CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 50758

Trade Name: CELLCEPT INTRAVENOUS

Generic Name: MYCOPHENOLATE MOFETIL HYDROCHLORIDE for INJECTION

Sponsor: ROCHE GLOBAL DEVELOPMENT

Approval Date: 08/12/98

Indication(s): FOR PROPHYLAXIS OF ORGAN REJECTION IN PATIENTS RECEIVING ALLOGENIC RENAL TRANSPLANTS AND IN PATIENTS RECEIVING ALLOGENIC CARDIAC TRANSPLANTS.

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)	X			
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

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Application Number: 50758

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-758

AUG 12 1998

Roche Global Development
Attention: Carmen Rodriguez
Regulatory Project Manager
3401 Hillview Avenue
Palo Alto, CA 94304-1397

Dear Ms. Rodriguez:

Please refer to your new drug application (NDA) dated August 29, 1998, received September 2, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection). We note that this application is subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated as follows.

August 29, 1997
September 2, 1997
December 8, 1997
January 6, 1998
January 30, 1998
February 10, 1998
February 20, 1998
March 11, 1998
May 22, 1998
June 16, 1998
June 18, 1998
July 20, 1998
August 7, 1998

The user fee goal date for this application is September 2, 1998.

This new drug application provides for the use of CellCept® Intravenous (mycophenolate mofetil hydrochloride for injection) for prophylaxis of organ rejection in patients receiving allogeneic renal transplants and in patients receiving allogeneic cardiac transplants.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert dated August 7, 1998, immediate container and carton labels dated August 7, 1998). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 50-758." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

APPEARS THIS WAY
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Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Mary Dempsey, Project Manager, at (301) 827-2127.

Sincerely,

/S/

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 50758

MEDICAL REVIEW(S)

Date Submitted:	8/29/1997
Date Received:	8/30/1997
Date Assigned:	7/10/1998
Date Review Completed:	8/10/1998
Medical Reviewer:	Joyce Korvick, M.D.

Applicant:	Roche Pharmaceuticals Global Development-Palo Alto a Division of Syntex (U.S.A.) Inc. 3401 Hillview Avenue Palo Alto, California.
Drug:	Established Name: Mycophenolate mofetil (RS-61443) Proprietary Name: CellCept®
Drug Class:	Immunosuppressant, Antibiotic
Formulation:	Mycophenolate mofetil, as the hydrochloride salt for intravenous infusion
Proposed Indication: recipients	prevention of acute rejection in kidney and heart transplant during the initial 5 days post-transplantation until patients can receive oral therapy

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I. BACKGROUND

Mycophenolate mofetil (CellCept), an immunosuppressive agent, has been approved for the prophylaxis of organ rejection in patients receiving allogenic renal transplants (May 3, 1995: NDA 50-722). The initial approval was granted for the 250 mg capsule at a dose of 1 g BID. Subsequent submissions were made which led to the approval of the 500 mg tablet to be used at the same daily dose (June 19, 1997: NDA 50-723). Recently, February 11, 1998, CellCept was approved for use in the cardiac transplant recipient at up to a dose of 1.5 g BID. This application was submitted prior to the approval of CellCept for cardiac transplantation. At the time of this submission, approximately 25,000 patients had received oral CellCept since marketing started in 1995.

CellCept (mycophenolate mofetil; MMF)

The subject of this application, MMF intravenous formulation, is a lyophilizate containing the hydrochloride salt of MMF

It has an empirical formula of C23H31NO7 HCl, and a molecular weight of 470.0. The active ingredient in the formulation is mycophenolate mofetil.

The intravenous (IV) dose form of mycophenolate mofetil (MMF) was conceived as an alternative to MMF capsules (or tablets) for use in patients unable to tolerate solid dose forms. From 1 in 7 patients (renal transplant recipients) to up to 1 in 3 patients (cardiac transplant recipients) participating in the registrational trials were unable to take the oral formulation from 3-5 days after transplantation. Since the risk of allograft rejection is high during the initial period following transplantation, this formulation would lead to the availability of the immunosuppressive agent to be administered in the peri-operative period.

This review will focus on the safety data from the comparative trial (Study MYCS/2172/USA), and briefly comment upon the safety data from the pharmacokinetic studies which utilized the intravenous formulation. Do to the limited duration of administration of intravenous mycophenolate mofetil, efficacy was not examined in this application. Instead, the applicant compared the safety of intravenous administration with the oral administration, utilizing a placebo intravenous preparation.

A. Relevant human experience

The following is a summary of registry information on kidney, and heart transplantation available in Clinical Transplants 1996 (Terasaki PI, Cecka JM, Eds., Los Angeles,

Renal transplantation has become the treatment of choice in the United States for patients with end-stage renal disease. The leading causes of end-stage renal disease that lead to renal transplantation in the U.S. include diabetes mellitus, glomerulonephritis and hypertension. Stable renal transplant recipients, more than six months post transplantation, represent the largest population receiving immunosuppressive therapy for prevention of allograft rejection. In 1995 the total number of renal transplants performed in the United States was reported to be 11,289 including 8,163 cadaveric transplants, 3,126 living donor transplants, and 953 multi organ transplants. Approximately 90% of the latter were simultaneous kidney pancreas grafts. With available immunosuppressive therapy the one-, 5-, and projected 10-year graft survival rates for the 36,417 cadaveric transplants reported to the UNOS Scientific Renal Transplant Registry between January 1, 1991 and December 31, 1995 were 84%, 60%, and 43% respectively. The corresponding results of transplantations from living donors were 92%, 75%, and 62%.

These survival figures reflect current practice using a variety of immunosuppressive regimens based on cyclosporine for the prophylaxis of renal allograft rejection. There is no consensus as to what constitutes the optimal immunosuppressive regimen in renal transplantation. Cyclosporine is always used with adrenal corticosteroids (dual therapy) which may be tapered over time. Initial therapy with azathioprine or MMF is often added to this regimen (triple therapy). Approximately 50% of U.S. kidney transplant centers prefer to add a brief course of antilymphocyte antibody (induction therapy) to the triple regimen. In addition to corticosteroids, products approved for use in immunosuppressive regimens in renal transplantation in the U.S. include: Sandimmune® (cyclosporine U.S.P.), Neoral® (cyclosporine for microemulsion), Prograf® (tacrolimus), Imuran® (azathioprine), CellCept® (mycophenolate mofetil), and ATGAM® (antithymocyte immunoglobulin), Zenapax® (diclizumab) and Simulect® (basiliximab). OKT3, a murine monoclonal antibody against a human pan-T-lymphocyte antigen has been approved by the FDA for the treatment of steroid resistant rejection.

Rejection is a common phenomenon. Approximately 50% of renal transplant recipients will experience at least one rejection episode, commonly occurring during the first three months post transplant. Steroids are also always the first line treatment for rejection. There are several acute and chronic side effects that are associated with the use of

steroids in transplantation. These include, but are not limited to, insulin-dependent diabetes, severe infection and bone disease.

The number of heart transplant operations performed in the United States was 2,360 in 1995. The most frequently reported indication for heart transplantation in the US is all cardiomyopathies followed closely by coronary artery disease. Overall patient survival at one year was 84% in 1995. The 3-year survival rate for patients transplanted in 1993 was 74.5%. These rates have remained stable over the past 5 years.

As in kidney transplantation there is no consensus as to what would constitute an optimal immunosuppressive regiment in heart transplantation. Results of various protocols of cyclosporine maintenance have not been validated in clinical trials. Most protocols remain based mostly on a single-center cohort of patients who were at best compared with historical controls.

Maintenance Immunosuppression in Heart Transplantation
Conventional immunosuppression protocol in the pre-cyclosporine era: Azathioprine and prednisone
Cyclosporine-based immunosuppressive regimens: Double drug treatment: Cyclosporine and prednisone Triple drug treatment: Cyclosporine, prednisone, and azathioprine Steroid-sparing treatment: Cyclosporine, azathioprine

Information on the use of immunosuppressants in heart transplantation is also available from published surveys, registry data and collaborative studies. The most favored regimen in the US appears to be triple drug treatment followed by the steroid-sparing treatment. Adding azathioprine to cyclosporine and prednisone is believed to have allowed a reduction in the dose of cyclosporine and to have improved the short-term and mid-term renal function of heart transplant recipients.

B. Important information from related INDs and NDAs

CellCept (mycophenolate mofetil) 250 mg capsules were approved for prophylaxis of graft rejection in allogeneic kidney transplant recipients in the United States on May 3, 1995 (NDA 50-722), and an application for the 500 mg Tablet was approved on June 19, 1997 (NDA 50-723). The approval was based on three double blind, randomized, controlled studies in de novo renal transplantation recipients. The approved dose was 1 g PO bid.

Medical Officer Comment:

Approximately one in seven patients was unable to initiate oral treatment with MMF until Day 3 following transplantation. At the time these studies were conducted there

was no available investigational intravenous formulation for MMF. Patients who were unable to take oral medications on Day 3 were excluded in from these studies.

On August 29, 1997 the applicant submitted an efficacy supplement for CellCept (mycophenolate mofetil) 250 mg capsules for prophylaxis of rejection in recipients of allogeneic heart transplants. This supplement was based on a single large randomized, double blind, controlled study comparing MMF to azathioprine in de novo heart transplant recipients receiving combination immunosuppression with cyclosporine, corticosteroids and antilymphocyte antibody induction therapy. The proposed recommended dose in heart transplantation is 1.5 g PO bid.

Medical Officer Comment:
Approximately 11% of the patients randomized in this study were unable to initiate oral mediation within 48 hours following transplantation. Again, no intravenous formulation was available at the time this study was conducted.

C. Foreign experience

CellCept 250 mg capsules and 500 mg tablets were approved for marketing in the European Union on February 14, 1996 using the Centralized Procedure. Cellcept 250 mg capsules and 500 mg tablets have been approved in a number of other countries. Approximately 25,000 patients have received Cellcept since marketing started in 1995.

D. Other relevant background information (meetings, commitments)

During an end-of-phase-II teleconference, on June 20, 1996 to discuss the phase III studies for this product the following agreements were made:

"No further characterization of MMF (parent drug) pharmacokinetics should be performed".

"A study would be conducted to evaluate the pharmacokinetics of a dose of 1 g BID administered over 2 hours. This study would focus on MPA AUC which was to be compared with that observed an the day immediately following a 5 day period of intravenous dosing as part of the proposed controlled study MYCS2172. The purpose of these investigations would be to provide additional controlled safety information for intravenous MMF and to compare the pharmacokinetics of intravenous and oral dose forms".

Subsequently, because of the constraints imposed by the blinded study design of protocol MYCS2172, the applicant proposed to separate the pharmacokinetic component of the study into Study MYCS2734

Medical Officer Comment:
It was recognized that MYCS2734 would not be considered a formally valid bioequivalence study since period/sequence effects could not be reliably excluded due to the sequential design.

II. Chemistry:

CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolate acid (MPA) an immunosuppressive agent.

CellCept Intravenous is available as a sterile lyophilized formulation containing the equivalent to 500 mg per vial of mycophenolate mofetil (as the hydrochloride salt). The excipients in the proposed intravenous formulation include polysorbate 80, citric acid, and sodium hydroxide (for pH adjustment).

Medical Officer Comment:
No manufacturing and control problems of any clinical significance have been identified in consultation with the reviewing chemist.

III. Animal Pharmacology/Toxicology

Preclinical evaluation of IV MMF showed rapid metabolism at a number of tissues sites, including the liver, kidney, gut, and lungs, initially to mycophenolic acid (MPA), the pharmacologically active species, and then to the glucuronide of MPA (MPAG) the major final metabolite which is excreted in the urine. The metabolism, disposition, and excretion of MMF and its metabolites were similar for IV and oral administration within species (rat, dog, and monkey).

The toxico-pharmalogical profile of CellCept intravenous was characterized by studies submitted to the approved NDA for CellCept 250 mg capsules (NDA 50-722). The intravenous toxicology studies included acute (single dose) and repeat-dose 2-week and 1-month studies, venous irritation and in vitro blood compatibility studies. The duration and design of the IV toxicology studies was limited by local irritant properties of the formulation. Formulations equivalent to or greater than 5 mg/mL MMF concentrations were found to be irritating to the injection vein upon repeat administration. IV toxicology studies were limited to a maximum of mg/kg/day as a 15 minute infusion in rats and monkeys in repeat dose 1-month studies, and 200 mg/kg/day in up to 2-hour infusion in monkeys for 14 days.

The systemic toxicity profile in the IV studies included anemia and lymphoid atrophy in rats, and anemia in monkeys.

No additional information on the mechanism of action was submitted.

Medical Officer Comment:

As noted in the original NDA's Pharmacological and Toxicological Review potential targets of mycophenolic acid toxicity identified in preclinical studies include the hematologic and lymphoid systems. The duration of the toxicological evaluations in animals supports a proposed clinical use not exceeding 14 days.

IV. HUMAN PHARMACOLOGY, PHARMACO-KINETICS/DYNAMICS

Plasma concentration-time curves for MMF, MPA and MPAG in healthy human subjects infused with IV MMF over 1 hour indicate that detectable concentrations of MMF are present during the infusion and drop rapidly to undetectable levels within minutes following termination of the infusion.

Medical Officer Comment:

Because MMF is rapidly metabolized in the gut to MPA, no detectable concentrations of MMF are found in human serum after oral administration.

A dose ascending study of IV MMF in healthy subjects showed dose: AUC proportionality and the predicted relationship between input rate and steady state concentration. A subsequent study demonstrated that IV and oral MPA AUC and MPAG AUC were formally bioequivalent.

Bioequivalence was defined as the 90% confidence intervals for the ratio of mean natural log MPA AUC values for IV and oral MMF being fully contained

Urinary excretion of MMF metabolites was similar for the two routes and supports that virtually all of the oral dose is absorbed.

Multiple dose IV and PO pharmacokinetic parameters in renal transplant recipients were compared in three trials (MYC 061, IID 2176, and MYCS2734). These studies were performed in the immediate post transplant period. In all cases the sequence of administration of the formulations was IV followed by PO. The analysis of mean MPA AUC and 90% confidence intervals following the switch from IV to PO dosing produced variable results across the three studies. Overall, the MPA AUC following IV administration of MMF appears about 25% greater than that measured following the oral administration of MMF. At the proposed recommended dose and infusion regimen (1 gram over 2 hours) the ratio of mean Cmax values for IV to PO was 113% (120% for log transformed values).

Medical Officer Comment:
Although the sequence used in these studies mimics clinical switching from IV to PO, the study design does not allow one to distinguish between period effects and potential pharmacokinetic differences between formulations.

As previously observed, both IV and PO MPA AUC_{0-12} values in renal transplant patients, in the immediate post transplant phase were considerably smaller than MPA_{tot} in healthy subjects. Data contained in the efficacy supplement for heart transplantation in NDA 50-722, support that the pharmacokinetics of oral MMF in heart transplant recipients are similar to those in renal transplant recipients. Thus, the pharmacokinetics of IV MMF in renal transplant recipients are considered to be reasonably predictive of the pharmacokinetics of IV MMF in heart transplant recipients. No additional studies in heart transplant recipients were requested by FDA to support the potential extension of indication for the IV formulation to de novo heart transplant recipients.

The proposed recommended does of IV MMF (1 gram BID infused over 2 hours) should provide an MPA AUC equal to, or greater than, that provided by 1 gram BID PO MMF. Because of the increased acute exposure to MMF and MPA following IV administration compared to oral administration, the applicant was requested to conduct clinical studies to evaluate the safety of IV MMF in de novo renal transplant recipients.

There were insufficient numbers of patients in these studies to evaluate the possible effects of age, gender, or race on pharmacokinetic parameters.

V. Clinical Review:

A. Pediatric Safety in PK studies:

A single dose study was performed in 40 children stratified into one of 3 age groups (3 months - · . Each patients was assigned to one of three dose levels of oral MMF (15 mg/kg BID, 23 mg/kg BID, and 30 mg/kg BID). Most patients received oral MMF for 1-2 years.

Only 2 pediatric patients were able to take the iv formulation because it became unavailable during the study because of production problems. One patient reported periobital edema, hypertension, post operative pain and hives. These were of grade 1-2 in severity. The second patient had no reported adverse events on the day of the infusion. No reports of peripheral infusion site adverse events were reported in either of the patients.

Medical Officer Comment:

There are too few pediatric patients in this submission who received iv CellCept to draw any conclusions regarding its safety in the pediatric population.

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B. Safety Review Study MYCS 2172-USA

The study report synopsis supplied by the applicant follows:

Final Study Report -- Protocol MYCS 2172/USA: A randomized, double-blind comparative study of the safety of intravenous mycophenolate mofetil and oral mycophenolate mofetil in renal transplant recipients in the immediate post operative period.

INDICATION	Prevention of Renal Allograft Rejection
INVESTIGATORS	Multi-Center: USA and Canada
PUBLICATION	N/A
PERIOD OF TRIAL	July 24 1996 to Feb 11 1997. Clinical Phase III
OBJECTIVE	To provide an assessment of the safety of intravenous (IV) mycophenolate mofetil (MMF) administered as a 2-h IV at a dose of 1g every 12-h over 5 days to renal transplant recipients in the immediate post-transplant period. This is the first study in which MMF was administered as a 2-h infusion.
STUDY DESIGN	Multicenter, randomized, double-blind (for the first 5 days, then open-label) parallel group study in which first or second renal transplant patients received MMF 1 g bid as a 2-h IV infusion (MMF IV-PO group) for 5 days (10 or 11 doses) or as oral capsules (MMF PO-PO group) followed by PO MMF 1g bid on study Days 6-21. Patients were randomized in a 2:1 ratio.
NUMBER OF SUBJECTS	160 (153 received study drug and were therefore evaluable)

DEMOGRAPHIC DATA

Treatment Group	No. Evaluable Males	No. Evaluable Females	Mean age (y)
MMF IV-PO	62	36	46.6
MMF PO-PO	38	17	44.2

DOSE ADMINISTRATION	Double-blind MMF 1g/PO or IV/ bid. Study days 1-5 Open label MMF 1g/PO/bid study days 6-21.
STATISTICAL METHODS	All safety data were summarized using descriptive statistics and presented in patient listings. No hypothesis testing was performed for efficacy.
SAFETY RESULTS:	No patient died during the first 21 days of treatment. Overall, the adverse event (AE) experience of patients in this study appeared to be unrelated to the treatment group during both the 5-day, double-blind IV phase of the study and the open-label oral follow-on phase. The overall incidence of AEs at the sites of peripherally administered infusions also appeared to be unrelated to treatment group (ie. IV MMF vs IV placebo) with the exception of the particular events, injection site hemorrhage, phlebitis, thrombosis which were observed only in the

MMF IV-PO treatment group. None of these events resulted in interruption or discontinuation of IV administration of MMF.

Medical Officer Comments:

Review of the data base supplied by the applicant will discuss the following aspects of this study:

1.) *General Comments Regarding Study Design*
2.) *Demographics*
3.) *Premature Withdrawals*
4.) *All Adverse Events*
5.) *Serious Adverse Events*
6.) *Specific Intravenous Related Adverse Events*
7.) *Opportunistic Infections*
8.) *Deaths*
9.) *Rejection rates*
10.) *Laboratory Abnormalities*

1.) Study Design:

Prior to transplantation, eligible patients were randomized in a 2:1 ratio to groups designated "MMF IV-PO" (blinded IV MMF bid and oral placebo capsules through study day 5 followed by open label PO MMF) or "MMF PO-PO" (blinded IV MMF placebo bid and oral MMF capsules through study day 5 followed by open label PO MMF). Treatment with IV study drug began within 24 hours after transplantation, and oral study drug began as soon as the patient could take the study capsules within a 72-hour period following transplantation.

The IV solution of MMF (and placebo MMF) were administered, if possible, via a dedicated peripheral venous catheter which was flushed with D5W (dextrose 5% water) prior to infusion of the study drug. A central line could be used if a peripheral line could not be established or if local irritation developed. The IV solutions were infused via an infusion pump at a rate of 84 mL per hour for 2 consecutive hours. Other drugs were not to be given simultaneously with MMF through the infusion line or mixed in the infusion bag. Peripheral infusion sites were changed every 72 hours.

This study included patients aged 16 years and older.

The following concomitant medications were NOT PERMITTED during the period from the day of transplantation until study drug termination: Azathioprine, Cholestyramine, Tacrolimus (FK 506), Cyclophosphamide, Methotrexate, Vincristine, Prostaglandin- E1 or E2, Rapamycin, 15-Deoxyspergualin, Brequinar. Investigational drugs other than MMF were not permitted during this study.

Medical Officer Comment:

This study was designed and executed prior to the approval of the tablet formulation of CellCept and the approval of CellCept for use in cardiac transplant recipients. Therefore, this study was performed in renal transplant recipients utilizing the capsule formulation.

The pharmacokinetic of intravenous CellCept have been studied and were submitted in this application (see biopharmaceutics review). In addition, the safety regarding intravenous dosing was evaluated in this trial. Because intravenous MMF is rapidly converted (about 5 minutes) to the active metabolite, mycophenolic acid (MPA), this study was designed to evaluate the potential acute toxicities of intravenous infusion of MMF as well as the overall systemic effects which were well documented in previous oral renal studies. Finally, the development of intravenous MMF was intended for short term use in the post-operative period, prior to the patient's ability to take oral medications. Thus, the duration of the intravenous portion of the study is 5 days, with additional follow-up through study day 21, while the patient was on oral MMF. This follow-up period permits additional comparisons to be made between the intravenous and oral dosing periods.

2.) Demographics:

Fifteen study sites (3 in Canada; 12 in the USA) enrolled a total of 160 patients: 104 patients into the MMF IV-PO group and 56 in the MMF PO-PO group. The majority of patients enrolled were male (MMF IV-PO = 63%; MMF PO-PO = 69%) and Caucasian (MMF IV-PO = 67%; MMF PO-PO = 62%), and an average age of 45 years. The next most frequently enrolled race was designated "Black" (MMF IV-PO = 13%; MMF PO-PO = 11%).

Induction therapy was administered to 42% of patients in the MMF IV-PO group and to 31% of the patients in the MMF PO-PO group. A higher frequency of ATG only was seen in the MMF PO-PO group (76% vs 59%), while a lower frequency of OKT3 only was seen in the MMF PO-PO group (18% vs 34%).

The transplant characteristics including first allograft, donor of current allograft, HLA A+B+DR, Last PRA, Cold ischemic time, were fairly evenly distributed across the two treatment groups. The number of mismatches between donor and recipient of A,B, and DR antigens appeared to be slightly higher in the MMF IV-PO group than in the MMF PO-PO group.

Medical Officer Comment:

The distribution of patients enrolled in the study appear to represent the transplant population in the USA. The slightly higher mis-match in the MMF IV-PO group may account for the higher use of induction therapy in the same group.

3.) Premature Withdrawals:

Exposure to study medications was as follows:

- between 4 to 6 days of intravenous administration MMF IV-PO = 97%, MMF PO-PO = 96%.
- receipt of the first dose of oral in the MMF PO-PO group was within 48 hours for 90% of patients.
- Forty percent of all evaluable patients experienced one or more AE that ded to dose reduction or interruption (42% (41/98) in the MMF IV-PO group and 36% (20/55) in the MMF PO-PO group.

A total of 160 patients were enrolled into the study and randomized in a 2:1 ratio into: the MMF IV-PO group (104 patients) or the MMF PO-PO group (56 patients). Of those enrolled 98 patients in the MMF IV-PO group and 55 patients in the MMF PO-PO group are evaluable for safety endpoints. Six patients in the MMF IV-PO group never received study medication (4 not transplanted; 1 patient changed his mind regarding participation in the study; 1 patient's physician incorrectly recorded the use of OKT3 as a prohibited medication and withdrew the patient from the study). Only 1 patient in the MMF PO-PO group changed their mind regarding participation in the study.

The table below lists the reasons for premature termination from the study.

Reasons for Premature Withdrawal from Study

Reason for Premature Withdrawal	**MMF IV-PO N=104 % (n)**	**MMF PO-PO N=56 % (n)**
Any Reason	19% (20)	14% (8)
AE/Intercurrent Illness/New or Worsening Lab Abnormality	11 (11)	7 (4)
Unsatisfactory Therapeutic Response	0	2 (1)
Noncompliance	1 (1)	0
Need for Prohibited Medications	2 (2)	2 (1)
Other	6 (6)	4 (2)

Source: Table 4, Vol 73

A brief description of the specific reasons for early withdrawal follows considering the AE category last. One patient in the MMF PO-PO group was terminated by the investigator due to an unsatisfactory response, and treated for acute rejection. One patient in the MMF IV-PO group withdrew early for noncompliance. Two patients in the MMF IV-PO group were withdrawn because of the need for prohibited medications (OKT3 [an error by the physician], tacrolimus), and one patients in the MMF PO-PO group was treated with tacrolimus.

Specific reasons for withdrawal under the "other" category in the MMF IV-PO group included 5 patients who never received CellCept (as noted above) and one patient whose physician determined that the patient was "over immunosuppressed" at day 16 of study drug therapy. Of the two patients in the MMF PO-PO group categorized as "other", one did not take study drug, and a second terminated for personal reasons after receiving 15 days of study drug.

Withdrawal Due to Adverse Event/Intercurrent Illness/New or Worsening Lab Abnormality

Patient ID	Treatment Group	Reason for Withdrawal	Relatedness	Days of treatment
18104	IV-PO	Vomiting	Probably	17
18106	IV-PO	Thrombocytopenia	Probably	16
18185	IV-PO	Perinephric hematoma	Not related	11
18200	IV-PO	A. fib, renal vein thrombosis	Intercurrent	4
18312	IV-PO	Hemolytic uremic syndrome	Possibly	17
18354	IV-PO	Small bowel obsrtuction	Not related	6
18356	IV-PO	Ileus	Probably	6
18361	IV-PO	Increased LFT's	Probably	6
18438	IV-PO	Colonic ileus	Intercurrent	7
18439	IV-PO	Hemorrhage s/p kidney biopsy	Not related	12
18780	IV-PO	Multiple GI bleeding, CMV	Probably	22
18194	PO-PO	Nausea/vomiting	Probably	3
18203	PO-PO	IV infusion site infiltration	Not Related	3
18316	PO-PO	Renal vein thrombosis	Not Related	7
18775	PO-PO	Nausea/vomiting	Possibly	5

Source: Table 11, Vol 73.

There were slightly more patients in the MMF IV-PO group (11%) than the MMF PO-PO group (7%) who withdrew prematurely due to an adverse event/intercurrent illness/new or worsening lab abnormality. Only one of the patients withdrew from the study in the first 5 days of therapy due to an adverse event which was related to the infusion site. This patient was in the MMF PO-PO group and was noted to have "difficult veins" in which to start a peripheral IV. Adverse events recorded as renal vein thrombosis and perinephric hematoma were considered by the physicians to be of a technical nature and not related to study medication.

Comparisons of the adverse events listed as possible/probable between groups follows. In the MMF PO-PO group 2 patients were discontinued for nausea/vomiting of a mild to moderate nature (a known side-effect of MMF), while one patient in the MMF IV-PO group had vomiting. Additional events seen in the MMF IV-PO group include thrombocytopenia (1), Hemolytic Uremic Syndrome (HUS) (1), increased liver function tests (1), GI system (2). All of the events resolved. The microangiopathic anemia

resolved 3 days after discontinuation of CellCept and cyclosporine. The patient was started on tacrolimus. The patient was re-hospitalized 7 days after discontinuation of CellCept with pulmonary edema. During this it was felt by the physician that the recurrent HUS was due to tacrolimus as it occurred after MMF was discontinued.

Events requiring withdrawal from study medication related to the GI system (other than nausea/vomiting) occurred more frequently in the MMF IV-PO group (4). Two patients with small bowel obstruction and Colonic Ileus were considered to be due to intercurrent illness by the investigators. In another patient with ileus, CellCept was felt to be probably related. The last patient had a GI bleed and concurrent CMV disease. This case was felt to be probably related to CellCept.

Medical Officer Comment:
Review of the Case Report Forms and the Patient Summaries of the adverse events requiring premature withdrawal from study medication, is in agreement with the applicant's report. Only one patient on the placebo IV MMF infusion was withdrawn due to difficulty with peripheral veins. The other adverse events reported for early withdrawal have been describe with the oral use of CellCept.

4.) All Adverse Events:

The following tables list adverse events reported during the entire 21 days of the study as well as the 5 day period while patients were receiving intravenous study drug by body system and COSTART terms.

All but one patient (MMF IV-PO group) experienced at least one adverse event during the IV phase of the study. In general, the number and proportion of patients reporting adverse events in each body system were evenly distributed. A slightly larger proportion of patients in the IV-PO group (51%, 50/98) had cardiovascular events (chiefly EKG abnormalities) than did those in the PO-PO group (40%, 22/55). These were without any clinical consequence (e.g. arrhythmia, atrial fibrillation/flutter and bigeminy). Additionally thrombosis was reported in 4(4.1%) MMF IV-PO patients (refer to following table).

A slightly larger proportion of patients in the PO-PO group (35%, 19/55) had adverse events in the Nervous System during the IV phase of the study than did those in the IV-PO group (25%, 24/98).

Comparison of Renal Patients with One or More Adverse Events During the First 21 Days on Study and While on IV Treatment by Body System (Study 2172)

Body System	Number (%) of Patients with Adverse Events (MMF 2 g/day)			
	MMF IV-PO First 21 Days	**MMF PO-PO First 21 Days**	**MMF IV-PO IV Phase**	**MMF PO-PO IV Phase***
Total Patients in Summary	98 (100%)	55 (100%)	98 (100%)	55 (100%)
Any Body System	98 (100.0%)	55 (100.0%)	97 (99.0%)	55 (100.0%)
Body as a Whole	85 (86.7%)	50 (90.9%)	79 (80.6%)	47 (85.5%)
Metabolic/Nutritional	82 (83.7%)	48 (87.3%)	71 (72.4%)	43 (78.2%)
Digestive System	82 (83.7%)	44 (80.0%)	77 (78.6%)	39 (70.9%)
Cardiovascular System	63 (64.3%)	26 (47.3%)	50 (51.0%)	22 (40.0%)
Nervous System	39 (39.8%)	26 (47.3%)	24 (24.5%)	19 (34.5%)
Urogenital System	40 (40.8%)	25 (45.5%)	29 (29.6%)	17 (30.9%)
Hemic/Lymphatic System	38 (38.8%)	22 (40.0%)	30 (30.6%)	17 (30.9%)
Respiratory System	31 (31.6%)	12 (21.8%)	25 (25.5%)	10 (18.2%)
Skin and Appendages	23 (23.5%)	15 (27.3%)	14 (14.3%)	9 (16.4%)
Musculoskeletal System	10 (10.2%)	4 (7.3%)	5 (5.1%)	0 (0 %)
Special Senses	8 (8.2%)	6 (10.9%)	3 (3.1%)	3 (5.5%)
Endocrine System	3 (3.1%)	2 (3.6%)	1 (1.0%)	2 (3.6%)

SOURCES: Appendices 3.10 and 3.7
* IV placebo administered during IV phase

The following table displays, by treatment group, body system, and preferred term, the adverse events that were reported in 10% or more of patients in either treatment group during the entire 21 days of study and the IV phase of the study. Adverse events reported in 10% or more of patients in either treatment group during the IV phase of the study, including those at the injection site (injection site pain, injection site edema, and injection site reaction), were fairly evenly distributed across the treatment groups. The greatest difference between the treatment groups was for the preferred term hypophosphatemia, which was reported in 40% (22/55) of patients in the PO-PO group and 29% (28/98) of patients in the IV-PO group.

Nausea remained the most frequently reported adverse event across the treatment groups during both IV treatment and during the first 21 days of treatment. Similar types of adverse events were reported for the two treatment groups during the first 21 days of

treatment; these were also similar to the types of adverse events reported during IV treatment. There were a number of adverse events, however, for which marked increases were noted when the rates on IV treatment (columns 3 and 4) and the first 21 days (columns 1 and 2) were compared.

Hypophosphatemia in the PO-PO group occurred in 22/55 patients (40.0%) while on IV placebo and 23/55 (41.8%) for the period up to 21 days. In contrast hypophosphatemia occurred in 28/98 (28.6%) patients during IV MMF treatment and 39/98 patients (39.8%) for the period up to 21 days; however the hypophosphatemia rate for the period up to 21 days was similar for both groups.

Comparison of Renal Patients with One or More Adverse Events During the First 21 Days on Study and While on IV Treatment Occurring in 10% or More of Patients* by Preferred Term (Study 2172)

Body System Preferred Term for Adverse Event	Number (%) of Patients with Adverse Events (MMF 2 g/day) MMF IV-PO First 21 Days (N=98)	MMF PO-PO First 21 Days (N=55)	MMF IV-PO IV Phase (N=98)	MMF PO-PO** IV Phase (N=55)
Body as a Whole				
Pain	41 (41.8%)	26 (47.3%)	31 (31.6%)	20 (36.4%)
Injection Site Reaction	23 (23.5%)	15 (27.3%)	23 (23.5%)	15 (27.3%)
Fever	23 (23.5%)	10 (18.2%)	20 (20.4%)	7 (12.7%)
Injection Site Pain	20 (20.4%)	12 (21.8%)	20 (20.4%)	11 (20.0%)
Headache	18 (18.4%)	10 (18.2%)	14 (14.3%)	5 (9.1%)
Reaction Unevaluable	14 (14.3%)	13 (23.6%)	10 (10.2%)	7 (12.7%)
Abdominal Pain	14 (14.3%)	11 (20.0%)	8 (8.2%)	6 (10.9%)
Back Pain	10 (10.2%)	6 (10.9%)	5 (5.1%)	4 (7.3%)
Abdomen Enlarged	7 (7.1%)	7 (12.7%)	6 (6.1%)	7 (12.7%)
Injection Site Edema	10 (10.2%)	4 (7.3%)	10 (10.2%)	4 (7.3%)
Metabolic and Nutritional				
Hypophosphatemia	39 (39.8%)	23 (41.8%)	28 (28.6%)	22 (40.0%)
Peripheral Edema	28 (28.6%)	8 (14.5%)	12 (12.2%)	8 (14.5%)
Disorders Hypokalemia	18 (18.4%)	9 (16.4%)	14 (14.3%)	8 (14.5%)
Hypomagnesemia	15 (15.3%)	9 (16.4%)	8 (8.2%)	6 (10.9%)
Hyperkalemia	15 (15.3%)	6 (10.9%)	8 (8.2%)	4 (7.3%)
Creatinine Increased	15 (15.3%)	4 (7.3%)	5 (5.1%)	1 (1.8%)
Hyperglycemia	14 (14.3%)	7 (12.7%)	7 (7.1%)	5 (9.1%)
Generalized Edema	12 (12.2%)	9 (16.4%)	11 (11.2%)	8 (14.5%)
Hypocalcemia	10 (10.2%)	5 (9.1%)	9 (9.2%)	5 (9.1%)
Edema	8 (8.2%)	6 (10.9%)	4 (4.1%)	3 (5.5%)

Digestive System				
Nausea	47 (48.0%)	27 (49.1%)	40 (40.8%)	25 (45.5%)
Constipation	40 (40.8%)	20 (36.4%)	32 (32.7%)	16 (29.1%)
Vomiting	33 (33.7%)	11 (20.0%)	26 (26.5%)	10 (18.2%)
Diarrhea	32 (32.7%)	12 (21.8%)	19 (19.4%)	6 (10.9%)
Dyspepsia	19 (19.4%)	11 (20.0%)	16 (16.3%)	9 (16.4%)
Flatulence	12 (12.2%)	1 (1.8%)	8 (8.2%)	1 (1.8%)
Cardiovascular System				
Hypertension	44 (44.9%)	22 (40.0%)	30 (30.6%)	19 (34.5%)
Tachycardia	13 (13.3%)	5 (9.1%)	10 (10.2%)	5 (9.1%)
Nervous System				
Insomnia	16 (16.3%)	13 (23.6%)	11 (11.2%)	8 (14.5%)
Tremor	9 (9.2%)	8 (14.5%)	1 (1.0%)	3 (5.5%)
UrogenitalSystem				
Tubular Necrosis	10 (10.2%)	4 (7.3%)	10 (10.2%)	4 (7.3%)
Hemic and Lymphatic System				
Anemia	22 (22.4%)	9 (16.4%)	19 (19.4%)	8 (14.5%)
Leukocytosis	12 (12.2%)	9 (16.4%)	0 (0%)	2 (3.6%)
Thrombocytopenia	11 (11.2%)	4 (7.3%)	11 (11.2%)	3 (5.5%)
Respiratory System				
Lung Disorder	11 (11.2%)	6 (10.9%)	9 (9.2%)	6 (10.9%)
Dyspnea	11 (11.2%)	5 (9.1%)	9 (9.2%)	1 (1.8%)
Skin and Appendages				
Pruritus	10 (10.2%)	5 (9.1%)	9 (9.2%)	4 (7.3%)

SOURCES: Appendices 3.10 and 3.7
* For at least one of the treatment groups
** IV placebo administered during IV phase

Medical Officer Comment:

As described above hypophosphatemia was seen more frequently in the MMF PO-PO group during the IV phase but occurred at a similar rate between both groups during the entire 21 days of study.

The largest difference by body system was cardiovascular events, which occurred more frequently in the MMF IV-PO group (51% vs 40.0% respectively) during the intravenous portion of the study. Further exploration of the preferred terms revealed a small number of cases where ECG abnormalities were documented (9% [9/98] vs 1.8% [1/55] in PO-PO group). Only 2 patients with atrial flutter/fibrillation were rated as severe by the investigators.

Dyspnea occurred more frequently in the MMF IV-PO group than the MMF PO-PO group during the first 5 days of the study (9.2% vs 1.8%, respectively). None of these

was rated as severe. Only one severe respiratory event occurred during IV Infusion of MMF which was described as apnea.

Five patients experienced a complaint related to the musculo-skeletal system in the MMF IV-PO group during the first 5 days of therapy and none were reported in the MMF PO-PO group. None of these were rated as severe and none was felt to be related to study drug by the investigators.

The intravenous administration did not prevent the digestive system adverse events as the rates are similar between both treatment groups.

Overall, the safety profile of MMF IV (1 g BID) infused over 2 hours is similar to that of oral MMF (CellCept).

5.) Serious Adverse Events:

Medically serious adverse events were defined in this study as:

- premature termination from the study because of an AE, clinical laboratory abnormality, or intercurrent illness;
- death while on study drug or after discontinuation of drug;
- lymphoma/lymphoproliferative disease or other malignancy (except squamous cell skin carcinoma or basal cell skin carcinoma) while on study or after discontinuation of drug;
- perforation of the gastrointestinal tract;
- gastrointestinal bleeding requiring hospitalization;
- severe neutropenia, defined as an absolute neutrophil count (ANC) of less than 500/mL;
- severe thrombocytopenia defined as a platelet count of less than 25,000/mL.

In addition to those patients designated as having a medically serious adverse events defined as early withdrawal from study due to an adverse event, intercurrent illness or worsening laboratory abnormality, only 6 additional events Serious Medical Adverse Events were reported. One patient in the MMF PO-PO group (18775) was withdrawn on day 5 due to nausea and vomiting, but subsequently died due to a CNS lymphoma on study day 124. The remaining 5 events were related to Gastrointestinal bleeding or perforation. Four patients in the MMF IV-PO group were reported. One patient had a transverse colon perforation which was determined by the physician not to be related to study drug. The three other patients all had upper gastrointestinal bleeding which was determined to be possibly or probably related to study drug. All occurred at about day 22. Only one patient on the MMF PO-PO group presented with upper gastrointestinal bleed possibly related to study drug.

Medical Officer Comment:
Malignancies have been documented to occur in the presence of immunosuppression for the prevention of graft rejection. Only one such event was documented in this study. There is no reason to suspect the iv formulation should increase the likelihood for malignancy. No further comments regarding malignancy can be made due to the short follow-up period of this study.

Gastrointestinal bleeding or perforation requiring hospitalization occurred in 2% of the patients on the MMF PO-PO group versus 4% of the patients in the MMF IV-PO group. This is a known rare event associated with CellCept in the label. The iv formulation did not appear to prevent the occurrence of this serious adverse event. Intercurrent illness and concomitant medications may contribute to the occurrence of this event.

6.) Specific Intravenous Related Adverse Events

The following table summarizes, by body system and preferred term, the number and proportion of patients in each treatment group who experienced adverse events at peripheral infusion sites during the first 21 days of treatment. These adverse events were collected during the first 21 days of treatment rather than during the IV phase alone, in order to include those infusion site events (primarily reports of phlebitis and thrombosis) that were reported after conclusion of the IV phase.

Summary of Renal Patients with One or More Infusion Site Reactions During the First 21 Days on Study by Body System and Preferred Term (Study 2172)

Body System Preferred Term for Infusion Site Reaction	Number (%) of Patients with Infusion Site Events (MMF 2 g/day) MMF IV-PO (N = 78)	 MMF PO-PO** (N = 45)*
Body as a Whole	47 (60.3%)	29 (64.4%)
Injection Site Reaction	23 (29.5%)	15 (33.3%)
Injection Site Pain	20 (25.6%)	12 (26.7%)
Injection Site Edema	10 (12.8%)	3 (6.7%)
Injection Site Inflammation	6 (7.7%)	1 (2.2%)
Reaction Unevaluable	2 (2.6%)	4 (8.9%)
Injection Site Hypersensitivity	2 (2.6%)	2 (4.4%)
Injection Site Hemorrhage	1 (1.3%)	0 (0%)
Cardiovascular System	6 (7.7%)	0 (0%)
Phlebitis	3 (3.8%)	0 (0%)
Thrombosis	3 (3.8%)	0 (0%)

SOURCE: Appendix 3.13
* 2 g/day PO patients in Study 2172 received IV placebo on study Days 1–5.
** IV placebo administered during IV phase

A similar proportion of patients in each of the treatment groups received at least one dose of IV MMF or IV placebo via peripheral infusion. Injection site reactions that were categorized within the system Body as a Whole were reported with similar frequency in both treatment groups. In the IV-PO group, three patients each experienced phlebitis and thrombosis, while none of these events were reported in the PO-PO group.

Only one patient in the study (Patient No. 18203, PO-PO group) was terminated from the study because of a peripheral infusion site reaction (infusion site infiltration and edema aas described above Section V.B.3).

Medical Officer Comment:
The number of events for each category is small, and in general, similar between treatment groups. However, there were slightly more of the following events reported in the MMF IV-PO group: edema, inflammation, phlebitis and thrombosis. These rates are low, and of mild severity which did not require discontinuation of study drug. As noted above no significant difference in systemic adverse events occurred between treatment groups during the intravenous infusion.

7.) Opportunistic Infections:

During the study 7% of all evaluable patients developed an OI. All OIs were mild or moderate in severity.

Of the 6 patients in the MMF IV-PO group who developed an OI, three had received induction therapy (two with OKT3 and one with ATG); one additional patients in the MMF IV-PO group had received immunosuppressants for the treatment of a rejection episode prior to the onset of the OI. Of the 4 patients in the MMF PO-PO group who developed and OI, one had received induction therapy (OKT3) and none had received immunosuppressants for the treatment of a rejection episode.

The one patient who developed CMV viremia/syndrome was CMV seropositive pretransplant and received a kidney from a CMV seropositive donor.

Opportunistic Infections While on Study

Diagnostic Category	**MMF IV-PO N=98 % (n)**	**MMF PO-PO N=55 % (n)**
Any Opportunistic Infection	6 (6)	7 (4)
Candida, mucocutaneous	4 (4)	6 (3)
Herpes simplex	1 (1)	2 (1)
CMV viremia/syndrome	1 (1)	0
Herpes zoster, cutaneous	0	2 (1)

Source: Table 12 vol 77

Medical Officer Comment:

The types and distribution of opportunistic infections are those which have been reported during the use of CellCept. The rates are similar between the IV and PO groups.

8.) Deaths:

No patient died during the first 21 days of treatment. One patient on the MMF PO-PO group developed multiple post transplant complications, including a large cell CNS lymphoma, died 124 days after transplant.

9.) Rejection Rates:

Although this study is not powered to evaluate the graft loss and rejection rates between treatment groups, the data was collected by the applicant and displayed in the following table.

Table 3.19 Reasons for Graft Losses Occurring During the First 21 Days on Study (Renal Study 2172)

	Number (%) of Patients with Graft Loss (MMF 2 g/day)	
	MMF IV-PO	**MMF PO-PO***
Total Patients Receiving Treatment	98 (100%)	55 (100%)
Total Patients with Graft Loss	4 (4.1%)	1 (1.8%)
Transplant Nephrectomy	4 (4.1%)	1 (1.8%)
Retransplantation	0 (0%)	0 (0%)
Primary Reason for Graft Loss:		
Graft Rejection	1 (1.0%)	0 (0%)
Recurrence of Underlying Disease	0 (0%)	0 (0%)
Technical Complications	1 (1.0%)	1 (1.8%)
Other	2 (2.0%)	0 (0%)

SOURCE: Appendix 3.22
* IV placebo administered during IV phase

A total of 5 patients (4/98 in the IV-PO group and 1/55 in the PO-PO group) experienced graft loss during the first 21 days of treatment and underwent transplant nephrectomy. In the MMF IV-PO group, Patient No. 18438 experienced graft loss 10 days posttransplant because of rejection, Patient No. 18439 experienced graft loss 12 days posttransplant because of technical complications, Patient No. 18185 experienced graft loss 12 days posttransplant because of perinephric hematoma, and Patient 18200 experienced graft loss 5 days posttransplant because of renal vein thrombosis. In the MMF PO-PO group, Patient No. 18316 experienced graft loss 8 days posttransplant because of technical complications.

Medical Officer Comment:
Only one patient in this study had a document graft rejection during the first 21 days of therapy. This patient was in the MMF IV-PO arm. This rate is too small upon which to base any conclusions on the efficacy of the iv formulation.

10.) Laboratory Abnormalities:

Selected clinical laboratory results were presented by the applicant: Minimum absolute neutrophil count, minimum platelet count, minimum hemoglobin, maximum serum

creatinine, maximum total bilirubin, maximum alkaline phosphatase, maximum SGOT and SGPT. The results are listed below.

The distribution of test results for these eight key laboratory parameters was similar across the treatment groups with the exception of maximum serum creatinine values. During the first 21 days of treatment, 47% of patients (72/153) had at least one post-baseline serum creatinine concentration equal to or above the maximum cutpoint for serum creatinine (2.5 mg/dl). These included 53% (52/98) of patients in the MMF IV-PO group and 36% (20/55) of patients in the MMF PO-PO group. During the first 21 days of treatment, 5 patients had values above/below the maximum/minimum cutpoints for the seven key laboratory parameters other than serum creatinine. One patient in the IV-PO group had a minimum hemoglobin <6.5 g/dl. Two patients each in the IV-PO and PO-PO groups had maximum SGPT > 400 U/l.

Medical Officer Comment:

Similar laboratory abnormalities were seen in each group. The abnormalities seen are similar to those previously reported in association with the administration of the oral preparation of CellCept for liver and cardiac transplant recipients.

11.) Pregnancy:

No pregnancies occurred during this study.

V. SUMMARY:

The most common adverse events encountered during IV MMF treatment among this patients population included nausea, constipation, pain and hypertension. Overall, the adverse event experience of patients in these studies appeared to be unrelated to the treatment group (IV vs Oral CellCept). Few new adverse events were seen when patients were followed into the oral treatment period (first 21 days of treatment). In general, there was little difference between the IV and oral groups in the proportion of patients with adverse events that resulted in study drug discontinuation or study drug interruption and/or reduction.

The proportions of patients who experienced opportunistic infections and graft loss were similar for the IV and oral MMV treatment groups. There were no deaths during the first 21 days on study.

Over all incidence of adverse events at the sites of peripherally administered infusions also appeared to be unrelated to treatment groups (IV vs oral). However, peripheral IV infusion of MMF appeared to be associated with a higher incidence of local edema and inflammation. Injection site hemorrhage, phlebitis, and thrombosis were observed only in the MMF IV treatment groups and my be a drug effect. These adverse events may be dose related since they occurred with greater frequency in the MMF 3 g/day IV group. However, none of these events resulted interruption or discontinuation of IV administration of MMF. The recommendation for dosing infusions of no less that 2 hours may alleviate this problem, since this would mimic the pharmacokinetics of the 2 g/day dose were these events were seen with less frequency.

In conclusion, the IV form of CellCept provides an acceptable alternative dose form to use in renal and cardiac recipients in the immediate post-transplantation period.

VI. LABELING:

Please refer to final approved label, dated 8/12/98.
Major considerations for inclusion included infusion rate of 2 hours minimum, approval for cardiac as well as renal transplant recipients, and duration of treatment with the IV formulation up to 14 days post-transplantation. The recommended intravenous dose approved for renal transplant recipients is 1 g BID and is 1.5 g BID for cardiac recipients. Pharmacokinetic data presented for cardiac transplant recipients mimicked those of renal transplant recipients.

VII. RECOMMENDATIONS:

The single, double-blind, controlled study (MYCS 2172) in addition to several controlled pharmacokinetic studies submitted in support of CellCept for the safety of the intravenous formulation to be used to prevention of acute cardiac and renal allograft rejection during the first 14 days post transplantation meets the regulatory requirements for approval of this indication. Pursuant to 21 CRF 314.105 (a) the study performed was an adequate and well-controlled investigation and established that an intravenous dose of CellCept has a similar safety profile to that of the oral formulation, and that minor peripheral vein symptoms were reported with its use. CellCept is recommended for approval for this indication.

Recommend Approval of NDA 20-842: intravenous formulation of CellCept for the prevention of renal and cardiac transplant rejection for up to 14 days post transplantation, to be given over a 2 hour period of infusion at a dose not to exceed 1.5 mg BID.

Concurrence:
HFD-590/ Mark Goldberger, MD/ Division Director /S/
HFD -590/Marc Cavaillé-Coll, MD/Team Leader

CC:
HFD -590/Division Files
NDA 50-758 files
HFD -590/Chem/M Seggel
HFD -590/Biopharm/K Kumi
HFD -590/MOTL/ M Cavaillé-Coll
HFD -590/CSO/ M Dempsey
DDMAC