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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-791

Pharmacology Review(s)

CDER STANDARD COVERSHEET

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA#:	50-791
Product Name:	Myfortic® (Mycophenolic Acid)
Sponsor:	Novartis
Indication:	Renal Transplantation
Division:	Special Pathogen and Immunologic Drug Products HFD-590
Reviewer:	Stephen Hundley, Ph.D., DABT Acting Pharmacology/Toxicology Team Leader, HFD-590
Date:	2/26/04

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EXECUTIVE SUMMARY

Recommendations

Recommendation on Approvability:

The proposed indication for Myfortic® can be approved from the nonclinical pharmacology/toxicology perspective.

Recommendation for Additional Nonclinical Studies:

The Pharmacology/Toxicology Reviewer requested that the sponsor conduct as a post-marketing commitment a prenatal postnatal developmental toxicity study in pregnant rats.

Recommendations on Labelling:

The labelling should be consistent with currently approved labelling for mycophenolate mofetil due to the 505 (b) (2) designation for Myfortic® (mycophenolate sodium). The label should include the black box warning and language included in the mycophenolate mofetil label regarding the possible development of lymphomas and other neoplasms due to the immunosuppressive activity of mycophenolate. The sections of the label that deal with carcinogenicity, mutagenicity, fertility, and pregnancy category also need to be consistent with the mycophenolate mofetil label. Information from the mycophenolate mofetil label can also be referred to in these sections. Where possible the sponsor should make test animal to human therapeutic dose comparisons based upon mycophenolate plasma AUC data and may utilize these comparisons as a measure of systemic exposure. Absent AUC values, the comparsions between test animals and humans should be based upon body surface area (BSA) calculations.

The sponsor cannot include in the label results from the 26-week carcinogenicity study in $p53^{+/-}$ heterozygous transgenic mice. The Executive Carcinogenicity Assessment Committeee concluded that this study was inadequate for assessing the tumorigenic potential of mycophenolate sodium because of an absence of tumorigenic findings with the positive reference compound, benzene (Executive CAC Meeting Minutes, 12/2/03). Results from a study that are judged inadequate cannot be referred to in the product label.

Summary of Nonclinical Findings

Pharmacologic Activity:

The Myfortic® NDA was submitted under 505 (b) (2) and relied in part on mycophenolate information from approved drug products regarding its nonclinical pharmacologic activity. Mycophenolate is a potent uncompetitive reversible inhibitor *in*

vitro of inosine monophosphate dehydrogenase, the rate-limiting enzymatic activity in *de novo* guanosine nucleotide synthesis. Both T- and B-lymphocytes require *de novo* synthesis of guanosine; inhibition of guanosine synthesis results in cytostatic effects reducing the proliferation capacity of lymphocytes and diminishing the production of adhesion molecules. This results in immunosuppression and enhances organ transplant acceptance.

Mycophenolate sodium was evaluated in both *in vitro* and *in vivo* transplantation models for pharmacologic activity. Included were kidney and heart *in vivo* rat transplantation models each of which indicated pharmacologic activity for mycophenolate sodium. IgG response was also substantially inhibited by mycophenolate sodium in the murine model for inhibition of the *in vivo* antibody response elicited by Type I and Type II T cell independent antigens. Data from these studies concurred with published studies that evaluated mycophenolate mofetil and mycophenolate.

Overview of Nonclincial Findings:

Mycophenolate sodium was evaluated by the sponsor in repeat-dose toxicity studies in mice, rats, and dogs. CD1 mice were dosed daily by oral gavage for 13 consecutive weeks. The highest dose of 300 mg/kg/day resulted in mortality due to gastrointestinal infections resulting from the gastrointestinal toxicity associated with mycophenolate. Anemia, bone marrow pathology, and gastrointestinal histopathology were observed at dose levels ranging from 100 to 300 mg/kg/day. The no-observed adverse-effect level (NOAEL) for this study in mice was 50 mg/kg/day. Wistar rats were similarly dosed for a 13-week period and displayed excessive mortality at the two highest dose levels (20 and 40 mg/kg/day). As with mice, the major toxicological effects were severe gastrointestinal histopathology, bone marrow pathology, and marked anemia. Minimal effects were observed at the 10 mg/kg/day dose level. The NOAEL was 5 mg/kg/day for the rat study. Male Wistar rats dosed daily by oral gavage for a period of 4 weeks at a 20 mg/kg/day dose level of mycophenolate sodium did not exhibit clinical effects and only modest anemia and histopathology of the spleen and thymus. No gastrointestinal pathology was observed. The toxicity data for Wistar rats at the 20 mg/kg/day dose level indicated that a dosing duration greater than one month was necessary for the development of gastrointestinal pathology and histopathology.

Beagle dogs were also sensitive to the gastrointestinal effects of mycophenolate sodium. Male beagle dogs dosed orally at a 20 mg/kg/day dose level of mycophenolate sodium exhibited a range of gastrointestinal toxicity that included severe effects resulting in early sacrifice for one animal (*in extremis* sacrifice at Day 21) to minor pathological and histopathological effects to the other dogs at this dose level. Anemia was not observed. Plasma mycophenolate AUC averaged 36 μg · hr/ml and Cmax averaged 3.5 μg/ml. No other mycophenolate sodium dose levels were included in this 4-week toxicity study. In a study with the enteric tablet (180 mg mycophenolate sodium), male beagle dogs received twice daily dosing of the 180 mg tablet (12 hr, bid). This study was terminated at Day 20 due to excessive morbidity. The gastrointestinal pathology and histopathology

were characterized as severe to massive. Pancreatic and bone marrow atrophy were also observed. The 360 mg daily dose level was approximately 45 mg/kg/day.

The genotoxic activity of mycophenolate sodium was evaluated in a battery of genotoxicity assays. It was negative for mutagenicity in the *in vitro* bacteria mutagenicity assay in the presence and absence of an S-9 metabolic activation system with the following strains of *Salmonella typhimurium*: TA 1535, TA 97a, TA 98, TA 100, and TA 102. Mycophenolate sodium was weakly positive for clastogenic activity in the *in vitro* micronucleus assay using V79 Chinese hamster cells in the presence and in the absence of an S-9 metabolic activation system. Results from the Mouse Lymphoma L5178Y ($tk^{+/-}$) cell culture assay were positive for genotoxicity and possibly mutagenicity in the presence of an S-9 metabolic activation system. Both large and small mutant colonies resulted from incubations with mycophenolate sodium with a much larger percentage increase in the small colonies (indicative of chromosomal damage) than large colonies which are indicative of mutagenic activity.

The clastogenic activity of mycophenolate sodium was also evaluated in the cultured human peripheral blood lymphocyte assay for chromosome aberration. Mycophenolate sodium was negative under standard assay conditions both in the presence and absence of an S-9 metabolic activation system. A weakly positive response was achieved under an extended incubation time, however, the inhibition of the mitotic index (77 percent) was above the acceptable range (50 to 65 percent) for this assay. Mycophenolate sodium was examined in the *in vivo* mouse bone marrow micronucleus assay. Micronucleus formation was induced above control rates at dose levels (125 and 395 mg/kg/day) that caused pronounced bone marrow toxicity. By comparison, triethylenemelamine (the positive control) which induced a 10-fold increase in the frequency of micronucleated polychromatic erythrocytes did not cause bone marrow toxicity.

Mycophenolate sodium exhibited embyro lethality and teratogenicity in an embryo-fetal developmental toxicity study with pregnant female Wistar rats that received daily oral gavage doses of mycophenolate sodium from Day 6 through 17 of gestation. No live fetuses were observed at the highest dose level (12 mg/kg/day) and early resorption of over 90 percent of all embryos occurred at the next highest dose level of 6 mg/kg/day. The 3 mg/kg/day dose level resulted in embryo lethality that was modestly higher than the vehicle control. Fetuses from the 3 mg/kg/day dose level exhibited multiple craniofacial malformations, visceral malformations, skeletal malformations, and skeletal variations. The only statistically significant observation at the lowest dose level (1 mg/kg) was embryo lethality (early resorptions) at a level marginally higher than that observed in the vehicle control group. The approximate average AUC for mycophenolate at the 1 mg/kg/day dose level was 5.7 $\mu g \cdot hr/ml$.

No effects on fertility indices in female Wistar rats were observed at oral dose levels ranging from 0.2 to 20 mg/kg/day. Dosing was continued to Day 6 of gestation resulting in embryo lethality (post-implantation and early resorptions) at the 20 mg/kg dose level. No embryotoxic effects were noted at the 0.2 and 2.0 mg/kg dose levels. The NOAEL was 2.0 mg/kg/day for embryo toxicity and 20 mg/kg/day for fertility. No effects on

male fertility were observed in Wistar rats at oral mycophenolate sodium dose levels ranging from 2 to 18 mg/kg/day. Doses were administered daily beginning 70 days prior to mating. No compound-related effects were noted for sperm count, mobility, and morphology. Clinical evidence of toxicity to male rats was obeserved at the 18 mg/kg/day dose level (including mortality during mating). The NOAEL for male reproductive performance was 18 mg/kg/day, whereas the NOAEL for general toxicity was 6 mg/kg/day.

The potential carcinogenic activity of mycophenolate sodium was evaluated in male and female Wistar rats at the following oral gavage dose levels: 1, 3, 6, and 9 mg/kg/day. Two zero-level vehicle control groups were incorporated into this study. The overall survival rates for the 2-year bioassay ranged from 68 to 88 percent and were independent of the mycophenolate sodium dose level. The highest mycophenolate sodium dose level resulted in transitory weight gain effects in males and mild hypochromic microcytic anemia in males and females. The only observed neoplastic lesion was benign thymoma of the thymus which was only statistically significant by trend analysis in female rats. This effect was not statistically significant by pairwise analysis and the study was considered negative for tumorigenic activity. Mycophenolate AUC values at the 9 mg/kg/day dose level were approximately 71 $\mu g \cdot hr/ml$ in males and 131 $\mu g \cdot hr/ml$ in females.

The sponsor conducted a 26-week carcinogenicity study in $p53^{+/-}$ heterozygous transgenic mice at oral gavage dose levels of 50, 100, 150, and 200 mg/kg/day. An MTD was established based upon anemia, abnormal RBC morphology, and splenic histopathology at the 150 and 200 mg/kg/day dose levels. Compound-related neoplastic lesions were not observed at any of the mycophenolate sodium dose levels. However, neoplastic lesions were not observed with the positive reference compound, benzene, at a 100 mg/kg/day dose level. The study was assessed as not adequate for determining the tumorigenic potential of mycophenolate sodium due to the absence of sensitivity in identifying benzene as a tumorigen at the 100 mg/kg/day dose level.

Nonclinical Safety Issues:

The nonclinical toxicities observed with mycophenolate sodium were identical to those previously established for mycophenolate mofetil. These toxicological issues were addressed in product labelling and safety monitoring for mycophenolate mofetil and will be reflected in product labelling for Myfortic®.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

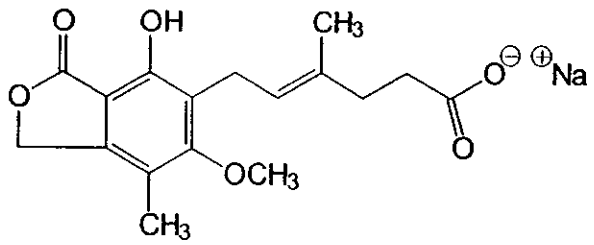
NDA#: 50-791
Sequence: 000
Submission Date: 4/30/03
Type of Submission: Original; 505 (b)(2) designation
Information To Sponsor: Yes
Sponsor: Novartis Pharmaceutical Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Drug Substance Manufacturer: Novartis Pharma

Reviewer: Stephen G. Hundley, PhD, DABT
Division: Special Pathogen and Immunologic Drug Products
HFD#: 590
Review Completion Date: 2/26/04

Drug Information:

Trade Name: Myfortic®
Generic Name: Mycophenolate sodium
Code Name: ERL 080A
Chemical Name: (E)-6-(4-Hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt
CAS#: 24280-93-1 (free acid)
Molecular Formula: $C_{17}H_{19}O_6Na$
Molecular Weight: 342.3 (320 for the free acid)
Molecular Structure:



Relavent Submissions: NDA 50-722; IND's 50,807; 31,747; 40,050; & 33,872

Drug Class: Immunosuppressant

Indication: Prophylaxis of acute rejection of allogenic renal transplants.

Clinical Formulation: Enteric-coated delayed-release tablet

Route of Administration: Oral

Proposed Use: 750 mg Tablet bid (one every 12 hours), daily for lifetime prophylaxis of renal transplant rejection.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless stated otherwise.

Titles of studies reviewed within this submission:

FTY720 and ERL080: 4-Week Toxicity Study by Oral Route (Gavage) in Rats Followed by a 4-Week Treatment-Free Period. Study No. 21950 (Study no. 0120046).

4-Week Comparative Exploratory Study in Dogs. Study no. 0110058.

4-Week Toxicity Study by Oral Route (Gavage) in Beagle Dogs Followed by a 4-Week Treatment-Free Period. Study No. 21951 Report no. 0120047].

Mutation Assay at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells. Study No. 0112301.

An Oral Female Fertility and Early Embryonic Developmental Study in Rats. Study No. 987100

An Oral Male Fertility Study in Rats. Study No. 987099.

ERL 080 Local Intravenous Tolerance Study in Rabbits. Study no. 992044.

Exploratory Side Effect Studies on ERL 080 and Mycophenolate Mofetil, with or without Cyclosporine A, in the Rat. Study No. RD 2000-2310.

Absorption and Disposition of ^{14}C-Labeled ERL 080 as the Sodium Salt in Male Mice Following a Single Oral Dose of 50 mg/kg Compared with a Single Intravenous Dose of 15 mg/kg (Doses Indicated as Free Acid). Report no. R01-1198.

Absorption and Disposition of ^{14}C-Labeled ERL 080 in Male Rats Following a Single Oral Dose of 5 mg/kg of the Sodium Salt and Comparison with a Single Intravenous Dose of 5 mg/kg. Report no. R01-943.

Titles of studies within the NDA submission that were reviewed under previous IND submissions.

Exploratory Side Effect Study on ERL 080 and Mycophenolate-Mofetil (CellCept®), with or without Cyclosporine (Neoral®), in the Rat. Report # 22.11.97.

ERL 080: 13-Week Oral Dose-Range Finding Study in Mice. Study No. 16126.

ERL 080: 13-Week Oral Dose-Range Finding Study in Rats. Study No. 16125.

ERL 080: An Oral Embryo-Fetal Development Study in Rats. Study No. 974064.

ERL 080: Mutagenicity Test using *Salmonella typhimurium*. Study No. 971617.

ERL 080: Micronucleus Test *in vitro* with V79 Chinese Hamster Cells. Study No. MIC 116.

ERL 080: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLH) using the Microtitre® Fluctuation Technique. Study No. 1463/43 – 1052.

ERL 080: Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLH) using the Microtitre® Fluctuation Technique. Study No. 981851.

ERL 080: Induction of Chromosome Aberration in Cultured Human Peripheral Blood Lymphocytes. Study No. 1463/39 – 052.

ERL 080: Induction of Chromosome Aberration in Cultured Human Peripheral Blood Lymphocytes. Study No. 1463/15 – D5140.

ERL 080: Mouse Bone Marrow Micronucleus Test by the Oral Route. Study No. Mk 50.

ERL 080: Mouse Bone Marrow Micronucleus Test by the Oral Route. Study No. Mk 54.

ERL 080: Determination of Test Compound Blood Levels in Mice for Assessing Exposure in the Bone Marrow Micronucleus Test. Study No. 981861.

Validation of an HPLC Analytical Method for the Determination of ERL 080 in Biological Matrices. 1997/069.

Oral Bioavailability of Three Different Tablet Formulations in Dogs Versus Capsule Reference. N98 – 019.

13-Week Oral Dose-Range Finding Study in Mice. Addendum:Toxicokinetic Report. Study No. 16126 1998/010.

13-Week Oral Dose-Range Finding Study in Rats. Addendum:Toxicokinetic Report. Study No. 16125 1998/012.

An Oral Embryo-Fetal Development Study in Rats. Addendum:Toxicokinetic Report. Study No. 974064. 1997/397.

Determination of Test Compound Blood Levels in Mice for Assessing Exposure in the Bone Marrow Micronucleus Test, Contribution of BAPK to the Toxicology Report. 98-865.

Carcinogenicity Study by Oral Administration (Gavage) in Rats. SDZ ERL 080; Study No. 17316 Reference No. 982032.

Carcinogenicity Study by Oral Administration (Gavage) in Rats. CellCept®; Study No. 17208 Reference No. 982033.

ERL 080: 26-Week Oral Carcinogenicity Study in $p53^{+/-}$ (Heterozygous) Mice. Study No. 991035.

Studies not reviewed within this submission:

In vitro and *in vivo* Efficacy of ERL 080, Mycophenolate-Mofetil and Mycophenolic Acid. Report # 23.1.98.

Efficacy of ERL 080 and Mycophenolate-Mofetil (CellCept®), with or without Cyclosporine (Neoral®), SDZ RAD and / or Brequinar Sodium, in Rat Transplantation Models. Report # 14.08.98.

Effect of ERL 080 and Mycophenolate-Mofetil (CellCept®), in Rat Aorta Transplantation. Report # 10.03.98.

CellCept®: 13-Week Oral Dose-Range Finding Study in Mice. Study No. 16128.

CellCept®: 13-Week Oral Dose-Range Finding Study in Rats. Study No. 16127.

CellCept®: An Oral Embryo-Fetal Development Study in Rats. Study No. 974063.

CellCept® (SDZ 207-97): Mutagenicity Test using *Salmonella typhimurium*. Study No. 971618.

CellCept® (SDZ 207-97): Micronuclues Test *in vitro* with V79 Chinese Hamster Cells. Study No. MIC 118.

CellCept® (SDZ 207-97): Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLH) using the Microtitre® Fluctuation Technique. Study No. 1463/44-1052.

CellCept® (SDZ 207-97): Induction of Chromosome Aberration in Cultured Human Peripheral Blood Lymphocytes. Study No. 1463/40.

CellCept® (SDZ 207-97): Induction of Chromosome Aberration in Cultured Human Peripheral Blood Lymphocytes. Study No. 1463/52 – D5140.

CellCept®: Mouse Bone Marrow Micronucleus Test by the Oral Route. Study No. Mk 55.

Expert Commentary on the Genotoxicity of CellCept® and SDZ ERL 080. Study No. 1463/046 and 1463/047.

3.2 PHARMACOLOGY

3.2.1 Brief Summary:

Myfortic® (mycophenolate sodium) is a 505 (b) (2) submission relying upon published information regarding the pharmacologic activity of mycophenolate and mycophenolate mofetil (the approved prodrug of mycophenolate). No information in addition to that presented in the Pharmacologic Activity section of the Executive Summary of this review is presented in the current section.

3.2.2 Primary Pharmacodynamics

The primary pharmacodynamics of mycophenolate was addressed in the Pharmacologic Activity section of the Executive Summary.

3.2.3 Secondary Pharmacodynamics

Not applicable for this review.

3.2.4 Safety Pharmacology

Nonclinical safety pharmacology was not addressed in this submission. Extensive clinical safety pharmacology information on mycophenolate mofetil was considered sufficient to address safety pharmacology concerns.

3.2.5 Pharmacodynamic Drug Interaction

Clinical pharmacodynamic drug interaction studies with Myfortic® and mycophenolate mofetil were presented to address drug interaction issues.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief Summary

Orally administered mycophenolate sodium and mycophenolate mofetil are delivered to systemic circulation as mycophenolate. Oral bioavailability of mycophenolate sodium

was approximately 100 percent in rats and mice. In dogs, the relative bioavailability of mycophenolate from enteric-coated tablets containing mycophenolate sodium was 2.7-fold greater than mycophenolate mofetil in gelatin capsules. Pharmacokinetic data from rats and dogs resulted in plasma half-lives for mycophenolate of 8 to 9 hours; the approximate mycophenolate plasma half-life in human subjects was 10 hours. In mice, the plasma half-life was approximately 5 hours. Plasma protein binding was reported to be approximately 93 percent for rats and 98 percent or higher in mice and humans.

The plasma mycophenolate pharmacokinetic profiles for rats following oral dosing revealed a secondary peak, or plateau, indicative of enterohepatic circulation. Enterohepatic circulation was also demonstrated in human pharmacokinetic studies. Analytical evaluation of sequential plasma samples from mice, rats, and humans indicated substantial levels of a metabolite that was structurally characterized as the 7-O-glucuronide of mycophenolate. Studies with ^{14}C-mycophenolate demonstrated that the 7-O-glucuronide of mycophenolate represented approximately 40 percent of the total ^{14}C plasma AUC in rats and 25 percent in mice. Minor metabolites were detected in plasma from mice and rats that typically represented 1 percent or less of the total ^{14}C plasma AUC.

The primary excretion route in mice and rats was in urine and accounted for 63 to 75 percent of an administered ^{14}C-mycophenolate sodium dose. Approximately 20 to 30 percent of the administered dose was excreted in feces from mice and rats. Most of the urinary radioactivity in mice and rats was identified as the 7-O-glucuroninde of mycophenolate with a small percentage being mycophenolate. In humans 87 percent of a mycophenolate sodium dose was excreted in urine as the 7-O-glucuronide of mycophenolate.

3.3.2 Absorption, Excretion, and Metabolism

Quantitative estimations of absorption and bioavailability were made in the following two studies in the NDA submission (not previously submitted).

Absorption and Disposition of ^{14}C-Labeled ERL 080 as the Sodium Salt in Male Mice Following a Single Oral Dose of 50 mg/kg Compared with a Single Intravenous Dose of 15 mg/kg (Doses Indicated as Free Acid). Report no. R01-1198.

Male Swiss mice received single oral gavage or *iv* doses of [^{14}C]-ERL 080 (— radiochemical purity) for the purpose of generating plasma pharmacokinetics for total drug derived ^{14}C radioactivity (liquid scintillation counting) and quantitation of mycophenolate and mycophenolate glucuronide in plasma by HPLC/UV analysis. Total urinary and fecal excretion of ^{14}C radioactivity derived from [^{14}C]-ERL 080 were determined for each 24-hour interval up to 72 hours following dose administration. Urine samples and fecal extracts were also analyzed by HPLC/radioactivity detection and [ ] to characterize the metabolite profile for ERL 080 in urine and feces.

Each blood timepoint for pharmacokinetic analysis was provided by 3 mice. The post-*iv* timepoints were 5 and 30 minutes and 1, 3, 8, 24, 48, and 72 hours while the post-oral gavage timepoints only differed by substituting a 15 minute post-dosing timepoint for the 5 minute post-*iv* dosing timepoint. Plasma radioactivity levels were at the limit of reliable quantitation by liquid scintillation counting at the 48- and 72-hour timepoints. The levels of mycophenolate and mycophenolate glucuronide (the major metabolite) were at or below quantitation by HPLC/UV analysis at the 24-hour timepoint. The timecourse for these analytical limits to plasma quantitation were observed following the *iv* and oral gavage routes of administration.

The AUC values for total ^{14}C radioactivity were approximately 74 µg eq. · hr/ml after the *iv* dose and 261 µg eq. · hr/ml after the oral dose. The oral dose was approximately 3.3-fold greater than the *iv* dose which is comparable to the 3.5-fold difference in AUC values indicating complete mycophenolate oral bioavailability. Similar comparisons were observed for plasma mycophenolate AUC values (49 and 166 µg · hr/ml for *iv* and oral dosing, respectively). The Tmax for oral dosing ranged from 15 to 30 minutes with a mycophenolate Cmax of 18.6 µg/ml. Plasma AUC values were also generated for mycophenolate glucuronide and were 34 and 151 µg eq. · hr/ml for the *iv* and oral doses, respectively. The percent of plasma radioactivity (expressed on a µmolar basis) was 61 and 25 for mycophenolate and mycophenolate glucuronide, respectively. Three minor metabolites were present in plasma and combined represented approximately 3 percent of total plasma radioactivity. The plasma $t_{1/2}$ for mycophenolate following *iv* administration was 4.8 hours.

The total urinary excretion of administered ^{14}C radioactivity averaged 63 to 65 percent and fecal excretion averaged from 29 to 31 percent over the 72-hour period following *iv* or oral gavage dosing. Urinary mycophenolate represented approximately 4 percent of the dose (*iv* and oral gavage administration) and mycophenolate glucuronide represented 31 and 51 percent of the *iv* and oral gavage doses, respectively. The major excretion product in feces was mycophenolate averaging 27 and 16 percent of the *iv* and oral doses, respectively. Mycophenolate glucuronide was not detected in fecal extracts (*iv* and oral gavage dosing). Minor metabolites in urine included a phenolic glucoside, isomeric glucuronides of O-demethylated ERL 080, O-demethylated ERL 080, and trace levels of a taurine conjugate of ERL 080. Fecal extracts contained O-demethylated ERL 080 and the taurine conjugate of ERL 080.

Absorption and Disposition of 14C-Labeled ERL 080 in Male Rats Following a Single Oral Dose of 5 mg/kg of the Sodium Salt and Comparison with a Single Intravenous Dose of 5 mg/kg. Report no. . R01-943.

Male Wistar rats received oral gavage or *iv* doses of [^{14}C]-ERL 080 , — radiochemical purity) for the purpose of generating plasma pharmacokinetic, metabolism, excretion, and tissue distribution information. Pigmented rats ' 'LE)BR strain) were also used to generate tissue distribution data. Serial blood samples were drawn at the following time

intervals following *iv* administration; 5, 15, and 30 minutes, 1, 2, 4, 8, 24, and 48 hours. Blood samples were collected at the same time intervals following the oral gavage dose with the exception of the 5-minute timepoint which was eliminated. Urine and feces were collected at 24-hour intervals for a period of 7 days following the *iv* and oral gavage doses. Each dosing routine consisted of three male Wistar rats.

Plasma AUC values from the 5 mg/kg oral-gavage and *iv* doses indicated 100 percent oral bioavailability based upon total ^{14}C (118 and 131 µg eq. · hr/ml, *iv* and oral doses, respectively). The total plasma ^{14}C AUC represented by mycophenolate was approximately 46 percent following the *iv* dose and 58 percent after the oral dose. The major metabolite, mycophenolate glucuronide, represented 42 and 30 percent of the AUC following the *iv* and oral doses, respectively. Four minor metabolites in plasma represented a total of 1 to 2 percent of the total plasma AUC. Mycophenolate pharmacokinetics following the 5 mg/kg *iv* dose resulted in the following values: AUC = 77 µg · hr/ml; C_O = 59 µg/ml; $T_{1/2}$ = 9.3 hr; Volume of Distribution (Vss) = 0.5 L/kg; Clearance (C_L) = 0.9 mg/min/kg; and Mean Residence Time (MRT) = 8.8 hr.

Excretion of ^{14}C radioactivity derived from [^{14}C]-ERL 080 was substantially completed by 72 hours following oral or *iv* dosing. Approximately 95 percent of the dose was accounted for with 68 to 75 percent excreted in urine and 21 to 26 percent excreted in feces. No meaningful differences in excretion were observed for the oral and *iv* doses. The metabolite excretion patterns are listed in the following table.

Percent of Administered [^{14}C]-ERL 080

	iv 5 mg/kg		Oral 5 mg/kg	
	Urine	Feces	Urine	Feces
Mycophenolate	9.9	10.9	5.1	8.2
Mycophenolate Glucuronide	36.4	n.d.	46.5	n.d.
Isomeric Glucuronides	4.5	n.d.	5.9	n.d.
Side Chain Oxidation A	1.5	3.1	1.7	3.0
O-Demethyl-ation	0.7	3.9	0.3	2.4
Side Chain Oxidation B	0.4	0.3	0.8	0.3
Methyl Hydroxylation	0.7	n.d.	0.6	n.d.

The listed minor metabolites were determined by τ ɜ analysis and are defined as:

Isomeric Glucuronides: Glucuronides of the O-demethylated and side chain oxidation products of mycophenolate

Side Chain Oxidation:	Hydroxylation of, or carbonyl formation on, the side chain of mycophenolate with loss of olefinic double bond, [two distinct HPLC peaks (A & B)].
O-Demethylation:	O-demethylated mycophenolate
Methyl Hydroxylation:	Hydroxylated aromatic ring methyl group of mycophenolate

Tissue distribution of ^{14}C radioactivity derived from [^{14}C]-ERL 080 was examined at post-dosing timepoints of 15 and 30 minutes, and 1, 4, 24, and 168 hours following oral doses to pigmented rats. Each timepoint consisted of a single animal and ^{14}C levels were estimated by autoradioluminography of whole body slices generated with a cryogenic ultramicrotome. The data from this portion of the study did not indicate that organs or tissues accumulated ^{14}C radioactivity. The 24-hour timepoint demonstrated that the highest concentrations of ^{14}C radioactivity from [^{14}C]-ERL 080 were in bile and kidneys (26 and 28 nmole equivalents/g). Whole blood contained approximately 1.4 nmole equivalents/ml while the only other tissues or organs with higher levels than blood were: adrenal cortex (1.9 nmole equivalents/g); duodenum epithelium (4.9 nmole equivalents/g); kindey cortex (2.5 nmole equivalents/g); and liver (2.0 nmole equivalents/g). These values were approximations due to the method used for quantitative estimations with only one animal at each timepoint.

The highest concentrations of ^{14}C radioactivity were observed in the bile at the 15 and 30 minute timepoints and were approximately 100 nmole equivalents/ml. Tissue distribution in albino rats was determined only at the 168 hr post-dosing timepoint with no detectable radioactivity in the whole body slice except for the kidney cortex which contained radioactivity at the limit of detection (— nmole equivalents/g). Similar levels were observed in subcutaneous skin and brown and white fat from pigmented rats at the 168 hour timepoint. These data were indicative of minimal retention of ^{14}C from [^{14}C]-ERL 080.

3.3.3 Pharmacokinetic Drug Interactions

Clinical pharmacokinetic drug interaction studies with Myfortic® and mycophenolate mofetil were presented to address drug interaction issues.

3.3.4 Comparative Toxicokinetic Summary

Systemic exposure data for the various pivotal toxicity studies are presented in the following table as Cmax and AUC (area under the plasma concentration time curve) values.

Species	Dose Level (mg/kg)	AUC (μg · hr/ml)	Cmax (μg/ml)	Study Description
Mice	50	91 (males) 153 (females)	9.3 (males) 17 (females)	13-Week Tox. Study; NOAEL
Rats	5	54 (males) 67 (females)	5.5 (males) 12 (females)	13-Week Tox. Study; NOAEL
Dogs	20	36.3 (males)	3.5 (males)	4-Week Tox. Study; Lowest Effect Level
Rats (females)	1	5.7	2.2	Embryo-Fetal Developmental Tox. Study; Lowest Effect Level
Rats	9	71 (males) 131 (females)	13.4 (males) 16.7 (females)	2-Year Carcinogenicity Study; Highest Dose Level; Non Tumorigenic
Rats (males)	20	216	21.2	13-Week Toxicity Study; No Testicular Effects
Rats (females)	20	369	27.1	13-Week Toxicity Study

The human AUC cited by the sponsor as representative of the 720 mg bid (every 12 hours) therapeutic dose was 111 μg · hr/ml (0-24 hr AUC). The following systemic exposure ratios were calculated based upon the AUC values for the different animal studies compared to the human AUC value.

Types of Studies	AUC Ratios
13-Week Mouse NOAEL	Male = 0.8; Female = 1.4
13-Week Rat NOAEL	Male = 0.5; Female = 0.6
4-Week Dog LOAEL	Male = 0.3
Embryo-Fetal Developmental Toxicity (Lowest Level for Developmental Tox.)	Pregnant Females = 0.05
Rat Carcinogenicity NOEL for Tumors	Male = 0.6; Female = 1.2
Rats, Male Testicular & Female Fertility (No Effects at Highest Dose Tested)	Male = 1.9; Female = 3.3

A no-effect level was not established for repeat-dose toxicity in dogs and embryo-fetal toxicity in pregnant female rats. No tumorigenic effects were observed in male and female rats at any dose level in the 2-year carcinogenicity study. The no-effect levels in animals were typically at systemic exposures similar to or a fraction of (0.5 to 0.8) the human systemic exposure to mycophenolate at therapeutic doses. The lowest systemic exposure ratio of 0.05 for all toxicity studies was observed in the embryo-fetal developmental toxicity study with pregnant female rats.

3.4 NONCLINICAL TOXICOLOGY

3.4.1 Nonclinical Toxicology Summary

General toxicology:

Mycophenolate sodium was evaluated by the sponsor in repeat-dose toxicity studies in mice, rats, and dogs. CD1 mice were dosed daily by oral gavage for 13 consecutive weeks. The highest dose of 300 mg/kg/day resulted in mortality due to gastrointestinal infections resulting from the G.I. toxicity associated with mycophenolate. Anemia, bone marrow pathology, and gastrointestinal histopathology were observed at dose levels ranging from 100 to 300 mg/kg/day. The no-observed adverse effect level (NOAEL) for this study in mice was 50 mg/kg/day. Wistar rats were similarly dosed for a 13-week period and displayed excessive mortality at the two highest dose levels (20 and 40 mg/kg/day). As with mice, the major toxicological effects were severe gastrointestinal histopathology, bone marrow pathology, and marked anemia. Minimal effects were observed at the 10 mg/kg/day dose level. The NOAEL was 5 mg/kg/day for this study in rats. Male Wistar rats dosed daily by oral gavage for a period of 4 weeks at a 20 mg/kg/day dose level of mycophenolate sodium did not exhibit clinical effects and only modest anemia and histopathology of the spleen and thymus. No gastrointestinal pathology or histopathology was observed. The toxicity data for Wistar rats at the 20 mg/kg/day dose level indicated that a dosing duration greater than one month was necessary for the development of gastrointestinal pathology and histopathology.

Beagle dogs were sensitive to the gastrointestinal effects of mycophenolate. Male beagle dogs dosed orally at a 20 mg/kg/day dose level of mycophenolate sodium exhibited a range of gastrointestinal toxicity that included severe effects resulting in early sacrifice for one animal (*in extremis* sacrifice at Day 21) to minor pathological and histopathological effects to the other dogs at this dose level. Anemia was not observed. Plasma mycophenolate AUC averaged 36 μg · hr/ml and Cmax averaged 3.5 μg/ml. No other mycophenolate sodium dose levels were included in this 4-week toxicity study. In a study with the enteric tablet (180 mg mycophenolate sodium), male beagle dogs received twice daily dosing of the 180 mg tablet (12 hr, bid). This study was terminated at Day 20 due to excessive morbidity. The gastrointestinal pathology and histopathology were characterized as severe to massive. Pancreatic and bone marrow atrophy were also observed. The dose level (360 mg daily) was approximately 45 mg/kg/day.

Genetic toxicology:

The genotoxic activity of mycophenolate sodium was evaluated in a battery of genotoxicity assays. It was negative for mutagenicity in the *in vitro* bacteria mutagenicity assay in the presence and absence of an S-9 metabolic activation system with the following strains of *Salmonella typhimurium*: TA 1535, TA 97a, TA 98, TA 100, and TA 102. Mycophenolate sodium was weakly positive for clastogenic activity in the *in vitro* micronucleus assay using V79 Chinese hamster cells in the presence and in the absence of an S-9 metabolic activation system. Results from the Mouse Lymphoma

L5178Y ($tk^{+/-}$) cell culture assay were positive for genotoxicity and possibly mutagenicity in the presence of an S-9 metabolic activation system. Both large and small mutant colonies resulted from incubations with mycophenolate sodium with a much larger percentage increase in the small colonies (indicative of chromosomal damage) than large colonies which are indicative of mutagenic activity.

The clastogenic activity of mycophenolate sodium was also evaluated in the cultured human peripheral blood lymphocyte assay for chromosome aberration. Mycophenolate sodium was negative under standard assay conditions both in the presence and absence of an S-9 metabolic activation system. A weakly positive response was achieved under extended incubation time, however, the inhibition of the mitotic index (77 percent) was above the acceptable range (50 to 65 percent) for this assay. Mycophenolate sodium was examined in the *in vivo* mouse bone marrow micronucleus assay. Micronucleus formation was induced at dose levels (125 and 395 mg/kg) that caused pronounced bone marrow toxicity. By comparison, triethylenemelamine (the positive control) which induced a 10-fold increase in the frequency of micronucleated polychromatic erythrocytes did not produce evidence of bone marrow toxicity.

Carcinogenicity:

The potential carcinogenic activity of mycophenolate sodium was evaluated in male and female Wistar rats at the following oral gavage dose levels: 1, 3, 6, and 9 mg/kg/day. Two zero-level vehicle control groups were incorporated into this study. The overall survival rates for the 2-year bioassay ranged from 68 to 88 percent and were independent of the mycophenolate sodium dose level. The highest dose level resulted in transitory weight gain effects in males and mild hypochromic microcytic anemia in males and females. The only observed neoplastic lesion was benign thymoma of the thymus which was only statistically significant by trend analysis in female rats. This effect was not statistically significant by pairwise analysis and the study was considered negative for tumorigenic activity. Mycophenolate AUC values at the 9 mg/kg dose level were approximately 71 µg · hr/ml in males and 131 µg · hr/ml in females.

The sponsor conducted a 26-week carcinogenicity study in $p53^{+/-}$ heterozygous transgenic mice at oral gavage dose levels of 50, 100, 150, and 200 mg/kg/day. An MTD was established based upon anemia, abnormal RBC morphology, and splenic histopathology at the 150 and 200 mg/kg dose levels. Compound-related neoplastic lesions were not observed at any of the mycophenolate sodium dose levels. However, neoplastic lesions were not observed with the positive reference compound, benzene, at a 100 mg/kg dose level. The study was assessed as not adequate for determining the tumorigenic potential of mycophenolate sodium due to the absence of sensitivity in detecting benzene as a tumorigen at the 100 mg/kg/day dose level.

Reproductive Toxicology:

Mycophenolate sodium exhibited embyro lethality and teratogenicity in an embryo-fetal developmental toxicity study with pregnant female Wistar rats which received daily oral

gavage doses of mycophenolate sodium from Day 6 through 17 of gestation. No live fetuses were observed at the highest dose level (12 mg/kg/day) and early resorption of over 90 percent of all embryos occurred at the next highest dose level of 6 mg/kg/day. The 3 mg/kg/day dose level resulted in embryo lethality modestly higher than the vehicle control. Fetuses from the 3 mg/kg/day dose level exhibited multiple craniofacial malformations, visceral malformations, skeletal malformations, and skeletal variations. The only statistically significant observation at the lowest dose level (1 mg/kg) was embryo lethality (early resorptions) at a level marginally higher than that observed in the vehicle control group. The approximate average AUC for mycophenolate at the 1 mg/kg dose level was 5.7 μg · hr/ml.

No effects on fertility indices in female Wistar rats were observed at oral dose levels ranging from 0.2 to 20 mg/kg/day. Dosing was continued to Day 6 of gestation resulting embryo lethality (post-implantation and early resorptions) at the 20 mg/kg dose level. No embryotoxic effects were noted at the 0.2 and 2.0 mg/kg dose levels. The NOAEL for embryo toxicity in this study was 2.0 mg/kg and 20 mg/kg/day for fertility. No effects on male fertility in Wistar rats were observed at oral mycophenolate sodium dose levels ranging from 2 to 18 mg/kg/day. Doses were administered daily beginning 70 days prior to mating. No compound-related effects were noted for sperm count, mobility, and morphology. Clinical evidence of toxicity to male rats was obeserved at the 18 mg/kg dose level (including mortality during mating). The NOAEL for male reproductive performance was 18 mg/kg/day, whereas the NOAEL for general toxicity was 6 mg/kg/day.

Special Toxicology:

Intravenous and perivenous administration of mycophenolate sodium to male rabbits resulted in clinical, gross pathology, and histopathology effects. These effects were classified as minimal to slight and were not considered problematic. The perivascular dosing was undertaken to present the worst case scenario for misdosing of an *iv* dose (30 mg mycophenolate sodium in one ml over a 2-minute infusion). Multiple compound-related perivascular effects were observed by clinical, gross pathological, and histopathological analyses. Most of the histopathological effects were classified as slight to moderate at the 7-day post perivascular dosing sacrifice.

3.4.2 Single-Dose Toxicity

Nonclinical single-dose toxicity studies were not submitted or conducted by the sponsor.

3.4.3 Repeat-Dose Toxicity

FTY720 and ERL080: 4-Week Toxicity Study by Oral Route (Gavage) in Rats Followed by a 4-Week Treatment-Free Period. 'Study No. 21950 'Study no. 0120046).

ERL 080 (mycophenolate sodium, batch no. 0044031, — analytical purity) and FTY 720 (Novartis drug candidate, batch no. 9923014, — analytical purity) were examined as combined doses in a general toxicity study with young adult male Wistar rats. All rats on study received a single daily oral-gavage dose for 30 consecutive days in accordance with the following dosing regimen chart.

Dosing Regimen	Principal Group	Recovery Group
Zero-level Vehicle Control	10 Male Rats	6 Male Rats
5 mg/kg FTY720	10 Male Rats	6 Male Rats
20 mg/kg ERL080	10 Male Rats	6 Male Rats
1 mg/kg FTY720 plus 10 mg/kg ERL080	10 Male Rats	6 Male Rats
5 mg/kg FTY720 plus 20 mg/kg ERL080	10 Male Rats	6 Male Rats

All animals in the principal groups were sacrificed 24 hours following the terminal dose. The post-dose recovery groups were held four weeks following the terminal dose and then sacrificed. The study was contracted by the sponsor to [redacted] and was conducted in accordance with GLP requirements and audited by a Quality Assurance group.

Observations for morbidity or mortality were conducted twice daily during the dosing period and once daily during the post-dosing recovery period. Clinical signs were monitored and recorded once daily during the dosing and post-dosing periods. Body weights were determined prior to the initial dose and once weekly thereafter. Food intake was measured once weekly. Ophthalmological examinations were conducted on each animal prior to the initiation of the dosing routines, once during Week 4, and during Week 8 for the recovery groups. Blood samples for toxicokinetic determinations were drawn from the orbital sinus under light anesthesia on Day 1 and Day 29 at the following timepoints: pre-dose, 2, 4, 8, and 24 hours post-dosing (2 animals from each dose group supplied blood for each timepoint). Total plasma concentrations were determined for ERL 080 and FTY 720.

Blood samples for hematology and serum chemistry were drawn from the orbital sinus under light anesthesia at the end of Week 4 (principal groups) and the end of Week 8 (post-dose recovery groups). The hematological measurements included: erythrocytes (RBC), hemoglobin (HB), mean cell volume (MCV), packed cell volume (PCV), mean cell hemoglobin concentration (MCHC), mean cell hemoglobin (MCH), thrombocytes (PLAT), leucocytes (WBC), differential white cell count to include neutrophils, eosinophils, basophils, lymphocytes, monocytes, and reticulocytes. Serum chemistry included the following measurements: sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphorus, glucose, urea, creatinine, total bilirubin, cholesterol, triglycerides, alkaline phosphatase (ALP), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), total protein, albumin, alpha-1-globulin, alpha-2-globulin,

beta-globulin, gamma-globulin, and A/G ratio (albumun to globulin). Urine samples were also collected at the end of Week 4 and Week 8 for the following measurements: volume, pH, specific gravity, protein, glucose, ketones, bilirubin, nitrites, blood, urobilinogen, and sediment cytology.

Gross pathology was conducted upon necropsy at the terminal sacrifice for the principal toxicity groups and the 4-week post-dose recovery groups. The following organs were weighed upon removal at sacrifice: adrenal glands, brain, heart, kidneys, liver, pituitary glands, prostate, spleen, testes, thymus, and thyroids. The organ and tissues that were removed, preserved, and prepared for histopathology (light microscopic analysis) from each animal are listed in the following table.

Adrenals	Lacrymal Gland
Aorta	Liver
Brain	Lungs
Cecum	Lymph Nodes (mandibular and mesenteric)
Colon	Sciatic Nerve
Duodenum	Seminal Vesicles
Epididymides	Skeletal Muscle
Esophagus	Spinal Cord
Eyes	Spleen
Harderian Glands	Stomach with Forestomach
Femoral Bone (with articulation)	Testes
Heart	Thymus
Ileum	Thyroids with Parathyroids
Jejunum	Trachea
Kidneys	Urinary Bladder

Compound-related mortality and morbidity were not observed during the dosing routine. Two animals died due to aspiration of the oral-gavage dose. In addition several animals from three different dosing regimens exhibited intermittent regurgitation that may have resulted from oral-gavage dosing errors. The only compound-related clinical observation was pallor of the extremities in several animals at the combination dose of FTY 720 and ERL 080 (5/20 mg/kg) during the 4-week dosing period. Body weight gain was depressed by 13 and 25 percent at the two combination dose levels of FTY 720 and ERL 080 (1/10 and 5/20 mg/kg) compared to the zero-level vehicle controls. Food consumption was reduced in rats at the FTY 720 and ERL 080 combination dose level of 5/20 mg/kg. Both body weight gain and food consumption recovered during the 4-week post-dosing period.

Hematological effects associated with ERL 080 included depressed erythrocyte, hemoglobin, and lymphocyte levels and elevated platelet levels. FTY 720 caused 3- to 4-fold decreases in lymphocyte and leucocyte levels. The combination doses of ERL 080 and FTY 720 exhibited a combination of effects associated with each compound individually. There was no indication of any synergistic effect at the 5/20 mg/kg combination dose level. The serum chemistry effects were nominal to mild for both

compounds individually and in combination. The 5/20 mg/kg combination dose level resulted in increased serum urea, albumin, cholesterol, and the albumin/globulin ratio. Modest decreases were observed in globulin levels, alkaline phophatase, and ASAT. The extent of these effects compared to zero-level vehicle control values ranged from 14 to 32 percent. All of the compound-related serum chemistry effects were reversible. There were no compound-related effects in any of the urinalysis parameters.

Gross pathology for the principal toxicology groups indicated pale livers and thyroids and reduced size of seminal vesicles and the prostate for the FTY 720 and ERL 080 combination dose of 5/20 mg/kg. Organ weight effects were also noted for this dosing regimen and included depressed liver, prostate, spleen, and thymus weights. Absolute brain weights were elevated at the 5/20 mg/kg combination dose level. The effect upon spleen weights appeared to result from FTY 720 based upon the same observation at the 5 mg/kg dose level of FTY 720, whereas the reduced thymus weight was entirely due to ERL 080 based upon results from the 20 mg/kg dose level of ERL 080. The 20 mg/kg dose level of ERL 080 resulted in spleen histopathology (atrophy of the marginal zone, atrophy of the periarterial lymphatic sheath, and germinal center development) and thymus histopathology (lymphocytolysis and darkening medulla). The same histopathological effects were observed in the spleen and thymus from rats dosed with FTY 720 (5 mg/kg dose level) with the additional observation of cortical atrophy in the thymus. The combination FTY 720 and ERL 080 dose regimen (5/20 mg/kg) resulted in the previously mentioned histopathological effects to the spleen and thymus with a greater degree of severity (histopathological ratings of slight to moderate).

Toxicokinetic data indicated that the combination dosing of ERL 080 and FTY 720 did not have any impact upon the toxicokinetics for each compound administered separately. The ranges for ERL 080 Cmax and AUC values following 20 mg/kg doses were — µg/ml and 85 to 100 µg • hr/ml, respectively. The Cmax and AUC values for FTY 720 following 5 mg/kg doses were — µg/ml and 3.8 to 4.3 µg • hr/ml, respectively. The plasma AUC values for each compound did not appreciably increase between Day 1 and Day 30 of dosing.

4-Week Toxicity Study by Oral Route (Gavage) in Beagle Dogs Followed by a 4-Week Treatment-Free Period. [Study No. 21951 Report no. 0120047].

Male beagle dogs received daily oral gavage doses of ERL 080 (mycophenolate-sodium) and FTY 720 (a Novartis experimental drug product) for a period of four weeks according to the following regimens: 3 mg/kg FTY 720; 20 mg/kg ERL 080; 1 mg/kg FTY 720 plus 10 mg/kg ERL 080; and 3 mg/kg FTY 720 plus 20 mg/kg ERL 080. Each dosing regimen consisted of five male beagle dogs, three of which were designated as the main toxicity group and the remaining two at each dose level designated as the 4-week post-dose recovery group. The study design also included a zero-level vehicle control group. This study was conducted in accordance with GLP requirements and was audited by a Quality Assurance group. The sponsor contracted the study to [

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Morbidity and mortality were monitored twice daily during the dosing phase while clinical evaluations were conducted once daily. Body weights were determined prior to the initiation of the dosing routines and then on Day 1, 8, 15, and 29; the post-dose recovery animals were additionally weighed on Day 35, 43, 50, and 56. Food consumption was determined daily during the dosing phase and weekly for the post-dose recovery animals after Week 4. Blood samples were drawn for hematology and serum chemistry prior to the initiation of the dosing regimens, and on Day 26 (prior to dose administration on that day). Blood samples were drawn on Day 55 from the post-dose recovery animals. Electrocardiograms were generated with standard leads (I, II, and III) prior to the initiation of the dosing regimens on Day 1 and during Week 4. ECG's were generated at multiple timepoints during the day and included a zero timepoint and 1, 2, 4, 6, 8, and 24 hours after dosing. Blood pressure was also determined at the same time intervals as ECG's. Ophthalmological examinations were conducted prior to the initiation of the dosing routines and once during Week 4 of the study. Sequential blood samples were drawn for plasma pharmacokinetics on Day 1 and during Week 4 at the following time intervals: 0, 2, 4, 8, and 24 hours post-dosing.

Gross pathology was conducted at the terminal sacrifices (24 hours after the terminal dose for the main toxicity groups and 4-weeks following the last dose for the post-dose recovery groups) and at sacrifices for cause prior to the scheduled sacrifice. The following organs and tissues were excised and weighed: adrenals, brain, heart, kidneys, liver, pituitary gland, prostate, spleen, testes, thymus, and thyroids with parathyroids. The following table lists the organs and tissues that were removed and prepared for histopathology.

Adrenals	Kidneys	Sciatic Nerve
Aorta	Lacrymal Glands	Skeletal Muscle
Brain	Liver	Skin
Cecum	Lungs with Bronchi	Spinal Cord
Colon	Mandibular Lymph Nodes	Spleen
Duodenum	Mesenteric Lymph Nodes	Sternum (Marrow)
Epididymides	Mammary Gland Area	Stomach
Esophagus	Optic Nerve	Testes
Eyes	Pituitary Gland	Thymus
Gall Bladder	Prostate	Thyroid (Parathyroid)
Heart	Rectum	Trachea
Ileum	Parotid Salivary Gland	Urinary Bladder
Jejunum	Submandibular Salivary Gland	

The tissue samples listed in the preceding table were prepared from each animal on study and were subsequently analyzed by light microscopy.

The 20 mg/kg ERL 080 dosing regimen resulted in excessive morbidity to one of the five male dogs resulting in an early sacrifice on Day 21. The clinical signs included weight

loss (emaciation), lethargy (hypoactivity), dehydration, and severe diarrhea. No clinical signs of toxicity were observed in the other dogs in the 20 mg/kg ERL 080 dosing regimen. Three of the five dogs receiving the 3 mg/kg FTY 720 plus 20 mg/kg ERL 080 regimen also exhibited emaciation, diarrhea, and weight loss. No adverse clinical effects were noted for the dogs receiving the 1 mg/kg FTY 720 plus 10 mg/kg ERL 080 dosing regimen.

The 20 mg/kg ERL 080 dosing regimen resulted in reduced systolic blood pressure two hours after dosing on Day 1. The average reduction in blood pressure was 40 mm Hg (approximately 38 percent). Normal blood pressure was observed at the next examination (6 hours post-dosing). No blood pressure effects were noted on Day 28. No blood pressure effects were observed in dogs from any of the other dosing regimens. There were no compound-related effects upon heart rate or ECG's. ERL 080 resulted in no observable hematological effects. All hematological effects were associated with FTY 720 (decreased white blood cell count, increased platelets, and reduced eosinophils, lymphocytes, and monocytes). Similarly, ERL 080 did not produce serum chemistry effects whereas FTY 720 was associated with decreased serum levels of alkaline phosphatase (2-fold reduction), alanine aminotransferase, and gamma-globulin.

Gross pathology of the dog from the 20 mg/kg ERL 080 dosing routine (sacrificed *in extremis*) revealed brown liquid content throughout the gastrointestinal tract, multiple reddish-purple foci on the urinary bladder, and reduced size of the thymus, prostate, testes, and epididymides. The only observations from one of the the remaining two dogs at the scheduled sacrifice were reduced size of the thymus and testes. Histopathological findings from the dog sacrificed *in extremis* included: atrophy and necrosis throughout the small and large intestine; lymphoid atrophy in the mesenteric and mandibular lymph nodes; centrilobular hepatic atrophy and congestion; urinary bladder congestion; zymogen granule depletion (pancreas); lymphoid atrophy in the spleen; diffuse atrophy of the thymus; tubular dilatation and fibrosis of the kidney; and acinar atrophy, ductal inflammation, and periductal inflammation of the salivary gland. One of the two remaining dogs from the 20 mg/kg ERL 080 dosing routine also exhibited single cell necrosis, inflammatory cell infiltration, and mucosal atrophy in the small and large intestine, and kidney fibrosis, although the severity was categorized as minimal. Histopathology noted in the two dogs at the scheduled post-dosing sacrifice at the 20 mg/kg ERL 080 dose level were also observed in the dogs from the the 3 mg/kg FTY 720 and 20 mg/kg ERL 080 dosing routine. Histopathological effects attributable to ERL-080 were not observed in dogs from the 1 mg/kg FTY 720 plus 10 mg/kg ERL 080 dosing regimen.

The toxicokinetic data from dogs receiving the 20 mg/kg ERL 080 dose level indicated a 2-fold increase in plasma AUC values for Day 28 compared to Day 1 (36.3 vs 15.8 μg · hr/ml) while an approximate 3-fold difference was observed in Cmax (3.5 vs 1.3 μg/ml). The increased toxicokinetic values did not appear to entirely be due to retention of mycophenolate as the 0 time (pre-dose) plasma value on Day 27 was only 0.36 μg/ml. The Tmax ranged from 4 to 8 hours.

Comments

One of ten dogs receiving daily oral administrations of dosing regimens that contained 20 mg/kg ERL 080 was sacrificed *in extremis* (Day 20) due to compound-related toxicity. None of the other dogs in the two dosing routines (a) 20 mg/kg ERL 080 and b) 3 mg/kg FTY 720 plus 20 mg/kg ERL 080) exhibited severe clinical effects during the dosing phase. Gastrointestinal histopathology typically associated with ERL 080 in dogs was also observed at the terminal dose sacrifice from the two groups receiving 20 mg/kg ERL 080 as part of the dosing regimen. These effects were generally classified as minimal to slight. Gross pathology and histopathology associated with FTY 720 were reported but are not relevant to the current Myfortic® NDA submission.

4-Week Comparative Exploratory Study in Dogs. Study no. 0110058.

Male beagle dogs were scheduled to receive oral doses of ERL 080, CellCept®, or 4-(2-hydroxyethyl) morpholine (a precursor to mycophenolate) for a period of 4 weeks. The oral doses of ERL 080 were the actual enteric coated tablet developed for human therapy as Myfortic®. Each tablet contained 180 mg of ERL 080, and each dog in the Myfortic® group received a 180 mg tablet twice daily (bid, 12 hours). CellCept® was also administered as the marketed drug capsule and was administered as a single 250 mg tablet twice daily (bid, 12 hours). The study design also included a group dosed twice daily with 4-(2-hydroxyethyl) morpholine (70 mg bid, 12 hours) and a zero-level vehicle control. Each dosing regimen consisted of 4 male beagle dogs.

All animals were scheduled to receive daily doses of the test compound for a period of four weeks. A standard battery of toxicological analyses were incorporated into the dosing phase of the study. The study was terminated, however, by Day 20 due to unacceptable clinical toxicity with ERL 080 (mycophenolate sodium) and CellCept® (mycophenolate mofetil). All dogs in these two groups were sacrificed *in extremis* and consequently many of the in-life analyses were not conducted. Clinical observations included; diarrhea, vomiting (occasionally with blood), salivation, hypoactivity, and tremor. Marked body weight loss and emaciation were also observed.

Gross pathology at necropsy included reddish mucosal discoloration of the small intestines, red foci of the mucosa of the large intestine, and reddish mucosa of the pyloric area. The major histopathological effects were observed in the small and large intestines and included; mucosal atrophy, necrosis, inflammation, glandular dilatation, and congestion. Additional compound-related histopathology included; necrosis and inflammation of salivary glands, retropharyngeal lymph node atrophy, pancreas degeneration (apoptosis, necrosis, and acinar atrophy), bone marrow atrophy, congestion of mesenteric lymph nodes, and decreased glycogen content in hepatocytes. These results were noted in animals from the Myfortic® and CellCept® groups.

Comments:

An abbreviated review was made of this study due to the overt toxicity observed in the male dogs dosed with Myfortic® and CellCept®. The original intent of this study was to determine if the enteric coating of the Myfortic® tablets would mitigate gastrointestinal toxicity associated with mycophenolate. The sponsor indicated in their initial IND submission that the enteric tablet containing mycophenolate sodium might have a safety advantage for gastrointestinal toxicity. No safety advantage was demonstrated under the conditions of this study. The sponsor may have had a better opportunity to complete this study and provide a better comparision between Myfortic® and CellCept® if the dosing schedule was once daily with 180 mg mycophenolate sodium (Myfortic® tablet) and 250 mg mycophenolate mofetil (CellCept® capsule).

3.4.4 Genetic Toxicology

Mutation Assay at the Thymidine Kinase Locus of L5178Y Mouse Lymphoma Cells. Study No. 0112301.

The test system was the mouse lymphoma L5178Y $TK^{+/-}$ cell culture. The study was conducted in accordance with GLP requirements and audited by a Quality Assurance group. ERL 080 (Batch no. 0044031 with —— % analytical purity) was evaluated for mutagenic potential at cell culture concentrations ranging from 0.2 to 3.2 mg/ml. Cell culture incubations with the different ERL 080 concentrations were conducted in the presence and absence of a rat hepatic S-9 (post-mitochondrial supernate) metabolic activation system. The chemicals used as positive controls were methanesulfonic acid methylester (incubations without the S-9 metabolic activation system), and benzo(a) pyrene (incubations with the metabolic activation system). All cell culture suspension incubations were conducted for 3 hours at 37° C.

Following the incubations the cells were pelleted by centrifugation, washed with culture media, and resuspended in fresh culture media for the 2-day expression period. The selection agent for the mouse lymphoma L5178Y $TK^{+/-}$ cell culture assay is 5-trifluorothymidine (TFT) in a subsequent 7-day incubation. Assay validation was based upon survival and relative survival rates as well as relative growth values. The viability criteria used for the upper limit of the test compound concentration was relative survivability greater than 10 percent and relative total growth not less than 0.10. For the incubations absent the S-9 metabolic activation system the highest acceptable ERL 080 cell culture concentration was 2.24 mg/ml (relative survivability = 60.5 %, relative total growth = 0.10). In the presence of the S-9 metabolic activation system the highest acceptable concentration was 1.6 mg/ml with relative survivability and relative total growth values of 58.9 % and 0.16, respectively.

Mutation frequency values increased with increased ERL 080 cell culture concentrations beginning at a cell culture concentraion of 0.20 mg/ml in the presence of the S-9

metabolic system and 0.37 mg/ml absent metabolic activation. The mutation frequency was 2.6-fold greater than the vehicle control frequency in incubations absent the S-9 metabolic activation system and 3.4-fold greater that the vehicle control in the presence of the S-9 metabolic activation system. The greatest fold increase was observed in small colonies (6- to 8-fold) compared to the approximate 2.3-fold in large colonies relative to the vehicle controls. In this cell culture system large colonies represent direct mutagenic activity due to base-pair substitutions or deletions while the small colonies reflect direct or indirect chromosomal damage (chromosomal aberrations). Both incubation systems were validated by positive mutagenic responses from the positive control chemicals (methanesulfonic acid methylester and benzo(a) pyrene).

3.4.5 Carcinogenicity

Carcinogenicity studies conducted by the sponsor were reviewed in previous toxicology amendments to the IND.

3.4.6 Reproductive and Developmental Toxicology

An Oral Female Fertility and Early Embryonic Developmental Study in Rats. Study No. 987100

The effect of ERL 080 (mycophenolate sodium) on female rat fertility was evaluated in sexually mature female Wistar rats. Daily doses of ERL 080 (Batch no. 97906; — % analytical purity) were administered orally by gavage at the following dose levels: 0.2, 2, and 20 mg/kg. The dosing regimens were initiated 2 weeks prior to mating and continued until Day 6 of gestation. Each dosing regimen (including a zero-level vehicle control) consisted of 25 female rats. The study was conducted by the sponsor in accordance with GLP requirements and audited by a Quality Assurance group.

In-life clinical evaluations of the females included mortality and morbidity twice daily; clinical observations twice daily during the dosing phase and once daily post-dosing; body weight and food intake determinations twice weekly prior to mating and on gestation Day 0, 3, 6, 9, and 13; and daily vaginal cytology prior to mating to determine estrous cycle effects. Mating was confirmed by the presence of vaginal plugs and listed as gestation Day 0. On Day 13 of gestation dams were anesthetized and C-sectioned. Gross examination was made of the major viscera. The reproductive parameters measured at C-section included gravid uterine weight, number of corpora lutea, and description of implantation sites (pre-implantation loss, post-implantation loss, and resorptions).

There was no clinical evidence of maternal toxicity at any dose level of ERL 080 during the pre-mating period and post-mating gestation. The average body weight at Day 9 of gestation was low (statistically significant) for the 20 mg/kg group compared to the zero-

level vehicle control group. Body weight gain was also lower on Day 0 to 3 of gestation and Day 6 to 9 of gestation for the 20 mg/kg group compared to control animals. Average food consumption was also lower for the 20 mg/kg group during Day 11 to 15 of pre-mating and Day 0 to 3 of gestation. The body weight and food consumption effects at the 20 mg/kg dose level were statistically significant and appeared to be greater during gestation. There were no compound-related effects on estrous cycle, mating indices, and pregnancy rates. No abortions or premature births were observed at any dose level of ERL 080. The uterine evaluations at the sacrifice and C-section on Day 13 of gestation indicated no compound-related effects on copora lutea, implantation sites, and pre-implantation loss (none observed at any dose level). Post-implantation losses and total resorptions were statistically significantly higher at the 20 mg/kg ERL 080 dose level compared to zero-level controls (15 % vs 7 %). All resorptions were early resorptions. No embryotoxic effects were observed at the 0.2 and 2.0 mg/kg dose levels.

Results of this study indicated that ERL 080 did not induce fertility effects at any dose level examined. Embryotoxicity and maternal toxicity were observed at the highest dose level of 20 mg/kg making the 2 mg/kg dose level the overall no effect level for this study.

An Oral Male Fertility Study in Rats. Study No. 987099.

This was a companion study to the female rat fertility study using the same rat strain and the identical Batch of ERL 080. Sexually mature male rats received daily oral gavage doses of ERL 080 for a pre-mating period of 70 days at dose levels of 2, 6, and 18 mg/kg. Each dosing regimen (including the zero-level vehicle control) consisted of 25 rats. Dose adminstration continued through the mating period of 2 weeks. This study was conducted in accordance with GLP requirements and audited by a Quality Assurance group.

In-life examinations of male rats included twice daily monitoring for mortality, morbidity, and clinical effects during the dosing phase of the study. Food intake and body weight determinations were made twice weekly during the course of the study. Mating was initiated after 70 days of dosing to males (2-week mating period). The female rats were monitored once weekly during mating for mortality, morbidity and clinical signs; daily monitoring was conducted during gestation. Body weight determinations were made every third day during gestation.

Males were sacrificed and necropsied at the termination of the 2-week mating period. Gross pathology included examination, excision, and weighing of the testes and epididymides. No histopathology was conducted on the testes and epididymides. Testicular samples were prepared for sperm count and sperm motility. Female rats were sacrificed on Day 13 of gestation; all gross pathology and uterine evaluations were conducted as described in the previously reviewed female fertility study.

Morbidity and mortality occurred in male rats at the 18 mg/kg dose level between Day 74 and 82 (following the conclusion of successful mating). One male was sacrificed *in*

extremis on Day 77 as the result of an intubation error (perforation of the esophagus during dosing). One male was sacrificed *in extremis* on Day 74 and one male was found dead on Day 82. Clinical signs for these two animals on the days preceding sacrifice included paleness, low body temperature (cool to touch), lethargy, hunched posture, piloerection, salivation, gasping, and recumbency. Clinical signs were also observed in two other male rats at the 18 mg/kg dose level and included salivation, pale appearance, and partially closed eyelids. No indication was given by the sponsor regarding the day of dosing that these effects appeared. No overt clinical signs of toxicity were noted in male rats from the 2 and 6 mg/kg dose levels. Food intake, body weight, and body weight gain were statistically lower at various intervals for the male rats at the 18 mg/kg dose level compared to the zero-level vehicle control group. The body weight differences ranged from 6 to 7 percent and occurred between Day 35 to 87. No clinical or body weight effects were observed in the female rats from gestation Day 0 to 13.

Gross pathological effects were observed in the two male rats from the 18 mg/kg dose level that died or was sacrificed in advance of the scheduled sacrifice. The probable compound-related observations included pale thymus, enlarged heart, discolored lung and liver, constricted stomach, and red fluid in urinary bladder (from the animal found dead). No gross pathology was observed in any of the remaining male rats at the 18 mg/kg dose level or from any of the male rats from the 2 and 6 mg/kg dose levels. No gross pathological effects were observed in any of the pregnant female rats sacrificed on Day 13 of gestation.

There were no compound-related effects on testicular and epididymal weights, sperm count, and sperm motility (measured as percent motile sperm) at any dose level. There were no effects on male fertility and mating indices at any dose level of ERL 080. No compound-related effects were observed in the female reproductive parameters (pregnancy rate, viable fetuses, fertility index, corpora lutea, implantation sites, pre- or postimplantation loss, and resorptions).

The no-effect level for male reproductive performance was 18 mg/kg while the NOAEL for general toxicity to males was 6 mg/kg based upon clinical and body weight effects.

3.4.7 Local Tolerance

The sponsor contracted this study to [ ] The study was conducted in accordance with GLP requirements and audited by a Quality Assurance group. ERL 080 (Batch no. Y059 0699) was solubilized in sterile water suitable for intravenous administration to a concentration of 30 mg/ml. Sterile physiological saline (0.9%) served as the *iv* control. Male New Zealand White rabbits were used to evaluate the effect of intravenous and perivenous injections of ERL 080.

Each of two dose groups consisted of five rabbits. ERL 080 was adminstered intravenously to the right ear and perivenously to the left ear to each rabbit in one group while the same dosing routine was followed with physiological saline to the control

group. All dose administrations were in a volume of 1.0 ml over a 2-minute infusion period. Clinical signs were monitored daily. Injection site observations were made and recorded 24 and 48 hours and 7 days following dose administration. Animals were sacrificed 7 days following dose administration and gross pathological evaluations were made at each injection site. The injection sites (even with the injection, distal to the injection, and proximal to the injection) were prepared for and examined by histopathology.

Intravenous injection of ERL 080 resulted in transitory observations of perivenous hemorrrhage infiltration in 2 of 5 animals. Perivenous administration of ERL 080 resulted in slight to well defined erythema in 5 of 5 animals that persisted until Day 7. Intravenous injection of physiological saline also resulted in observations of perivenous hemorrhagic infiltration in 5 of 5 animals and no effects were observed following intravenous injections. Gross pathology (Day 7 sacrifice) indicated perivascular edema, folliculitis, and hemorrhage in 1 of 5 animals dosed *iv* with ERL 080. All animals receiving the perivascular dose of ERL 080 exhibited acute inflammation of the dermis; 4 of 5 exhibited edema and hemorrhage of the dermis; and 2 of 5 exhibited acute inflammatory reaction. No gross pathological effects were noted in rabbits receiving the *iv* physiological saline dose. The perivascular physiological saline dose resulted in edema (2 of 5 rabbits), hemorrhage in the dermis (1 of 5 rabbits), and vascular damage (1 of 5 rabbits).

Histopathological analyses of the injection site areas from rabbits dosed *iv* with ERL 080 revealed effects in 3 of 5 rabbits that included focal perivascular edema, focal folliculitis, and focal hemorrhage with vascular damage. Perivascular dosing of ERL 080 resulted in histopathological effects in all 5 rabbits that included acute inflammation, edema, and hemorrhage in the dermis. Ulcerations were also observed in the epidermis from 2 of 5 rabbits. The *iv* injections of physiological saline did not result in histopathological effects. Perivascular injections of physiological saline resulted in focal dermis edema and hemorrhage (3 of 5 rabbits) as well as focal vascular hemorrhage (1of 5 rabbits).

Comments

Intravenous administration of ERL 080 resulted in effects observed clinically, by gross pathology, and by histopathology. These effects were classified as minimal to slight and were not considered problematic. The perivascular dosing was undertaken to represent the worst case scenario for misdosing of an *iv* dose. Multiple compound-related perivascular effects were observed by clinical, gross pathological, and histopathological analyses. Most of the histopathological effects were classified as slight to moderate at the 7-day post-perivascular dosing sacrifice.

3.4.8 Special Toxicology Studies

Exploratory Side Effect Studies on ERL and Mycophenolate Mofetil, with or without Cyclosporine A, in the Rat. Study No. RD 2000-2310.

This was a pilot or preliminary study that was not conducted in accordance with GLP requirements and not audited. The report submitted by the sponsor summarizes the methods and results and is not adequate for a critical or comprehensive review. The sponsor indicated that this study was generated for the purpose of providing preliminary or range-finding information regarding different dosing regimens of mycophenolate, mycophenolate mofetil, and these two compounds in combination dosing with Cyclosporine A.

Lewis rats (males) were used because this rat strain is commonly used in rat transplantation models. Each dosing group consisted of four rats. Daily doses of mycophenolate, mycophenolate mofetil, and Cyclosporine A were administered orally by gavage for 28 consecutive days. The dosing routines for ERL 080 were: 10 mg/kg Day 0 through Day 14 then 20 mg/kg Day 15 through Day 28; 20 mg/kg Day 0 through Day 14 then 30 mg/kg Day 15 through Day 28. These same dosing routines were duplicated with addition of a constant daily dose of 7.5 mg/kg Cyclosporine A (Day 0 through Day 28). The same dose levels and dosing routines were also conducted with mycophenolate mofetil. Limited toxicological evaluations were made of all animals including blood samples at Day 0, 7, 14, and 28 for hematology and limited serum chemistry.

None of the dosing routines resulted in observations of clinical toxicity. ERL 080 at the 20/30 mg/kg dosing routine and this dosing routine plus 7.5 mg/kg Cyclosporine A, resulted in the following hematological effects: depressed RBC count; depressed hemoglobin levels; elevated platelet levels; depressed lymphocytes; and depressed neutrophils. The combined dosing with Cyclosporine did not enhance the hematological effects caused by ERL 080. The effects on platelet, RBC, and hemoglobin levels were also observed at the 10/20 mg/kg ERL 080 dosing routine. The sponsor in the summary also cited histopathological effects in the G.I. tract and thymus due to ERL 080 at all dosing regimens. Cyclosporine A also induced lymphodepletion and atrophy in the thymus. The histopathological results mentioned for ERL 080 were also observed with mycophenolate mofetil.

In a separate phase of the pilot study, rats received daily oral gavage doses of 20 or 40 mg/kg ERL 080. The planned dosing duration was 28 days but the excessive clinical toxicity associated with the 40 mg/kg dose level resulted in termination of the study by Day 8 and 9 (morbidity). Hematology indicated thrombocytosis and leukocytopenia at the 40 mg/kg dose level. Serum ASAT and ALAT levels were depressed while alkaline phosphatase was elevated 3-fold at the 20 mg/kg dose level.

3.5 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

The nonclinical toxicities observed with the mycophenolate sodium drug substance were indentical to nonclinical toxicities associated with mycophenolate mofetil (a currently approved drug substance). Metabolism and pharmacokinetic data from animals and humans demonstrated that mycophenolate sodium and mycophenolate mofetil deliver only mycophenolate to the circulating blood following oral administration. Therefore, the dosing regimen for the Myfortic® drug product as indicated in this submission (720 mg, bid) can be approved from the Pharmacology/Toxicology perspective.

Unresolved toxicology issues:

There are no unresolved toxicology issues related to the proposed indication for Myfortic®.

Recommendations:

The Reviewer recommended that the sponsor conduct a prenatal postnatal developmental toxicity study in pregnant rats as a post-marketing commitment. Although the $p53^{+/-}$ heterozygous mouse 26-week carcinogenicity study was inadequate due to an absence of tumorigenic response from the positive control no additional mouse carcinogenicity study was requested.

Suggested Labelling:

Proposed labelling from the sponsor was reviewed and revised by the Pharmacology/Toxicology Reviewer. The following section reflects the labelling proposed by the Reviewer:

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week oral carcinogenicity study in rats, mycophenolate sodium was not tumorigenic at daily doses up to 9 mg/kg, the highest dose tested. This dose resulted in approximately 0.6 to 1.2 times the systemic exposure (based upon plasma AUC) observed in renal transplant patients at the recommended therapeutic dose of 1.44 g/day. Similar results were observed [

]

The genotoxic potential of mycophenolate sodium was determined in five assays. Mycophenolate sodium was genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in V79 Chinese hamster cells, and the in vivo mouse micronucleus

assay. Mycophenolate sodium was not genotoxic in the bacterial mutation assay (Salmonella typhimurium TA 1535, 97a, 98, 100, & 102) or the chromosomal aberration assay in human lymphocytes. Mycophenolate mofetil generated similar genotoxic activity. The genotoxic activity of MPA is probably due to the depletion of the nucleotide pool required for DNA synthesis as a result of the pharmacodynamic mode of action of MPA (inhibition of nucleotide synthesis).

Mycophenolate sodium had no effect on male rat fertility at daily oral doses as high as 18 mg/kg and exhibited no testicular or spermatogenic effects at daily oral doses of 20 mg/kg for 13 weeks (approximately 2-fold the therapeutic systemic exposure of MPA). No effects on female fertility were seen up to a daily oral dose of 20 mg/kg which was approximately 3-fold higher than the recommended therapeutic dose based upon systemic exposure.

The remainder of the label that includes reproductive toxicity information submitted by the sponsor (as produced below) appeared to be acceptable.

Pregnancy Category C

"In a teratology study performed with mycophenolate sodium in rats, at a dose as low as 1 mg/kg, malformations in the offspring were observed, including anophthalmia, exencephaly, and umbilical hernia. The systemic exposure at this dose represents 0.05 times the clinical exposure at the dose of 1.44 g/day Myfortic. In teratology studies in rabbits, fetal resorptions and malformations occurred from 80 mg/kg/day, in the absence of maternal toxicity (dose levels are equivalent to abourt 0.8 times the recommended clinical dose, corrected for BSA). There are no relevant qualitative or quantitative differences in teratogenic potential of mycophenolate sodium and mycophenolate mofetil. There are no adequate and well-controlled studies in pregnant women. Myfortic should be used in pregnant women only if the potential benefit outweighs the potential risk to the fetus."

Stephen G. Hundley, Ph.D., DABT
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Division of Special Pathogen and Immunologic Drug Poducts
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Concurrence:

Steve Gitterman, M.D.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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Executive CAC
Date of Meeting: 12/2/03

Committee: David Jacobson-Kram, Ph.D., HFD- 024, Chair
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The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA# 50-791
IND# 57,005 (084)
Drug Name Myfortic® (Mycophenolate sodium)
Sponsor Novartis

Background

Myfortic® (mycophenolate sodium) is an immunosuppressant being developed by Novartis for prevention of acute renal transplant failures and is a 505 (b) (2) application. CellCept® (mycophenolate mofetil) is currently marketed by Roche, Inc., and is the morpholinoethyl ester of mycophenolate. The ester is rapidly cleaved to mycophenolate in the epithelium of the G.I. tract and in the liver. Both mycophenolate sodium and mycophenolate mofetil were evaluated by the sponsor for genotoxic activity and found to be positive in the V79 Chinese Hamster micronucleus assay, Mouse Lymphoma L5178Y (tk+/- locus) assay, and the *in vivo* mouse micronucleus assay. Results from these assays prompted the sponsor to conduct rat carcinogenicity studies with both mycophenolate sodium and mycophenolate mofetil. These two studies shared identical study designs and were conducted concurrently. In addition, the sponsor conducted a 26-week carcinogenicity study in $p53^{+/-}$ heterozygous transgenic mice in an effort to address the question of whether lymphoid tumors associated with mycophenolate were the result of genotoxic or immunosuppression mechanisms. The product label for CellCept® contains a boxed warning for the possible development of lymphomas and other neoplasms due to immunosuppression.

Rat Carcinogenicity Study

The 2-year mycophenolate sodium carcinogenicity bioassay was conducted with the Wistar Han rat strain and included two zero-level control groups and four dose levels of mycophenolate sodium (1, 3, 6, and 9 mg/kg/day, administered orally by gavage). The overall study design was adequate for assessing the tumorigenic potential of

mycophenolate sodium although reservations were expressed by the Executive CAC (5/18/99, Minutes), regarding the likelihood that the highest dose level of 9 mg/kg would achieve an MTD.

Survival rates at all dose levels were sufficient for valid statistical analysis of tumor incidence rates (survival percentages ranged from 70 to 88 percent across all mycophenolate sodium dose groups). Statistically significant elevations (by trend analysis) of benign thymomas of the thymus were observed in female rats at the 6 and 9 mg/kg/day dose levels and were the only apparent compound-related neoplastic lesions observed in this study. Statistical significance was not established by pair-wise analysis. The incidence rate for benign thymomas was not statistically significant in male rats by trend analysis. Benign thymomas of the thymus were observed in control female Wistar Han rats at ranges from 2 to 10 percent (Charles River historical controls from 10 studies). The benign thymoma incidence rate for the combined female control groups (#1 and #2) in the current study was 11 percent.

The highest dose level (9 mg/kg) did not achieve an MTD based upon an absence of statistically significant and persistent body weight effects, gross pathology or histopathology. Mild hypochromic microcytic anemia was noted in male and female rats at the 9 mg/kg/day dose level and in female rats at the 6 mg/kg/day dose level. The 9 mg/kg/day dose level, however, was approximately one half of the dose level that resulted in compound-related mortality in a 13-week toxicity study with Wistar Han rats (15 and 35 percent mortality in males and females, respectively). Mycophenolate exhibits a steep mortality vs dose level curve making it difficult to select a high dose level in a chronic study that achieves an MTD without excess mortality.

Mouse Carcinogenicity Study

The Executive CAC (3/23/99, minutes) concurred with the overall study design of the 26-week carcinogenicity study in $p53^{+/-}$ heterozygous mice but did not concur with the selection of the highest dose level (150 mg/kg/day) in the protocol because the 13-week range-finding study was conducted with CD-1 mice rather than the wild type C57BL/6 strain used to generate the $p53^{+/-}$ heterozygous mice. As a result the sponsor altered the dose levels to include 200 mg/kg/day as the highest dose level. The other mycophenolate sodium dose levels were 50, 100, and 150 mg/kg/day. The sponsor selected benzene at 100 mg/kg/day as the positive reference compound (in accordance with the ILSI protocol from June, 1997). The Executive CAC requested that the sponsor confirm that the 100 mg/kg/day dose level was, as of 3/23/99, considered sufficient as the positive control.

Body weight gain reduction was noted at the 200 mg/kg/day dose level of mycophenolate sodium but was not statistically significantly different from controls. An MTD was achieved in both males and females at the 150 and 200 mg/kg/day dose levels based upon mild to moderate anemia, abnormal RBC morphology, and splenic histopathology. There were no compound-related neoplastic lesions at any of the mycophenolate sodium dose

levels. Compound-related neoplastic lesions were not observed in male and female mice dosed with benzene (100 mg/kg/day). Elevated mortality (5 of 15) was noted in male mice and both males and females exhibited splenic histopathology due to benzene. Males also exhibited mild anemia and depressed WBC counts. The $p53^{+/-}$ heterozygous mouse model in this study was not sufficiently sensitive to identify benzene at 100 mg/kg/day as a tumorigen.

Executive CAC Recommendations and Conclusions

Rat Study:

The Executive CAC concluded that the study was adequate for assessing the tumorigenic potential of mycophenolate sodium. An MTD was not established, however, the highest dose level was approximately one half of the dose level that produced mortality in both male and female rats in the 13-week range-finding study.

The Executive CAC concluded that the study results indicated mycophenolate sodium was negative for tumorigenic activity due to an absence of statistical significance in pairwise analysis for benign thymoma of the thymus.

Mouse Study:

The Executive CAC concluded that due to an absence of compound-related tumorigenic findings with the 100 mg/kg/day benzene positive reference compound the study was not adequate for assessing the tumorigenic potential of mycophenolate sodium.

The Executive CAC also suggested that the sponsor, if possible, consider evaluating the bone marrow smears from all dose groups for micronucleus incidence rates.

/s/

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:

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