
Day 3	0.90	13.9±5.52	1.90	24.6±11.5	3.40	39.1±18.3
Day 7	1.10	17.0±8.62	2.22	27.0±11.5	3.89	43.9±18.0
Day 11	1.12	17.8±5.34	2.44	30.5±10.5	4.22	51.0±18.9
Day 21	1.13	21.5±6.75	2.57	38.2±15.6	4.23	67.0±24.2
Day 28	1.12	21.4±6.72	2.55	41.9±14.7	4.15	76.2±29.5
Week 8	1.07	23.8±8.23	2.52	46.5±12.5	4.11	81.1±24.1
Week 12	1.03	27.1±9.65	2.49	51.7±14.1	3.98	86.0±27.3
Week 16	1.0	28.3±11.5	2.40	51.4±16.1	3.86	86.8±20.1
Week 20	0.97	27.6±12.3	2.27	54.8±15.3	3.84	96.7±32.2

Table 3. P values for bivariate logistic regression

	<i>BPR versus successful completion</i>	<i>BPR + PR versus successful completion</i>
Mycophenolic acid AUC	.0123	.0715
Mycophenolic acid C _{max}	.7537	.5179
Mycophenolic acid AUC	.0011	<.0001
Mycophenolic acid C _{predose}	.2601	.0129
Mycophenolic acid AUC	.0001	.0002
Cyclosporine C _{predose}	.0212	.0052
Mycophenolic acid AUC	.0001	<.0001
Mycophenolate mofetil dose	.2075	.0227

BPR, Biopsy-proved rejection; PR, presumed rejection; AUC, area under the concentration-time curve; C_{max}, maximum observed plasma concentration; C_{predose}, predose plasma concentration.

Review of Article 3 (V. Cox and MH Ensom. Mycophenolate mofetil for solid organ transplantation: does the evidence support the need for clinical pharmacokinetic monitoring? *Therapeutic drug Monitoring*, 25:137-157, 2003).

In the article 3, the authors summarized the results from 5 renal transplantation and 3 cardiac transplantation studies. The study design, the assay method, exposure measure, response, and the study results for each study are briefly described in the Table 1. The conclusions are as the follows:

1. For renal transplantation:
 - a. An MPA AUC value $>30 \mu\text{g}\cdot\text{h}/\text{mL}$ (determined via HPLC assay) and pre-dose plasma MPA concentration of $>2.0 \mu\text{g}/\text{mL}$ (determined via EMIT assay) may be appropriate.
 - b. The upper limit of the MPA concentration range for clinical efficacy cannot be determined.
2. For cardiac transplantation:
 - a. MPA AUC values as measured by HPLC may be the best predictor of clinical efficacy, with values of $42.8 \mu\text{g}\cdot\text{h}/\text{mL}$ associated with a lack of rejection.
 - b. The optimal range of MPA pre-dose concentrations and AUC values are yet to be determined.
 - c. No data are available to relate the MPA pharmacokinetic parameters and clinical toxicity.

Article 4 was not thoroughly reviewed because the contents were found to be either redundant to the content presented in article 3 or not relevant to the topic.

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Table 1. Summary of Studies of Renal and Cardiac Transplantations in Article 3

RENAL TRANSPLANTATION					
Author	Study Design	Assay	Exposure	Response	Results
Pillans	Retrospective in 27 patients; MMF: 1000 mg bid Prednisone: 0.3 mg/kg/d CsA trough: 175-200 µg/L	HPLC	MPA AUC at week 1	Rejection in 1 month	Significant difference in MPA AUC value between patients with rejection and those not experiencing rejection.
Krumme	Retrospective in 48 patients; MMF: 1000 mg bid methylprednisone: 0.3 mg/kg/d CsA trough: 175-200 µg/L	EMIT	MPA trough	Rejection in two months	C_{trough} was significantly lower in patients with rejection as compared with patients without rejection. (1.55 ±0.48 vs. 2.11±0.62 µg/mL)
Takahashi	Prospective, open label, multi-center in 32 patients. MMF: 1000, 2000, and 3000 mg daily prednisone: 10-20 mg/d CsA trough: 150 µg/L	Assay not reported	MPA trough and AUC at week 1, 2 and 3	Rejection in 3 months	<ul style="list-style-type: none"> At week 3 AUC ≥40 µg·h/mL, 1/12 rejection; AUC <40, 12/19 rejection No exposure/toxicity
Van Gelder	Prospective, randomized, double-blind, multi-center, controlled in 150 renal transplant patients. Target MPA AUC: 16.1, 32.2, or 60.6 µg·h/mL	HPLC	AUC at day 3, 7, 11, 21, 28, and then 4 weeks interval until 24 weeks.		<ul style="list-style-type: none"> Rejection is 27.5%, 14.9%, and 11.5% in low, intermediate, and high AUC group. Significant relationship between rejection and AUC by logistic analysis. C_{min}, C_{max} is not related to rejection. No relationship between AUC, C_{min} or C_{max} with toxicity.
Smak Gregoor	Prospective in 27 patients. MMF: start with 1000mg bid ; after 4 months switch to 750mg bid; after 8 months switch to 500 mg bid Prednisone: 10mg/d	EMIT	Trough at 4, 8 and 12 months	Rejection in 1 year	Rejection occurred only in 3 out of 27 subjects and found that rejection is not related to the trough concentrations.

CARDIAC TRANSPLANTATION					
Yamani	Retrospective in 215 patients.	EMIT	C _{trough} Group I: 0-6 month; Group II: 6-12 months; Group III: >12 months	Rejection in 1 year	C _{trough} >2µg/mL associate with lower rejection rate as compared with the subjects with C _{trough} <2 µg/mL for both group I (8.8% vs. 14.9%) and II (4.2% vs. 11.3%.
Meiser	The study was retrospective in 1st phase but prospective in 2 nd phase in 45 patients. 1 st phase: 15 patients received 1000 mg fixed dose of MMF. 2 nd phase: target C _{trough} to 2.5 to 4.5 µg/mL.	EMIT	C _{trough}	Rejection about 1 year	A correlation was evident between C _{trough} and the incidence of rejection but no statistical analysis was conducted.
DeNofrio	Prospective study in 38 patients	HPLC	Free C _{trough} and AUC by 2 hrs abbreviated MPA	Rejection (grade 0, grade 1 and grade 2/3) in 1 year	Lower total and free MPA AUC in patients with grade 2/3 rejection as compared with patients with grade 0 rejection. Total AUC: 26.1±6.6 vs 42.8±14.0 µg·h/mL Free AUC (0.49±0.11 vs 0.81±0.25 µg·h/mL)

C_{trough}: the pre-dose concentration;

MPA: mycophenolic acid;

MMF: mycophenolate mofetil;

EMIT: enzyme multiplied immunoassay technique;

D. OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
Information		Information		
NDA Number	50-791	Brand Name	Myfortic®	
OCPB Division (I, II, III)	III	Generic Name	Mycophenolate Sodium	
Medical Division	HFD-590	Drug Class	immunosuppressant	
OCPB Reviewer	Jang-Ik Lee	Indication(s)	prophylaxis of kidney transplant rejection	
OCPB Team Leader	Phillip Colangelo	Dosage Form and Strengths	Delayed release tablets: 180 mg and 360 mg	
		Dosing Regimen	720 mg bid	
Date of Submission	04/30/03	Route of Administration	PO	
Estimated Due Date of OCPB Review	1/29/04	Sponsor	Novartis Pharmaceuticals	
PDUFA Due Date	2/29/04	Priority Classification	Standard Review	
Division Due Date	2/12/04			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies to be reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:	x	(1)	(1)	<i>In vitro</i> study
Plasma protein binding:	x	1	1	0104
Pharmacokinetics (e.g., Phase I) - Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	x	1	1	0104
multiple dose:	x	4	4	0102, 2302, B301, B302
Dose proportionality -				
fasting / non-fasting single dose:	x	1	1	0105
fasting / non-fasting multiple dose:				
Drug-drug Interaction studies -				
In-vivo effects on primary drug:	x	1	1	0101
In-vivo effects of primary drug:	x	1	1	0102
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	(x)	(2)	(2)	(0109, 2302)
pediatrics:	x	1	1	0106
geriatrics:				
renal impairment:	x			literature only
hepatic impairment:	x			literature only
Exposure-Response Relationship	x			literature only
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
Therapeutic Drug Monitoring	x			
II. Biopharmaceutics				
Absolute bioavailability:	x	1	1	0104
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	4	4	MMF: 2302, B301, B302, W151
Bioequivalence studies -				
traditional design; single / multi dose:	x	3	3	2302, B302, W152
replicate design; single / multi dose:				
Food-drug interaction studies:	x	2	1	0109 (failed W154)
Dissolution:				chemistry section
(IVVC):				
Bio-wavier request based on BCS	x			chemistry section
BCS class	x			chemistry section
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics	x	2	2	B301, B302
Pediatric development plan				
Literature References	x			
Total Number of Studies		12	11	
Fileability and QBR comments				
	"X" if yes	Comments		
Application fileable?	X	Reasons if the application is <u>not</u> fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.		
QBR questions (key issues to be considered)		<p>Are MPA pharmacokinetics comparable between the doses of Myfortic[®] 720 mg and CellCept[®] 1000 mg?</p> <p>Can the bio waiver request be granted for 180-mg strength?</p> <p>Can Myfortic[®] be administered with food?</p>		
Other comments or information not included above				
Primary reviewer Signature and Date		Jang-ik Lee		
PM reviewer Signature and Date		Jenny Zheng		
Secondary reviewer Signature and Date		Phillip Colangelo		

CC: NDA 21-385, HFD-850 (P. Lee), HFD-590 (CSO), HFD-880 (TL, DD, DDD), CDR

End of Document

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jang-Ik Lee
2/25/04 04:33:46 PM
BIOPHARMACEUTICS

Phil Colangelo
2/27/04 09:21:45 AM
BIOPHARMACEUTICS