CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

50-791

Administrative/Correspondence Reviews

Patent Submission

Time Sensitive Patent Information
pursuant to 21 C.F.R. 314.53

for

NDA # *21-580*

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Myfortic™
- Active Ingredient(s): mycophenolate sodium
- Strength(s): 180 mg and 360 mg
- Dosage Form: delayed release tablet
- Approval Date: pending

A. This section should be completed for each individual patent

U.S. Patent Number: 6,025,391

Expiration Date: April 10, 2017

Type of Patent--Indicate all that apply:

1.	Drug substance (Active Ingredient)		N
2.	Drug Product (Composition/Formulation	Y	
3.	Method of Use	Y	

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:.

Prophylaxis of organ rejection in patients receiving allogenic renal transplants.

Name of Patent Owner: Novartis AG

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Novartis Pharmaceuticals Corporation

U.S. Patent Number: 6,172,107 B1

Expiration Date: April 10, 2017

Type of Patent--Indicate all that apply:

1.	Drug substance (Active Ingredient)		N
2.	Drug Product (Composition/Formulation	Y	
3.	Method of Use	Y	

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

Prophylaxis of organ rejection in patients receiving allogenic renal transplants.

Name of Patent Owner: Novartis AG

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Novartis Pharmaceuticals Corporation

U.S. Patent Number: 6,306,900 B1

Expiration Date: April 10, 2017

Type of Patent–Indicate all that apply:

1. Drug substance (Active Ingredient)	____	N
2. Drug Product (Composition/Formulation	Y	____
3. Method of Use	Y	____

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

Prophylaxis of organ rejection in patients receiving allogenic renal transplants.

Name of Patent Owner: Novartis AG

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Novartis Pharmaceuticals Corporation

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 6,025,391 covers the composition, formulation and/or method of use of mycophenolate sodium. This product is:

- ____ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

or

- Y the subject of this application for which approval is being sought.)

The undersigned declares that the above stated United States Patent Number 6,172,107 B1 covers the composition, formulation and/or method of use of mycophenolate sodium. This product is:

- ____ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

or

- Y the subject of this application for which approval is being sought.)

The undersigned declares that the above stated United States Patent Number 6,306,900 B1 covers the composition, formulation and/or method of use of mycophenolate sodium. This product is:

- ____ currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act)

or

- __Y__ the subject of this application for which approval is being sought.)

Signed: Thomas R. Savitsky

Thomas R. Savitsky

Title: Senior Patent Attorney

Date: March 25, 2003

Telephone Number: (862) 778-7909

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the ***The Orange Book,****** a deskcopy should be submitted to:

Mailing address: (US Mail)
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OR

Location address: (for FedX deliveries)
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

*Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the ***The Orange Book***.

Drug Regulatory Affairs

ERL080 (mycophenolate sodium)

Patent Certification

Author(s):	Daniel Gordin
Document type:	
Document status:	Final
Release date:	
Number of pages:	2

Patent Certification

Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category cannot list patents, and thus there are no listed patents for the reference listed drug. Accordingly, no patent certification is required under Section 505(b)(2) of the Act, and none is submitted in this NDA.

EXCLUSIVITY SUMMARY for NDA # 50-791 SUPPL #

Trade Name Myfortic Generic Name mycophenolic acid

Applicant Name Novartis Pharmaceutical Corporation HFD-590

Approval Date February 27, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

No, exclusivity determination is not needed because mycophenolic acid falls under Section 507 (old antibiotics).

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /___/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /___/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /___/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /___/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as

bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /___/ ! NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Rebecca D. Saville
Signature of Preparer Date
Title: Regulatory Project Manager

Renata Albrecht, M.D.
Signature of Office or Division Director Date

cc:
Archival NDA
HFD-590/Division File
HFD-590/RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Renata Albrecht
2/26/04 07:50:45 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 50,791 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: April 30, 2003 Action Date: February 27, 2004

HFD 590 Trade and generic names/dosage form: Myfortic (mycophenolic acid)

Applicant: Novartis Pharmaceuticals Corporation Therapeutic Class: Transplant

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1:
Prophylaxis of organ rejection in patients receiving allogenic renal transplants, administered in combination with cyclosporine, USP (modified) and corticosteroids

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☒ No: Please check all that apply: x Partial Waiver ___ Deferred x Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min 0	kg ___	mo. ___	yr. ___	Tanner Stage ___
Max 10	kg ___	mo. ___	yr. ___	Tanner Stage ___

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease to study
- ☐ There are safety concerns
- ☒ Adult studies ready for approval
- ☒ Formulation needed
- ☒ Other: no meaningful therapeutic benefit

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min 10	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max 16	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

Refer to the CLINICAL PHARMACOLOGY: Pediatric Use and DOSAGE AND ADMINISTRATION sections of the label.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

(See appended electronic signature page)

_____

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

cc:
NDA
HFD-960/ Grace Carmouze
(revised 10-14-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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

/s/

Rebecca Saville
2/23/04 09:22:05 PM
NDA 50,791

NDA No. 21-580

MYFORTIC® (mycophenolate sodium) delayed release tablets
180 mg and 360 mg

New Drug Application

NOVARTIS CERTIFICATION
IN COMPLIANCE WITH THE
GENERIC DRUG ENFORCEMENT ACT OF 1992

NOVARTIS PHARMACEUTICALS CORPORATION certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.

April 11, 2003
Date

M. Daniel Gordin
M. Daniel Gordin, Ph.D.
Director
Drug Regulatory Affairs

9 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

93 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

3/18/04

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 50-791	Efficacy Supplement Type N/A	Supplement Number N/A	
Drug Myfortic® (mycophenolic acid)		Applicant: Novartis Pharmaceutical Corporation	
RPM: Rebecca D. Saville		HFD-590	Phone # 301-827-2127
Application Type: ( ) 505(b)(1) (X) 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 50-722 CellCept Capsules, 250 mg and NDA 50-723 CellCept Tablets, 500 mg	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	Type 2
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	February 29, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted.	(X) Verified **(equivalent)**
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.	**N/A Approved under Section 507 (old antibiotics)** 21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X (February 26, 2004) N/A Approved under Section 507 (old antibiotics)
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X (February 4, 2004)
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes, via approvals email ( ) N/A
• Indicate what types (if any) of information dissemination are anticipated	**(X)** None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	N/A
• Most recent applicant-proposed labeling	X (February 27, 2004)
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X ODS (December 17, 2003) DDMAC (January 28, 2004)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	X
• Reviews	see Labeling
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	X (February 25, 2004)
• Documentation of discussions and/or agreements relating to post-marketing commitments	X (February 25, 2004)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	X (November 9, 1998)
• Pre-NDA meeting (indicate date)	X (December 14, 2001)
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	N/A

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	X (February 27, 2004)
❖ Clinical review(s) *(indicate date for each review)*	X (March 18, 2004)
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	X (February 26, 2004)
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X (February 23, 2004)
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	X (February 24, 2004)
❖ Biopharmaceutical review(s) *(indicate date for each review)*	X (February 27, 2004)
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
❖ CMC review(s) *(indicate date for each review)*	X (February 26, 2004)
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	X (February 26, 2004)
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: October 2, 2003 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	X (February 27, 2004)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	X (January 27, 2003)
❖ CAC/ECAC report	X (December 2, 2003)

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

/s/

Rebecca Saville
3/18/04 05:30:46 PM
NDA 50-791

MEMORANDUM OF TELECON

DATE: January 26, 2004

APPLICATION NUMBER:

NDA 50-791,
Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

BETWEEN: Novartis

Daniel Gordin, Ph.D., Director, Drug Regulatory Affairs

AND

Division of Special Pathogen and Immunologic Drug Products

Rebecca D. Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Myfortic (mycophenolic acid) NDA 50-791 Container Label

DISCUSSION:

The Division initiated a teleconference with Novartis to correspond CMC comments regarding the container labeling which was received by the Division on February 26, 2004.

The Division recommended that a type of statement such as "Myfortic is formulated as mycophenolate sodium" on the label, possibly as a footnote, to identify the active ingredient in the formulation.

The Division suggested that the net quantity to relocated so that it does not appear in close proximity to the strength. This will avoid any confusion of the strength with the number of units in the container.

The Division indicated that Novartis could agree to change prior to submitting the FPL, and the approval letter would indicate that the label was approved "with minor revisions" or Novartis could resubmit prior to or on February 27, 2004. Novartis agreed to consider and attempt to resubmit.

/S/

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
2/26/04 06:18:26 PM
CSO
NDA 50-791

MEMORANDUM OF TELECON

DATE: February 27, 2004

APPLICATION NUMBER:

NDA 50-791
Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

BETWEEN:

Novartis
Daniel Gordin, Ph.D., Director, Drug Regulatory Affairs

AND

Division of Special Pathogen and Immunologic Drug Products
Rebecca D. Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Myfortic Labeling NDA 50-791

The Division initiated this teleconference to indicate to Novartis that 2 minor revisions needed to be corrected in the labeling submitted on February 25, 2004. The Division requested that the following statement should be included in the Geriatric Use section according to CFR 201.57:

"Clinical studies of Myfortic did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy."

The Division indicated that "USP-MODIFIED" would need to be removed from the following sections of the label in order to provide for the use of generics and I.V. formulations of cyclosporine:

- INDICATIONS AND USAGE section.
- WARNINGS section.
- Drug Interactions: "Cyclosporine: When studied in stable renal patients...." section.

Novartis agreed to add the statement to the Geriatric Use section and to remove the "USP-MODIFIED" nomenclature from the indicated sections. Novartis will resubmit the revised labeling on February 27, 2004.

/S/

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
3/4/04 04:29:23 PM
CSO
NDA 50-791

M. Daniel Gordin, PhD
Director
Drug Regulatory Affairs
Transplantation &
Immunology

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel: 862-778-4784
Fax: 973-781-8364
Internet: daniel.gordin@pharma.novartis.com

NOVARTIS

February 25, 2004

Renata Albrecht, MD, Director
Division of Special Pathogen and
Immunologic Drug Products (HFD-590)
Office of Drug Evaluation IV
Document Control Room
9201 Corporate Blvd.
Rockville, MD 20854

NDA 50-791

MYFORTIC® (ERL080)
(mycophenolic acid) delayed-release tablets
180 mg and 360 mg

POST-MARKETING COMMITMENT: CORRECTION

Dear Dr. Albrecht,

The NDA for Myfortic delayed-release tablet was submitted to the FDA on April 30, 2003 for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine, USP (MODIFIED) and corticosteroids.

In a teleconference between Novartis and the FDA on Wednesday, February 25, 2004, Novartis agreed to conduct as a post-marketing commitment a prenatal-postnatal developmental toxicity study using mycophenolate sodium in pregnant female rats. Novartis plans to submit the study protocol for FDA review in May 2004; start the study in September 2004; and submit the final study report to the Agency in September 2005.

Lastly, Novartis acknowledges receipt of the FDA's CMC recommendation received via fax from the Agency (Fax date: February 23, 2004). Novartis commits to remove Microbial Testing from the Drug Substance Release Testing Monograph and Identity of Colorant, Residual Solvent and Microbial Testing from the Drug Product Release Testing Monographs. These tests will be re-submitted to the FDA in separate documents (one for drug substance and one for drug product) as Periodic Quality Indicator Tests. These changes may be made in the first Annual Experience Report or at a time specified by the FDA.

If there are any questions related to this application, please contact me at 862-778-4784 or in my absence, Inna Kissen, Ph.D. at 862-778-4782.

Sincerely,

M. Daniel Gordin, Ph.D.
Director, Drug Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	February 25, 2004
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
862-778-4784	973-781-8364
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
One Health Plaza East Hanover, NJ 07936-1080	M. Daniel Gordin, Ph.D.

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* NDA 50-791

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
mycophenolic acid delayed-release	Myfortic

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
(E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt

CODE NAME *(If any)*
ERL080

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Tablet	180 mg and 360 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
For the prophylaxis of organ rejection in patients receiving allogenic renal transplants

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☒ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 **THIS APPLICATION IS** ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related Licensee Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)
57,005
IFs

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
M. Daniel Gordin	M. Daniel Gordin, Ph.D.	February 25, 2004

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
One Health Plaza, East Hanover, NJ 07936-1080	(862) 778-4784

MEMORANDUM OF TELECON

DATE: February 25, 2004

APPLICATION NUMBER:

NDA 50-791, Myfortic® (mycophenolic acid) 180 mg and 360 mg Tablets

BETWEEN:

Novartis Pharmaceuticals

Daniel Gordin, Ph.D., Director, Regulatory Affairs
Peter Heining, Ph.D., Preclinical Safety Project Team Representative
Lutz Mueller, Ph.D., Section Head Investigational, PCS EU
Hans van Bronswijk, Ph.D., Global Head DRA, TX BU
Kenneth Somberg, M.D., Global Head of Clinical Research, Transplantation & Immunology

AND

FDA – Division of Special Pathogen and Immunologic Drug Products

Stephen G. Hundley, Ph.D., DABT, Pharmacology/Toxicology Team Leader
Sary Beidas, M.D., Medical Officer
Rebecca D. Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Pharmacology/Toxicology Postmarketing Commitment

BACKGROUND:

During the initial evaluation of the reproductive toxicology data package included with IND 57,005, submitted on October 2, 1998, the references were judged by the Pharmacology/ Toxicology reviewer to be adequate to comply with the requirements for Segment I, II, and III reproductive and developmental toxicity studies. This was communicated to Novartis on October 28, 1998 during a meeting discussion regarding their planned nonclinical reproductive toxicology program.

Subsequently, during the review of NDA 50-791, the Pharmacology/Toxicology Reviewer discovered that one of the cited references (NDA —— Medical Officer Review) could not be used as a reference source because NDA 50-791 was submitted as a 505(b)(2) application. This source contained the only reference to a Segment III developmental toxicity study.

Since this study reference cannot be used by the applicant, Novartis will need to conduct a Segment III developmental toxicity study in pregnant rats. A teleconference was coordinated to communicate the request for this study to be conducted as a postmarketing commitment.

DISCUSSION:

Following introductions, the Division requested that Novartis conduct a Segment III prenatal and postnatal developmental toxicity study using mycophenolate sodium in pregnant female rats as a postmarketing commitment. The Division explained that as a 505(b)(2) submission, NDA 50-791 does not contain a reference that can be used to address the requirements for a Segment III developmental toxicity study.

Novartis asked for justification. The Division explained that based on our understanding of 505(b)(2) applications in 1998, the reference from NDA —— would have been adequate. However, given our expanded understanding of 505(b)(2) applications, the reference is inadequate since NDA —— was not approved. The Division recommended that the postmarketing study requested would be the most appropriate course of action. Novartis agreed.

ACTION ITEMS:

Novartis will submit a correspondence stating their postmarketing commitment and timeline to conduct a prenatal/postnatal developmental toxicity study using mycophenolic acid in pregnant female rats.

Minutes Preparer: Rebecca D. Saville, Pharm.D., Project Manager
Concur: Stephen G. Hundley, Ph.D., DABT, Pharmacology/Toxicology Team Leader

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/s/

Rebecca Saville
2/26/04 01:03:04 PM
CSO
NDA 50-791

Steve Hundley
2/26/04 01:30:37 PM
PHARMACOLOGIST

MEMORANDUM OF TELECON

DATE: February 24, 2004

APPLICATION NUMBER:

NDA 50-791
Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

BETWEEN:

Novartis

Daniel Gordin, Ph.D., Director, Drug Regulatory Affairs

AND

Division of Special Pathogen and Immunologic Drug Products

Rebecca D. Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Minor Label Corrections NDA 50,791 Myfortic

Novartis contacted the Division regarding two items pertaining to the draft labeling that was forwarded to Novartis from the Division on February 23, 2004.

The first item was a minor editorial correction to the footnote "***" of Table 2. The word "prior" was added to the footnote so that it read "...without prior graft loss or death..." to be consistent with the similar footnote in Table 3. The Division agreed.

The second item was a revision in the WARNINGS section of the labeling. The paragraph that reads [redacted] based on a revision by the Division to replace [redacted]. Novartis asked for rationale, and the Division explained that the established name should be used to be consistent with the rest of the label. The Division Director was consulted and proposed a compromise. Novartis and the Division agreed to have the sentence read "There are no adequate and well-controlled studies in pregnant women conducted MPA, Myfortic, or mycophenolate mofetil."

/S/

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
2/26/04 04:41:33 PM
CSO
NDA 50-791

MEMORANDUM OF TELECON

DATE: February 23, 2004

APPLICATION NUMBER: NDA 50-791, Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

BETWEEN:

Novartis:

Daniel Gordin, Ph.D., Director, Drug Regulatory Affairs

AND

Division of Special Pathogen and Immunologic Drug Products:

Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader
Rebecca D. Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Labeling for Myfortic NDA 50-791

BACKGROUND:

This teleconference was initiated by the Division to indicate that the Division had forwarded revised labeling for Myfortic incorporating the Division's proposals and to request an update of their foreign marketing history.

DISCUSSION:

Following introductions, the Division indicated to Novartis that draft labeling for Myfortic had been forwarded to them. The labeling included the Division's recommendations for the revision of the Pediatric Use section in DOSAGE AND ADMINISTRATION as well as several minor editorial and grammatical corrections in the label (see correspondence from February 23, 2004).

The Division inquired whether Novartis had any plans for possible post-marketing studies. Novartis replied that they did not.

The Division requested Novartis submit an update of their foreign marketing history. Novartis indicated that they had received additional approval in Europe through a mutual recognition procedure in the European Union and agreed to send an update as a correspondence that included the approved labeling.

ACTION ITEMS:

1. Novartis will review the Division's proposed revisions to the labeling for Myfortic and submit a final draft of the labeling to the Division for their review.

2. Novartis will send an update of their foreign marketing history.

Minutes Preparer: Rebecca D. Saville, Pharm.D., Project Manager
Concur: Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader

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/s/

Rebecca Saville
2/26/04 01:58:26 PM
CSO
NDA 50-791

Marc Cavaille Coll
2/26/04 02:38:33 PM
MEDICAL OFFICER
NDA 50-791

MEMORANDUM OF TELECON

DATE: February 20, 2004

APPLICATION NUMBER: NDA 50,791
Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

BETWEEN:

Novartis Pharmaceuticals
Daniel Gordin, Director, Drug Regulatory Affairs

AND

FDA - Division of Special Pathogen and Immunologic Drug Products
Stephen Hundley, Pharmacology/Toxicology Team Leader
Rebecca Saville, Regulatory Project Manager

SUBJECT: Pharmacology/Toxicology Labeling Revisions

BACKGROUND:

The Division recommended that the Myfortic label be revised to include reference to the mouse carcinogenicity study listed in the CellCept® (mycophenolate mofetil) label in the "Carcinogenesis, Mutagenesis, Impairment of Fertility" section via a correspondence on February 20, 2004. The statement in bold was added, and the section is revised as follows:

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 0.6-1.2 times the systemic exposure (based upon plasma AUC) observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. **In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil was not tumorigenic at a daily dose level as high as 180 mg/kg (which corresponds to 0.6-times the proposed mycophenolate sodium therapeutic dose based upon body surface area).**

The applicant requested clarification, and this teleconference provided discussion between the applicant and the review team.

DISCUSSION:

Following introductions, the Division explained that the applicant had to eliminate reference to the 26-week oral carcinogenicity study in $p53^{+/-}$ heterozygous transgenic mice due to the failure

of the positive control (benzene) to produce a tumorigenic response. Not allowing a reference in the label to this type of study with a failed positive control is an ongoing policy established by the Executive Carcinogenicity Assessment Committee.

Subsequently, for labeling purposes, the applicant was provided with labeling language for the two-year mouse carcinogenicity study with mycophenolate mofetil (as modified from the CellCept label) to be included in the Myfortic® label. As a 505 (b) (2) submission the applicant can include language from the CellCept label to assist in meeting labeling requirements. The labeling requirement in this instance was to provide carcinogenicity testing information from studies with rats and mice in the Carcinogenesis section of the label.

ACTION ITEMS:

The applicant understood and agreed to incorporate the additional information in the label.

/S/

Preparer: Rebecca Saville, Pharm.D., Regulatory Project Manager
Concur: Stephen Hundley, Ph.D., DABT, Pharmacology/Toxicology Team Leader

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/s/

Rebecca Saville
2/20/04 05:14:53 PM
CSO
NDA 50,791

MEMORANDUM OF TELECON

DATE: February 19, 2004

APPLICATION NUMBER:

NDA 50-791
Myfortic (mycophenolic acid), 180 mg and 360 mg Tablets

BETWEEN:

Novartis Pharmaceuticals, Inc.
Hans van Bronswijk, M.D., Global Head, Drug Regulatory Affairs, Transplantation and Immunology
Anne-Claire Marrast, M.D., Clinical Project Leader, Transplantation and Immunology
Robert Schmouder, M.D., Clinical Pharmacology, Transplantation and Immunology
Daniel Gordin, Ph.D., Drug Regulatory Affairs, Transplantation and Immunology
Gilles Feutren, M.D., Global Head of Development, Transplantation and Immunology
Kenneth Somberg, M.D., Global Head of Clinical Research, Transplantation and Immunology
Jeff Maca, Ph.D., Project Biostatistician

AND

FDA - Division of Special Pathogen and Immunologic Drug Products
Renata Albrecht, M.D., Division Director
Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader
Sary Beidas, M.D., Medical Reviewer
Stephen G. Hundley, Ph.D., DABT, Pharmacology/Toxicology Team Leader
Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics, Team Leader, DPEIII
Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Shukal Bala, Ph.D., Microbiology Team Leader
Avery Goodwin, Ph.D., Microbiology Reviewer
Ramesh Sood, Ph.D., Chemistry Reviewer
Karen Higgins, Sc.D., Biometrics Team Leader, DB-III
Rebecca Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Labeling Discussion

BACKGROUND:

The Division reviewed Myfortic labeling that was initially submitted on April 30, 2003 and had been updated in a 120-day IND (57,005) Safety Report submitted on August 28, 2003. The Division forwarded a proposed label incorporating recommendations and revisions to Novartis on February 5, 2004. Preliminary discussions were conducted during a teleconference with

Novartis on February 6, 2004. Novartis submitted a revised label (which included non-reviewed pediatric dosing recommendations) and a table of counterproposals on February 13, 2004. Following an internal discussion on February 17, 2004, the Division modified the table to add rationale, recommendations, and revised pediatric labeling. The table and the most current draft of the label were forwarded to Novartis on February 18, 2004.

DISCUSSION:

Following introductions, the Division indicated that pediatric studies in children less than 10 years old would be waived based on several reasons. These reasons include too few children receiving a renal allograft in this age group to study, an appropriate formulation is not available, and Myfortic does not have any meaningful therapeutic benefits over currently available products in the class. Pharmacokinetics studies with the 10 – 16 year old age group have been conducted and appropriate recommendations will be incorporated in the labeling. The safety and efficacy in stable renal transplantation recipients in this age group can be extrapolated from the clinical study results in adults. Therefore, pediatric studies in this age group are considered complete. Novartis was encouraged to develop a lower strength formulation of Myfortic, [redacted] but the Division would not require any further pediatric development.

Novartis prepared a table of 24 items as topics of discussion (see attachment). The table was submitted to the Division on February 13, 2004, and the Division revised the table to incorporate rationale, recommendations, and revised labeling. The table was forwarded to Novartis on February 18, 2004. Dialogue continued following the order of items presented in the table (see Attachment) and the following agreements were determined:

1. The established name for Myfortic is mycophenolic acid.

2. The established name for Myfortic is mycophenolic acid.

3. Text referring to studies in humans will be retained in the label.

4. The Division agreed that the cutoff for adverse event reporting in Table 5 would be ≤20%.

5. Novartis accepted the proposed labeling.

6. Novartis accepted the proposed additions.

7. Novartis questioned the ease of use for the patient if Myfortic had to be taken on an empty stomach. The Division stated that dosing with respect to meals needs to be stated clearly in the label, as well as reflect what was done in the clinical trials so that health care professionals (e.g., nurses, pharmacists, etc.) can clearly convey these directions to the patient. The Division requested that "one hour prior to or two hours after meal" be added to the end of the sentence reading "It is recommended that Myfortic be administered on an empty stomach" and a cross reference to the DOSAGE AND

ADMINISTRATION section be added in the INFORMATION FOR PATIENT section. Novartis agreed.

8. Novartis requested clarification regarding the change in recommended dose of Myfortic in pediatric patients to 400 mg/m^2. The Division explained that based on the pediatric (Study 0106) and adult (Study 0102) PK studies, the mean AUC in pediatric patients was greater by approximately 20% than that of adults. The pediatric patients received a nominal dose of 450 mg/m^2 BSA, whereas the adult patients received 720 mg / patient (assumed to be 416 mg/ m^2 BSA for patients with BSA of 1.73 m^2). Therefore, the pediatric dose was a little bit higher than the adult dose. Even adjusting the higher dose, the mean AUC in children was 16% and still larger compared to that in adult patients. If a nominal dose of 400 mg/m^2 BSA is administered, the AUC would be similar between adults and children. In the absence of safety and efficacy data for Myfortic in children, this would be one of the feasible dosing methods for pediatric patients. However, since only two tablet strengths are available in Myfortic. The actual pediatric dose would be 360 mg, 540 mg, or 720 mg that is rounded up or down from the nominal dose calculated based on BSA. For younger children whose BSA from 0.90 m^2 to 1.35 m^2, the rounding would be up to 20%, whereas the rounding would be up to 14% for older children who have a BSA from 1.35 m^2 to 1.80 m^2. Therefore, the lower cut-off of BSA for Myfortic dosing was determined to be 1.19 m^2 so as to not exceed the rounding of more than 14%.

   Novartis agreed to add "in stable patients" to the pediatric dosing text and to consider possible recommendations for *de novo* pediatric patients.

9. Novartis requested clarification. The Division responded that (1) the mean AUC/Dose at 180-mg dose was greater by 17% (mean ratio, 1.17; 90% CI, 1.01 – 1.37) than that at 360-mg dose and (2) the r^2 values were determined with ignoring relative data variation/deviation at each concentration point. Novartis agreed.

10. Novartis accepted the proposed addition.

11. Novartis accepted the proposed revisions.

12. The Division accepted the proposed revision.

13. Novartis accepted the proposed revisions and additions.

14. The Division accepted the proposed revision.

15. Novartis accepted the proposed rationale.

16. Novartis accepted the proposed addition.

17. The Division accepted the proposed revision.

18. The Division accepted the proposed addition.

19. The Division accepted the proposed addition.

20. The established name for Myfortic is mycophenolic acid.

21. The established name for Myfortic is mycophenolic acid.

22. The established name for Myfortic is mycophenolic acid.

23. The Division accepted the proposed revision.

24. The Division accepted the proposed revision.

ACTION ITEMS:

1. Novartis will revise the label to reflect the agreements.

2. Novartis will submit the revised label incorporating dosing recommendations for *de novo* pediatric patients for review by the Division.

ATTACHMENTS

Label with Revisions, version February 18, 2004
Table of Counterproposals

Minutes Preparer: Rebecca D. Saville, Pharm.D., Project Manager
Concur: Renata Albrecht, M.D., Division Director

25 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Rebecca Saville
2/26/04 01:56:04 PM
CSO
NDA 50-791

Marc Cavaille Coll
2/26/04 02:34:49 PM
MEDICAL OFFICER
NDA 50-791

Teleconference Minutes

Teleconference Date: February 12, 2004

Application Numbers: NDA 50-791: Myfortic (mycophenolate sodium)

Sponsor: Novartis

Attendees:

Novartis Daniel Gordin, Ph.D.; Director, Drug Regulatory Affairs

FDA- Division of Special Pathogen and Immunologic Drug Products

Marc Cavaille-Coll, MD, Ph.D.; Medical Officer Team Leader
Norman Schmuff, Ph.D.; Chemistry Team Leader
Kristen Miller, Pharm.D.; Regulatory Project Manager

Background

Novartis proposed mycophenolic sodium as the established name for Myfortic in their application, NDA 50-791 submitted April 30, 2003. The revised label, which was sent to Novartis on February 5, 2004, recommended that mycophenolic acid should be the established name. Novartis requested clarification from the Division as to why the established name was mycophenolic acid, so a teleconference was coordinated to facilitate discussion.

Discussion

Following introductions, the Review Team explained that this call was to discuss the issue of the established name for Myfortic. Although Novartis had obtained a USAN of "mycophenolate sodium" for their drug substance, the most recent version of the Myfortic label, sent by the Division on February 5, 2004, indicated that the established name should be "mycophenolic acid." It was explained that this decision was based on an interpretation of the longstanding statement in the USP General Notices section entitled "Amount of Ingredient per Dosage Unit" which states that the strength should be based on whatever form is used in the title of the monograph.

Further clarification of this policy, it was pointed out, can be found in USP monograph revisions found in the Pharmacopeial Forum v 28(3) 2002 p74 for Aldronic Acid Tablets, and v 29(1) 2003 p64 for Doxazocin Tablets. The Review Team offered to send these references to Novartis, and they indicated that they would like to have them.

Dr. Gordin indicated that he was not, at that time, in a position to respond to FDA's proposal.

It was noted by the Review Team that use of the proposed established name may necessitate some other labeling changes, though it may not be necessary to change each mention of mycophenolate sodium to the mycophenolic acid. Additionally, these changes need not be made

prior to sending the labeling that was planned to be submitted this afternoon. Novartis agreed to this, and to refer to this teleconference in the cover letter.

Action Items

1. The Review Team will send the references (USP monograph revisions found in the Pharmacopeial Forum) to Novartis.
2. Novartis will submit revised labeling reflecting this discussion.

Minutes Preparer: Kristen Miller, PharmD; Project Manager
Concur: Norman Schmuff, Ph.D.; Chemistry Team Leader

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/s/

Rebecca Saville
2/26/04 02:05:28 PM
CSO
NDA 50-791

Kristen Miller
2/26/04 02:43:00 PM
CSO

Norman Schmuff
2/26/04 02:59:04 PM
CHEMIST

MEMORANDUM OF TELECON

DATE: February 6, 2004

APPLICATION NUMBER:

NDA 50-791
Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

BETWEEN:

Novartis Pharmaceuticals, Inc.
Robert Schmouder, M.D., Clinical Pharmacology, Transplantation and Immunology
Daniel Gordin, Ph.D., Drug Regulatory Affairs, Transplantation and Immunology

AND

FDA - Division of Special Pathogen and Immunologic Drug Products
Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader
Sary Beidas, M.D., Medical Reviewer
Stephen G. Hundley, Ph.D., DABT, Pharmacology/Toxicology Team Leader
Philip M. Colangelo, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics, Team Leader, DPE-III
Jang-Ik Lee, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Shukal Bala, Ph.D., Microbiology Team Leader
Avery Goodwin, Ph.D., Microbiology Reviewer
Rebecca Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Preliminary Labeling Discussion

BACKGROUND:

The Division reviewed the Myfortic labeling and forwarded recommendations to Novartis on February 5, 2004. Novartis requested several points of clarification from the Division, so a teleconference proceeded to facilitate preliminary discussion of the Division's labeling proposal. Since the label did not include dosing information for children, the Division needed to ask Novartis to incorporate recommendations for pediatric dosing.

DISCUSSION:

Following introductions, the Division asked Novartis to provide pediatric dosing recommendations based on age and weight groups based on the extrapolation of pharmacokinetic studies in adults, which would be included in the DOSAGE AND ADMINISTRATION section of the label. Novartis agreed.

The Division indicated that advice from OCTAP was being sought regarding whether additional pediatric studies would need to be deferred or waived. Upon clarification, the Division would address the issue with Novartis.

Novartis questioned the Division's rationale for the change in the established name for Myfortic. Although Novartis had obtained a USAN of "mycophenolate sodium" for their drug substance, the most recent version of the Myfortic label indicated that the established name should be "mycophenolic acid." The Division deferred comment and agreed to coordinate a teleconference for Chemistry to provide justification for the name change.

As a 505(b)(2) application, Novartis recognized the Division's adherence to incorporating reference text of the label for the reference listed drug, CellCept. Novartis posed the following four issues that they wanted to discuss:

1. A paragraph regarding the adverse effects on fetal development and the recommendation that Myfortic should not be administered to pregnant women (initiating on line 249 of the draft label) was removed from the WARNINGS section of the label. The Division indicated that the paragraph (1) discussed animal studies and should not be addressed in the WARNINGS section, (2) animal studies using Myfortic are consistent with Pregnancy Category C classification, and (3) the information is redundant since the animal studies are discussed in the Pregnancy Category C section of the label. Novartis will consider.

2. Regarding Table 5, Novartis requested clarification as to why the cutoff for adverse event reporting was adjusted to $\leq$ 10% for Myfortic although the CellCept label indicated the cutoff was $\leq$20%. The Division replied that CellCept had a lot more adverse events due to three indications, inclusion of azathioprine in the regimen, and extensive post-marketing reports and literature. The use of the 10% cutoff would provide a more rational representation of the reported adverse events. Novartis will consider.

3. Regarding Food Effect, Novartis inquired why the Division added the recommendation to administer Myfortic on an empty stomach one hour prior to or two hours after food intake. The Division responded that the data demonstrate a decreased rate of absorption of Myfortic during fast and fed studies and the dosing recommendations were derived from the how the clinical trials for Myfortic were conducted. Novartis will consider.

4. Novartis would like to replace "ingredient" with "moiety" in the first sentence of the DESCRIPTION section, which reads "Myfortic (mycophenolic acid) delayed-release tablet is an enteric formulation of mycophenolate sodium that delivers the active ingredient mycophenolic acid." The Division deferred comment until Chemistry could address.

ACTION ITEMS:

1. Novartis will provide labeling recommendations to address pediatric dosing.

2. The Division will coordinate a teleconference for Chemistry to discuss the adjustment of the established name for Myfortic.
3. Novartis will submit a correspondence regarding their points of clarification as topics for the labeling discussion teleconference scheduled for February 19, 2004.

Minutes Preparer: Rebecca D. Saville, Pharm.D., Project Manager
Concur: Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader

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/s/

Rebecca Saville
2/26/04 12:07:56 PM
CSO
NDA 50,791

Marc Cavaille Coll
2/26/04 01:35:45 PM
MEDICAL OFFICER
NDA 50,791

MEMORANDUM OF TELECON

DATE: February 5, 2004

APPLICATION NUMBER: NDA 50-791
Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

BETWEEN:

Novartis: Daniel Gordin, Director, Drug Regulatory Affairs

AND

FDA - Division of Special Pathogen and Immunologic Drug Products:

Marc Cavaille-Coll, Medical Team Leader
Rebecca Saville, Regulatory Project Manager

SUBJECT: FDA's Proposed Labeling for Myfortic

BACKGROUND:

The Division completed their review of the labeling for Myfortic and forwarded a proposed label to Novartis on February 5, 2004. A teleconference to discuss the label is scheduled to occur on February 6, 2004. The Division wanted to discuss with Novartis the opportunity for them to either reschedule the teleconference or to proceed with the labeling discussion.

DISCUSSION:

Following introductions, the Division indicated that the purpose of this call was to discuss whether Novartis would like to reschedule the teleconference scheduled for February 6, 2004 since they may not have had adequate time to review the proposed label. Novartis responded that they would prefer to have the teleconference and would utilize the opportunity to ask for clarification on the Division's proposals and to initiate preliminary labeling discussions. The Division agreed to conduct the teleconference.

The Division also suggested that the teleconference would provide the opportunity to address the pediatric development of Myfortic based upon the requirements of PREA. The Division indicated that post-marketing studies may be needed since the enteric-coated tablets are not crushable and there is not an appropriate formulation for children or any dosing recommendations in the label for pediatric patients. The Division indicated the need to seek clarification on the requirements of PREA from OCTAP.

The Division indicated to Novartis that the review team was moving towards an approval pending labeling agreements.

ACTION ITEMS:

1. The teleconference on February 6, 2004 will proceed as scheduled.
2. The Division will seek guidance regarding how the Division can comply with PREA.

/S/

Preparer: Rebecca D. Saville, Pharm.D., Regulatory Project Manager
Concur: Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader

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/s/

Rebecca Saville
2/24/04 09:23:29 PM
CSO
NDA 50,791

Marc Cavaille Coll
2/26/04 01:34:04 PM
MEDICAL OFFICER
NDA 50.791

2/4/04

NDA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

NDA # 50-791 Supplement # N/A SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: Myfortic®
Generic Name: mycophenolate sodium
Strengths: Tablets, 180 mg and 360 mg

Applicant: Novartis Pharmaceuticals Corporation

Date of Application: April 30, 2003
Date of Receipt: April 30, 2003
Date clock started after UN: N/A
Date of Filing Meeting: June 12, 2003
Filing Date: June 29, 2003
Action Goal Date (optional): February 27, 2003 User Fee Goal Date: February 27, 2003

Indication(s) requested:
Prophylaxis of organ rejection in patients receiving allogenic renal transplants, administered in combination with cyclosporine, USP (modified) and corticosteroids.

Type of Original NDA: (b)(1) _____ (b)(2) ___X___
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ___X___ P _____
Resubmission after withdrawal? ___No___ Resubmission after refuse to file? _____
Chemical Classification: (1,2,3 etc.) ___2___
Other (orphan, OTC, etc.) ___No___

User Fee Status: Paid ___X___ Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES NO
User Fee ID # ___4527___
Clinical data? YES ___X___ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

YES NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? YES NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES [NO]
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? [N/A] YES NO

- Does the submission contain an accurate comprehensive index? [YES] NO
- Was form 356h included with an authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? [YES] NO
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A [YES] NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If in Common Technical Document format, does it follow the guidance? [N/A] YES NO

- Is it an electronic NDA N/A [YES] NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- Patent information submitted? [YES] NO

- Exclusivity requested? YES, _____years [NO]
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? [YES] NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? [YES] NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? [YES] NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? [YES] NO

- List referenced IND numbers: 57,005

- End-of-Phase 2 Meeting(s)? [YES] Date(s) November 9, 1998
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? [YES] Date(s) December 14, 2001
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? [YES] NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? [YES] NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? [N/A] YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? [N/A] YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? [N/A] YES NO

- Has DOTCDP been notified of the OTC switch application? [N/A] YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? [N/A]

Chemistry

- Did applicant request categorical exclusion for environmental assessment? [YES] NO
  If no, did applicant submit a complete environmental assessment? YES [NO]
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES [NO]

- Establishment Evaluation Request (EER) submitted to DMPQ? [YES] NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? [N/A] YES NO

If 505(b)(2) application, complete the following section:

- Name of listed drug(s) and NDA/ANDA #:

  NDA 50-722 CellCept (mycophenolate mofetil) Capsules, 250 mg
  NDA 50-723 CellCept (mycophenolate mofetil) Tablets, 500 mg
  NDA 50-758 CellCept (mycophenolate mofetil) Injection, 500 mg/vial
  NDA 50-759 CellCept (mycophenolate mofetil) Oral Suspension, 200 mg/ml

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

  NDA 50-791 contains a different salt of the active moiety, mycophenolic acid (MPA). Myfortic contains the sodium salt of MPA where as the RLD, CellCept, conatins the mofetil ester of MPA. Myfortic is an enteric coated tablet formulated to deliver a delayed-release of MPA.

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  N/A Formerly approved under Section 507 (old antibiotics).

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES [NO]

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    [N/A] YES NO

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A [YES] NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    [N/A] YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    [N/A] YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    [N/A] YES NO

  - EITHER

    The number of the applicant's IND under which the studies essential to approval were conducted.

    IND # 57,005 NO

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    [N/A] YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  [YES] NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 12, 2003

BACKGROUND: NDA 50-791 (Myfortic) is a 505(b)(2) original NDA submission seeking an indication for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine, USP (MODIFIED) and corticosteroids. This application was originally was assigned a NDA # [redacted]). The active moiety was previously approved under Section 507. Thus, Myfortic is considered an old antibiotic and subsequently, its NDA # was changed to 50-791.

The purpose of this meeting is to determine if all the required and necessary information for this application has been submitted for filing.

ATTENDEES: Renata Albrecht, Marc Cavaille-Coll, Leonard Sacks, Sary Beidas, Karen Higgins, Zyoti Zalkiar, Philip Colangelo, Jang-Ik Lee, Kenneth Hastings, Steve Hundley, Norman Schmuff, Shukal Bala, Avery Goodwin, Dave Roeder, Yon Yu

ASSIGNED REVIEWERS:

Discipline	**Reviewer**
Medical:	Sary Beidas, M.D.
Secondary Medical:	Marc Cavaille-Coll, M.D., Ph.D.
Statistical:	Jyoti Zalkiar
	Kyung Lee
	Karen Higgins, Sc.D.
Pharmacology:	Stephen Hundley, Ph.D., DABT
Statistical Pharmacology:	N/A
Chemistry:	Ramesh Sood, Ph.D.
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Jang-Ik Lee, Pharm.D., Ph.D.
Microbiology, sterility:	Avery Goodwin, Ph.D.
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
Regulatory Project Management:	Yon Yu, Pharm.D.
	Rebecca Saville, Pharm.D.
Other Consults:	Iris Masucci, DDMAC
	Carol A. Holquist, R.Ph., ODA

Per reviewers, are all parts in English or English translation? [YES] NO
If no, explain:

CLINICAL FILE ___x___ REFUSE TO FILE _____

- Clinical site inspection needed: YES [NO]
- Advisory Committee Meeting needed? YES, date if known _____ [NO]

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

			N/A	YES	NO
CLINICAL MICROBIOLOGY	NA _____	FILE __x__		REFUSE TO FILE _____	
STATISTICS		FILE __x__		REFUSE TO FILE _____	
BIOPHARMACEUTICS		FILE __x__		REFUSE TO FILE _____	
• Biopharm. inspection needed:				YES	[NO]
PHARMACOLOGY	NA _____	FILE __x__		REFUSE TO FILE _____	
• GLP inspection needed:				YES	[NO]
CHEMISTRY		FILE __x__		REFUSE TO FILE _____	
• Establishment(s) ready for inspection?				[YES]	NO
• Microbiology			[N/A]	YES	NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

__x__ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

__x__ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

ATTACHMENT

POST-MEETING NOTES:

Novartis listed a review completed by a FDA Medical Officer of NDA [ ] as one of its references. This NDA was withdrawn prior to its action date. The questions raised concerning the sponsor's reference to the Division's review of [ ] were (1) whether the review can be referenced (i.e. if the review is not in the public domain) and (2) whether the review is being referenced as the sole source of required/necessary information for Myfotic. Pharm/Tox Reviewer and Team Leader expressed a concern since Novartis was referencing the review to provide supporting peri- and post-natal reproductive toxicity information for mycophenolic acid. All other disciplines stated that the Medical Officer's review of [ ] was not imperative to their reviews.

Following the filing meeting Novartis was contacted and asked if a right of reference was granted to them for the [ ] review by [ ] Novartis provided a written statement that (1) they do not have a right of reference to the review, (2) the information cited was disclosed to the public under FOIA and (3) the necessary toxicology information can be provided without referencing the review.

The Pharm/Tox Reviewer and Team Leader concluded that the necessary repro-tox information can be referenced from the CellCept labeling.

Yon Yu
Regulatory Project Manager, HFD-590

Rebecca Saville
Regulatory Project Manager, HFD-590

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/s/

Rebecca Saville
2/4/04 04:41:20 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Labeling for Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets (NDA 50,791)

Total no. of pages including cover: 25

Comments:
Dan,

Attached, please find the most recent version of the draft labeling for Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets (NDA 50,791).

The following recommendations were made and can be viewed in the tracking format:

1. Information was added to the Pediatric Use section.

2. Several minor editorial changes such as the deletion of extra spaces, and grammatical and spelling corrections.

If you have any questions, please feel to call me. Have a good evening.

Regards,
Rebecca Saville, Pharm.D., Regulatory Project Manager

Document to be mailed: ☐ YES ☑ NO

18 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Rebecca Saville
2/23/04 10:28:35 PM
CSO
NDA 50,791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Chemistry Recommendations for cGMP Compliance

Total no. of pages including cover: 3

Comments:

Document to be mailed: • YES ☑ NO

To: M. Daniel Gordin

Through: Norman Schmuff, Ph.D., Chemistry Team Leader
Ramesh Sood, Ph.D., Chemistry Reviewer

From: Rebecca Saville

Please refer to NDA 50,791 for Myfortic (mycophenolic acid) Tablets. We recommend the following in order to be compliant with the cGMP requirements, which do not allow the skip-lot testing concept for the product release:

1. Please do not include the periodic microbiological testing of the drug substance in the drug substance release specification. We recommend that this test be made a part of separate testing document "Periodic Quality Indicator Test (PQIT)".

2. Please do not include the periodic "Identity of Colorant", "Residual Solvents", and "Microbiological Testing" of the drug product in the drug product release specification. We recommend that these tests be made a part of PQIT.

If you have any questions, please call me.

/S/

Rebecca Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
2/23/04 09:47:15 PM
CSO
NDA 50,791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 23, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Myfortic NDA 50,791: Minutes from Executive CAC Meeting

Total no. of pages including cover: 5

Comments:

Dan,

Attached, please find a copy of the minutes from the Executive CAC Meeting.

If you have any questions, please call me.

Regards,

Rebecca

Document to be mailed: ☐ YES ☑ NO

Executive CAC
Date of Meeting: 12/2/03

Committee: David Jacobson-Kram, Ph.D., HFD- 024, Chair
Joseph Contrera; Ph.D., HFD-901, Committee Member
Abby Jacobs, Ph.D. HFD-024, Committee Member
Robert Osterberg, Ph.D., HFD-520, Rotating Committee Member
Stephen Hundley, Ph.D., HFD-590, Reviewer & Acting Team Leader
Kenneth Hastings, D.PH., AD, HFD-024

Author of Draft Minutes: Stephen Hundley, Ph.D.

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:

Division File, HFD-590
Stephen Hundley, Ph.D., Reviewer & Acting Team Leader, HFD-590
A.M. Homonnay Weikel, PM, HFD-590
Adele Seifried, HFD-024

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/s/

David Jacobson-Kram
12/4/03 03:59:15 PM

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/s/

Rebecca Saville
2/23/04 09:11:20 PM
CSO
NDA 50,791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 20, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Pharmacology/Toxicology Labeling Recommendations

Total no. of pages including cover: 2

Comments:

Document to be mailed: • YES ☑ NO

NDA 50,791 MYFORTIC® (mycophenolic acid) LABELING REVISION
PHARMACOLOGY/TOXICOLOGY

The "Carcinogenesis, Mutagenesis, Impairment of Fertility" section needs to be modified to include reference to the mouse carcinogenicity study listed in the CellCept® (mycophenolate mofetil) label. The additional language is in bold letters.

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 0.6-1.2 times the systemic exposure (based upon plasma AUC) observed in renal transplant patients at the recommended dose of 1.44 g/day. Similar results were observed in a parallel study in rats performed with mycophenolate mofetil. **In a 104-week oral carcinogenicity study in mice, mycophenolate mofetil was not tumorigenic at a daily dose level as high as 180 mg/kg (which corresponds to 0.6-times the proposed mycophenolate sodium therapeutic dose based upon body surface area).**

If you have any questions, please call me.

Regards,
Rebecca Saville
Regulatory Project Manager

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/s/

Rebecca Saville
2/20/04 10:32:55 AM
CSO
NDA 50,791

Food and Drug Administration
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Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 18, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: NDA 50,791 Label
Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

Total no. of pages including cover: 27

Comments:

Dan,

Good afternoon.

Attached, please find the table that you submitted on Friday, February 13th. We have revised the table by adding a column to the right that details our response or acceptance of your proposals. All items are open to discussion at tomorrow's teleconference. Attached, please also find the label that you submitted on the 13th February that has some revisions in the Clinical section that we have made and will be finalized after tomorrow's teleconference. These involve the definition of lost to follow-up component of the endpoints at 6 and 12 months.

Please call me to confirm that you received. We look forward to talking to you tomorrow morning. Thank you for the list of participants.

Thank you, and take care.

Regards,
Rebecca Saville, Pharm.D., Regulatory Project Manager

Document to be mailed: ☐ YES ☑ NO

25 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Rebecca Saville
2/20/04 07:33:44 PM
CSO
NDA 50,791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 17, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets (NDA 50,791)
505(b)(2) Application

Total no. of pages including cover: 3

Comments:

Dr. Gordin,

Since the reviewers have completed their reviews, the application and reviews are being evaluated to be sure that everything is correct and appropriately addressed in regards to the 505(b)(2) "new salt" application. In order to facilitate this, we would appreciate it if you could submit a general correspondence identifying which parts of the application and label rely on information that Novartis does not own or to which Novartis does not have a right of reference.

Thank you for your time and consideration of this request.

Regards,
Rebecca Saville, Pharm.D.
Regulatory Project Manager

Document to be mailed: ☐ YES ☑ NO

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/s/

Rebecca Saville
2/23/04 11:04:58 PM
CSO
NDA 50,791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 17, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: NDA 50,791
Information Request: Myfortic (mycophenolic acid) 180 mg and 360 mg Tablets

Total no. of pages including cover: 2

Comments:

Dan:

The following question arose following this morning's internal discussion of the labeling proposals from Novartis:

Were any patients lost to follow-up after having a biopsy-proven acute rejection but prior to a graft loss/death by 12 months in studies 301 and 302?

If you could address the question as soon as possible, it would be appreciated. Thank you.

Regards,
Rebecca

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/s/

Rebecca Saville
2/20/04 07:17:24 PM
CSO
NDA 50,791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: February 5, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: FDA Proposed Labeling for Myfortic

Total no. of pages including cover: 19

Comments:
Dan,

Attached, please find the labeling for Myfortic NDA 50-791 in the tracking format which includes the Division's recommendations and proposals.

The attendees for the teleconference tomorrow will be Marc Cavaille-Coll (Medical), Sary Beidas (Medical), Philip Colangelo (Clinical Pharm), Jang-Ik Lee (Clinical Pharm), and myself (Regulatory).

Thank you, and have a good day.

Regards,
Rebecca

Document to be mailed: ☐ YES ☑ NO

18 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Rebecca Saville
2/20/04 06:16:42 PM
CSO
NDA 50,791

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: January 9, 2004

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-~~8364~~ 6360	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2387

Subject: NDA 50-791 Myfortic Request for Information

Total no. of pages including cover: 2

Comments:

Dr. Gordin:

Please refer to NDA 50-791 for Myfortic (mycophenolate sodium) Tablets. We have the following Pharmacology-Toxicology request for information. If you have already submitted any of the information, please direct us to the location.

- Please provide plasma AUC values and calculations that were used to derive rat to human systemic exposure ratios at the human therapeutic dose for the following studies:
    1. Oral carcinogenicity study in rats
    2. Male and female fertility tests in rats
    3. Teratology study in rats

Thank you, and if you have any questions, please call.

Regards,

Rebecca D. Saville, Project Manager

Document to be mailed: • YES ☑ NO

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/s/

Rebecca Saville
1/9/04 09:56:10 AM
CSO
NDA 50-791

FACSIMILE COMMUNICATION

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 19, 2003

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-6360	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Clinical Pharmacology requests

Total no. of pages including cover: 4

Comments:

Document to be mailed: • YES ☑ NO

Attachment

FACSIMILE COMMUNICATION

To: M. Daniel Gordin

From: Rebecca Saville

Please refer to NDA 50-791 for Myfortic (mycophenolate sodium) Tablets. We have the following clinical pharmacology requests for information. If you have already submitted any of the information, please direct us to the location.

1. For all human pharmacokinetic studies submitted, please prepare a tabular summary to compare and contrast all analytical reports in terms of the assay method and assay performance for the determination of MPA and MPAG (MPA metabolite) concentrations in blood, urine, and other biological matrices. Specifically, for each site where each assay was conducted, please include information comparing the precision, accuracy, specificity, sensitivity, recovery, and linear range of calibration curve.

2. For Study 0102 (basic MPA pharmacokinetics and Myfortic-Neoral interaction):
   a. Please provide combined individual plots (i.e., spaghetti plots) drawn in normal and log scales for the concentration-time profiles of MPA, MPAG, and cyclosporine after stratifying by study visit. Please do not use symbols and dotted lines in the plots.
   b. Please provide the raw data and a complete summary (including SAS outputs) for the statistical comparisons of pharmacokinetic parameters for MPA, MPAG, and cyclosporine between study visits. Even though the study report referred to certain tables in the Appendices for the results of statistical analyses, these tables could not be located. For example, there are no tables in Appendix 6. Tables 5.1-4 and 9-1 do not match with the description in the report.
   c. Please provide a complete analytical report containing the in-process performance of an analytical method used for the determination of whole blood concentrations of cyclosporine including tables referred in the report.

3. For Study 0106 (pediatrics):
   a. Please provide the additional pharmacokinetic parameter values of MPA and MPAG (both individual patient and subgroup/group mean ± SD values) in a table format. The parameters include dose-normalized C_{max}, dose-normalized $AUC_{0-\infty}$, non-normalized CL/F, weight-normalized and non-normalized Vz/F, and non-normalized $t_{1/2}$.
   b. Please provide the results of correlation analysis between demographic variables and pharmacokinetic parameter values (see 3a) in table and graphic formats with a relevant statistical test (correlation coefficient, p value). The demographic variables include age, weight, and body surface area of the patients. In each normalization, calculation, or analysis, please use the actual dose administered to each individual patient (mg/patient), individual patient's weight, and individual patient's body surface area rather than subgroup/group mean values. Please also provide raw data in addition to summary tables and graphs.

4. For Study 2302 (multiple dose bioequivalence between Myfortic and CellCept), please provide combined individual plots (i.e., spaghetti plots) drawn in normal and log scales

for the concentration-time profiles of MPA, MPAG, and MPA acyl glucuronide after stratifying by treatment. Please do not use symbols and dotted lines in the plots.

5. For Study B301 (therapeutic equivalence between Myfortic and CellCept):
   a. Please provide detailed information on how the food intake (meals, snacks, beverages) was controlled from 2 hours before the previous evening dose of study drugs until the test dose administration next morning, and what the results were.
   b. Please provide complete demographic data and a descriptive statistical summary of the demographic data of the 28 patients who completed all study visits.
   c. Please provide the names of the three study centers where the clinical part of the pharmacokinetic substudy was conducted.

6. For Study B302 (comparison of gastrointestinal adverse events between Myfortic and CellCept):
   a. Please provide detailed information on how the food intake (meals, snacks, beverages, etc) was controlled from 2 hours before the previous evening dose of study drugs until the test dose administration next morning in each study visit, and what the results were.
   b. Please provide complete demographic data and a descriptive statistical summary of the demographic data of the 18 patients who completed all study visits.

7. For Study W152 (single dose bioequivalence between Myfortic and CellCept):
   a. Please provide combined individual plots (i.e., spaghetti plots) drawn in normal and log scales for the concentration-time profiles of MPA and MPAG after stratifying by treatment. Please do not use symbols and dotted lines in the plots.
   b. Please provide the raw data and a complete statistical summary (e.g., SAS outputs) that produced the least squares mean ratios of Cmax and AUC, and the corresponding 90% confidence intervals.

/S/

Rebecca Saville, Pharm.D., M.S.
Regulatory Project Manager

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/s/

Rebecca Saville
12/19/03 04:46:35 PM
CSO
Clinical Pharmacology Information Request

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 11, 2003

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Proprietary Name

Total no. of pages including cover: 2

Comments:

Dr. Gordin,

We have completed our final review of your proposed proprietary name "Myfortic", and we find that the proposed name is acceptable.

Please call me if you have any questions. Thank you.

Regards,

Rebecca Saville, Project Manager

Document to be mailed: • YES ☑ NO

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/s/

Rebecca Saville
12/11/03 07:15:08 PM
CSO
Re: Myfortic Proprietary Name

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 21, 2003

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2475
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Biometrics Information Request

Total no. of pages including cover: 1

Comments:

Good afternoon, Dr. Gordin -

We cannot validate some of the numbers given in your study reports with the electronic data provided. In study B301, you state in Table 10-2 that there were 170 G.I adverse events on ERL080 and 162 on MMF. However, we cannot duplicate your results using your dataset, adverse.xpt. Similarly, we cannot duplicate your results for G.I. adverse events for study B302. Please verify that the results as summarized in the study reports are accurate and please clarify what variables and cutoffs for start of adverse events you are using in your analyses.

We also are unable to verify your efficacy analysis for study B302. You state that 4 subjects on ERL080 and 6 subjects on MMF were lost to follow-up by month 6. We found 5 and 7 patients, respectively. Furthermore, this changes the numbers for the primary efficacy analysis of biopsy-proven acute rejection, graft loss, death and loss to follow-up. You state 6 and 10 patients had reached this endpoint by month 6, while we found 7 and 11 patients.

Thank you – Rebecca Saville, Project Manager

Document to be mailed: • YES ☑ NO

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/s/

Rebecca Saville
11/26/03 04:39:08 PM
CSO
Biometrics Information Request

MEMORANDUM OF TELECONFERENCE

Meeting Date:	December 1, 2003
Time:	8:30 a.m.
Location:	FDA/CDER/Corporate S-426, Rockville, MD
Application:	NDA 50-791 Myfortic® (mycophenolate sodium) Tablets
Sponsor:	Novartis Pharmaceuticals Corporation
Type of Meeting:	Teleconference
Meeting Chair:	Norman Schmuff
Meeting Recorder:	Rebecca Saville

Attendees:

Novartis

Robert Clark	Director, Global Regulatory CMC, US
Nancy Del Viscio	Associate Director, Global Regulatory CMC, US
Morten Garn	Group Head, Global Regulatory CMC, Basel
Daniel Gordin, Ph.D.	Director, Drug Regulatory Affairs, US
Andrew Milton, PhD.	Reg. Project Manager, Global Regulatory CMC, Basel
Trudi Haemmerli	Global Head Regulatory CMC
Juergen Roettele	Technical Research and Development
Roland Guenther	Regulatory CMC Basel
Christopher A. Morrison	Drug Regulatory Affairs, Basel

FDA

Norman R. Schmuff, Ph.D., Chemistry Team Leader, DSPIDP
Ramesh Sood, Ph.D., Chemistry Reviewer
Mark Seggel, Ph.D., Chemistry Reviewer
Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader, DSPIDP
Sary Beidas, M.D., Medical Officer, DSPIDP
Rebecca Saville, Pharm.D., Project Manager, DSPIDP

BACKGROUND:

Myfortic delayed-release tablets contain the sodium salt of mycophenolic acid. Details of the [ ] mycophenolic acid are contained in [ ] DMF [ ] The review of this DMF in support of NDA 50-791, submitted April 30, 2003, for Myfortic, revealed significant deficiencies which were conveyed to the DMF holder, [ ] We were informed by Novartis that [ ] wished to have a telecon with us which would include Novartis personnel.

DISCUSSION:

Following introductions, the Division indicated to Novartis that there were several CMC deficiency issues.

The Division indicated that it realizes that the ——— facility was recently inspected and is in compliance with cGMPs, but the information provided in the DMF is deficient. The Division conveyed that when the Division needs to request more information, the review process is delayed. This is unacceptable, especially given that more information exists, but was not provided in the DMF. A lot of experience may exist, but it is not being conveyed in the submission, and there is minimal information provided. The Division stated that assumptions should not have to be made from this information. We feel we are just guessing when we know other criteria must exist, and we want to see the data. Although we are confident from outside sources that you are operating correctly, we cannot discern that from the submission.

The Division realizes that our agency does not have ——— guidelines, but we recommend using the February 1987 "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances", which provides submission guidance.

Novartis apologized for the information deficiency and noted that they will continue on a learning curve regarding this type of data submission. Novartis indicated that they have a new system, so it was difficult to submit electronically. They state that they are open to any recommendations and will improve when the next opportunity presents. Novartis conveyed that they were still preparing a submission to address the Division's correspondence of October 9, 2003.

The Division indicated that there were general concerns regarding [ ] information submitted in the DMF. The specific concerns have already been communicated to the DMF holder in our October 9, 2003 correspondence. In response to the Divisions concern [ ] replied that [

[redacted] conveyed [redacted]

[redacted]

The Division requested [redacted]

[redacted] indicated [redacted]

[redacted] agreed to provide characterization as well as information regarding the controls implemented on the starting materials.

Novartis and [redacted] apologized for the lack of information in the DMF and indicated that they were committed to fulfilling our requests for information. They expressed that they were open to any further questions, and they would provide a response to both the issues that arose in the discussion today as well as a response to the Division's request dated October 9, 2003.

ACTION ITEMS:

Novartis and [redacted] will submit correspondence addressing the Division's request for information within a few weeks.

/S/

Minutes Preparer:
Rebecca Saville, Pharm.D., Project Manager

/S/

Concurrence
Norman Schmuff, Ph.D.
Chemistry Team Leader

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/s/

Rebecca Saville
2/27/04 03:11:41 PM
CSO
NDA 50-791

Norman Schmuff
2/27/04 04:02:36 PM
CHEMIST

MEMORANDUM OF TELECONFERENCE MINUTES

DATE: December 20, 2001

APPLICATION: IND 57,005 (ERL080)

BETWEEN:

Name: Maria Figliomeni, Ph.D., Associate Director, Drug Regulatory Affairs
Phone: (973) 781-8240
Representing: Novartis Pharmaceuticals Corporation

AND

Name: Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader
Ekopimo Ibia, M.D., M.P.H., Medical Officer
Matthew A. Bacho, Regulatory Project Manager

SUBJECT: The FDA requested a teleconference with Novartis to discuss the outcome of the pre-NDA meeting that was held on December 14, 2001, and provide more guidance on their proposed NDA for ERL080.

BACKGROUND: A pre-NDA meeting was held on December 14, 2001, at which Novartis presented data indicating their drug product, ERL080 or Myfortic™, exposed patients to an average of 32% more mycophenolic acid (MPA) than the comparator, mycophenolate mofetil (MMF).

SUMMARY: Dr. Cavaillé-Coll noted that the new pharmacokinetic data on ERL080's relative MPA exposure from Study B301 surprised a few reviewers at the pre-NDA meeting last Friday. At the time of the End-of-Phase II meeting (November 9, 1998), both parties assumed that Novartis' drug product would be bioequivalent to MMF (with respect to MPA exposure) and this understanding served as a basis for the subsequent clinical program that the sponsor embarked upon. He acknowledged the fact that Novartis had indeed followed the Division's advice on this matter but the pre-NDA meeting changed the situation completely. Extensive internal discussions held since December 14 have resulted in a number of differing views (ranging from Refuse-to-File to considering the matter a reviewable issue) about how the proposed NDA should be handled. However, everyone had agreed that there was very little chance that ERL080 could be approved based on the data presented on December 14, 2001. Like all immunosuppressants, ERL080 has a very narrow therapeutic index and any increase in exposure is usually matched by additional toxicity.

Dr. Cavaillé-Coll outlined three possible ways that Novartis could address the Division's concerns about ERL080's pharmacokinetics: 1) They could develop a new dosage form that is bioequivalent to MMF (the Division acknowledged the time and expense this would involve); 2) Novartis could conduct an additional clinical study that involved as many as 500 subjects per

treatment arm; or 3) The sponsor could conduct a pharmacokinetic crossover study supported by extensive safety data from the literature. The reason the Agency would suggest such a large number of subjects for option #2 is that it allows for adequate power to exclude the possibility that an increase in MPA exposure does not lead to an unacceptable level of toxicity. As for the third option, the Division would have to review the raw data that supported Novartis' chosen references (something that is generally not available).

Dr. Cavaillé-Coll noted the Division's dismay that this important new data was not as prominent in Novartis' background package as it was in their presentation on December 14. Dr. Figliomeni acknowledged this statement and noted that Novartis was aware of the labeling for CellCept®, which included safety data on the 1.5-gram twice-daily dosing regimen (assuming MPA exposures between this dose of CellCept® and ERL080 are similar), although it was not approved for kidney transplantation. These data and the extensive postmarketing experience that clinics had with CellCept® provided Novartis with the confidence to proceed with their plans to submit an NDA for Myfortic™. Dr. Cavaillé-Coll pointed out that the 1.5-gram twice-daily dosing regimen used in Roche's original NDA for CellCept® was not necessarily administered according to protocol. The pharmacokinetic data indicated that physicians lowered this dose, because of its intolerability, to the point where it closely resembled what was seen in subjects treated with the 1.0-gram twice-daily dosing regimen.

Dr. Figliomeni inquired about the types of serious adverse events associated with higher levels of MPA exposure that Novartis should be aware of besides neutropenia. Dr. Cavaillé-Coll noted that in addition to the adverse events of gastrointestinal intolerability, the Division was also concerned about increased rates of pancreatitis and pulmonary fibrosis, which were not seen in the Phase III studies of MMF and only appeared in the postmarketing data for this drug product. As a consequence, it was difficult to ignore the potential dose-dependent hazards of MPA exposure. Dr. Cavaillé-Coll was concerned that although pancreatitis and pulmonary fibrosis may not be detected in the limited Phase III clinical experience with ERL080, these events might increase in frequency along with a persistently high exposure to MPA. The bottom line was that Novartis did not have enough patients in their safety database to exclude the possibility of greater toxicity resulting from the higher MPA exposures evident with ERL080.

Dr. Figliomeni noted that Novartis had conducted a single dose pharmacokinetic study (W152), which indicated that the exposure to MPA with ERL080 was exactly the same as with MMF. Their assumption was that their drug product would also produce MPA AUCs resembling those associated with MMF when chronically dosed. It was not Novartis' intention to "surprise" the Division with pharmacokinetic data that did not meet anyone's expectation. Dr. Cavaillé-Coll acknowledged this statement and noted that many considered all immunosuppressants potential "therapeutic

poisons" in that their efficacy is directly tied to the toxicities associated with their use.

Dr. Figliomeni reminded us of the number of patients in their current safety database as well as the long duration of exposure (up to 24 months) for a fair portion of those in the same. Dr. Cavaill9-Coll noted that length of exposure was not a concern because one can assume that patients that were still on either ERL080 or MMF after a few weeks post-transplant would usually tolerate these drugs for a long period of time. As an aside, it would be important to study gastrointestinal tolerance, and the safety of ERL080's current bioavailability, in *de novo* kidney transplant patients for this very reason. He also added that the slight trends in Novartis' data (e.g., a greater number of dropouts among those treated with ERL080 compared to those on MMF 6 months after transplantation) are probably not specific to any one subpopulation of subjects and should be explored in a more substantial trial. Dr. Cavaill9-Coll then noted that the enteric coating may have some role to play in the greater bioavailability of ERL080 in transplant patients who receive concomitant Neoral®.

Dr. Figliomeni brought up the possibility of scheduling a teleconference in early 2002 to discuss the design of a pharmacokinetic crossover study. She asked if the study had to be 12 months in length. Dr. Cavaill9-Coll stated that it may not necessarily have to be that long and agreed that the Division would be willing to discuss this issue. He asked if Novartis had any ongoing, long-term studies for ERL080, and Dr. Figliomeni noted that there were none (b(4))

Dr. Figliomeni noted that the MMF dosing regimen of 1.5-gram twice daily was approved for liver and heart transplant recipients and wondered why it was not suitable for kidney transplantation. Dr. Cavaill9-Coll explained that experience taught him and others that immunosuppressive drugs and their safe and effective administration may differ depending on the organ being transplanted.

Dr. Figliomeni then inquired about the reason(s) the Division decided to bring up the fact that ERL080 would be considered an "old" antibiotic. Dr. Cavaill9-Coll stated that the Division merely wanted to note for the record that this drug product would be submitted and filed under section 505(b) and approved for safety and effectiveness under section 505(c). As a result of the repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act, new applications (those received on or after November 21, 1997) under section 505(b) or 505(j) for drugs that contain "old" antibiotics need not include patent information and are not eligible for exclusivity under sections 505(c) or 505(j). Dr. Figliomeni noted that she was aware of this information.

Again, Dr. Figliomeni stated that Novartis did not mean to be "underhanded" about revealing the relative bioavailability of ERL080 (as it compared to MMF). In their discussions with the French and Swiss drug regulatory

authorities, no one had expressed as much concern about the potential safety implications of their drug product's average 32% increase in MPA exposure over MMF. This experience with the French and Swiss regulatory agencies probably had something to do with the lack of prominence with which this new data was presented. Dr. Cavaill9-Coll acknowledged and understood these statements while noting that many placed a lot of importance on the single dose pharmacokinetic data. The Division was concerned about the uneven distribution of ERL080's C_{max} and AUC over time, especially the large number of outliers located at the upper end of that distribution. If Novartis had planned to use therapeutic drug monitoring (TDM) with this product then there would not be such a concern (Dr. Figliomeni confirmed that TDM was not being considered) about exposure to MPA with ERL080. Dr. Cavaill9-Coll stated that Novartis' goal should be to vigorously study the effect(s) of acute MPA exposures in *de novo* kidney transplant recipients if reformulation is not a viable option.

Dr. Figliomeni acknowledged these remarks and noted her intention of passing along this timely information to the rest of Novartis' ERL080 group. She also wanted to schedule a teleconference in January 2002 to discuss these issues in more detail.

11/19/03

Office of Drug Safety

MEMO

To: Renata Albrecht, M.D.
Director, Division of Special Pathogen and Immunologic Drug Products, HFD-590

From: Kristina C. Arnwine, PharmD
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Through: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Carol A. Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

CC: Rebecca Saville, PharmD
Project Manager, DSPIDP, HFD-590

Date: November 19, 2003

Re: ODS Consult 01-0224-1, Myfortic (Mycophenolate Sodium Tablets)
180 mg and 360 mg; NDA 50-791.

This memorandum is in response to a September 29, 2003 request from your Division for a final review of the proprietary name, Myfortic. The container label and package insert labeling were provided for review and comment.

The proposed proprietary name was found acceptable by DMETS on July 2, 2002 (ODS Consult 01-0224). Since that review, DMETS has identified three additional proprietary names: Mifeprex, Niferex, and Macrotec as having the potential to sound like Myfortic. In addition, the proprietary name Myproic and the medical term myopic were identified as having both sound-alike and look-alike similarities with Myfortic. DDMAC finds the proprietary name acceptable from a promotional perspective.

A. Myfortic and Mifeprex can sound similar when pronounced. Mifeprex is an abortifacient used to terminate uterine pregnancies. Myfortic and Mifeprex have different available strengths (180 mg and 360 mg vs. 200 mg) and different usual dosages (720 mg twice daily vs. 600 mg on Day 1 and 400 mg on Day 3). Mifeprex is under restricted distribution and is generally not dispensed in retail settings and is only dispensed in hospital pharmacy settings under strict regulations, thereby greatly decreasing the potential for medication errors.

B. Myfortic and Niferex can sound similar when pronounced. Niferex is an over the counter polysaccharide iron preparation used for iron supplementation. The beginnings of each name ('Myfor' vs. 'Nifer') may sound similar, depending on how they are pronounced. However, the endings of the names ('tic' vs. 'ex') are phonetically different which helps to distinguish the two names from each other. Myfortic and Niferex have different available strengths (180 mg and 360 mg tablets vs. 50 mg tablets and 100 mg/5 mL elixir) and different dosing frequencies (twice daily vs. once daily). The differing strengths between Myfortic and Niferex help to distinguish the two products, thereby reducing the potential for medication errors.

C. Myfortic and Macrotec can sound similar when pronounced. Macrotec is a Technetium Tc 99 Albumin Kit used as a lung imaging agent. Both names begin with the letter 'M' followed by a vowel which causes the first syllable of each name to sound similar. The last syllables each name are also phonetically similar ('tic' vs. 'tec'). However, the second syllable of

each name is phonetically different ('for' vs. 'cro') which helps to distinguish the two names. In addition, Myfortic and Macrotec have different routes of administration (oral vs. intravenous) and different usual dosages (720 mg twice daily vs. 37 MBq to 148 MBq (1-4 mCi)). Overall, the differing product characteristics help to distinguish the two products, which reduces the potential for medication errors.

D. Myfortic and Myproic can sound similar when pronounced and can look alike when written. However, after further research[1], DMETS has determined that Myproic Acid is only marketed as Valproic Acid, therefore the potential for confusion is greatly reduced as the sound-alike and look-alike potential no longer exists.

E. Myfortic and the medical term myopic can sound alike when pronounced and can look alike when written. Myopic is a medical term meaning nearsighted. The fact that myopic is a medical term used to describe a condition and generally would not be used in relation to a medication decreases the potential for medication errors.

In the review of the Myfortic container labels and package insert labeling, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. General Comments

DMETS questions the necessity of the 180 mg tablets. The recommended dose of Myfortic is 720 mg (2 x 360 mg) twice daily and does not require titration or dose reduction due to renal or hepatic impairment. Therefore, doses of 720 mg will be achieved using two 360 mg tablets and not four 180 mg tablets. Please comment.

B. Container Labels

1. The blue graphic interferes with the readability (color and size) of the established name. This detracts from the readability of the most important information on the main display panel. Revise accordingly.

2. Relocate the net quantity so that it does not appear in close proximity to the strength.

3. Ensure there is a child-resistant closure (CRC) on the unit-of-use bottles containing 120 tablets.

C. Package Insert Labeling

1. The term 'MMF' is used throughout the labeling without an adequate explanation of the term. Please use 'mycophenolate mofetil' instead of 'MMF'.

2. Dosage and Administration Section

The conversion information (i.e. mycophenolate mofetil 1000 mg to Myfortic 720 mg) is confusing. Please revise so practitioners can easily determine equivalent dosing.

In summary, DMETS has no objection to the use of the proprietary name, Myfortic. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

[1] After verification with Morton Grove Pharmaceuticals and the Office of Generic Drugs Labeling Division.

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/s/

Kristina Arnwine
12/15/03 01:39:39 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/16/03 04:20:09 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/17/03 11:08:10 AM
DRUG SAFETY OFFICE REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: November 13, 2003

To: M. Daniel Gordin	**From:** Rebecca Saville
Company: Novartis Pharmaceuticals Corporation	Division of Special Pathogen and Immunologic Drug Products
Fax number: 973-781-8364	**Fax number:** 301-827-2345
Phone number: 862-778-4784	**Phone number:** 301-827-2127

Subject: Request for Information

Total no. of pages including cover: 3

Comments:

Dr. Gordin:

Greetings! It was nice to meet you on the phone earlier today. I am looking forward to working with you during the review process of Myfortic.

Attached, please find two Microsoft Excel documents containing the study participants Case Review File (CRF) numbers from studies 301 and 302. The medical officer who is reviewing Myfortic (NDA 50-791) is requesting the CRFs for each of these study participants. Please submit these for his review. He does have several CRFs for other patients included in these studies, and they are not listed in these documents. If you have any questions, please feel free to contact me. Thank you.

Regards – Rebecca Saville, Project Manager

Document to be mailed: • YES ☑ NO

Study #301

SID1A

0002_00005
0003_00003
0003_00006
0012_00001
0013_00002
0015_00002
0016_00010
0017_00004
0022_00003
0022_00017
0022_00020
0023_00005
0023_00025
0023_00036
0031_00006
0031_00008
0031_00018
0041_00005
0048_00002
0048_00005
0053_00012
0054_00006
0064_00002
0064_00004
0064_00007
0501_00010
0502_00004
0511_00001
0511_00004
0511_00019
0511_00022
0511_00024
0512_00013
0514_00010
0516_00006
0516_00012

Study #302

SID1A
0011_00003
0011_00009
0015_00001
0015_00012
0015_00022
0021_00005
0021_00007
0033_00001
0501_00005
0501_00009
0504_00008
0507_00001
0511_00007
0511_00010
0511_00011
0511_00012
0512_00005
0512_00010
0516_00001
0516_00022
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0526_00001
0526_00002
0527_00011
0528_00007

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/s/

Rebecca Saville
11/26/03 04:33:47 PM
CSO
Request for Information - CRFs

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Division of Special Pathogen and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850
FACSIMILE TRANSMISSION

DATE:	10/9/03
TO:	M. Daniel Gordin, Ph. D. Director, Regulatory Affairs
COMPANY:	Novartis
FAX NUMBER:	(973) 781-8364
RE:	NDA 50-791

FROM: Yon Yu, Regulatory Project Manager
DSPIDP
TELEPHONE: (301) 827-2127
FAX NUMBER: (301) 827-2326
Number of Pages (including cover sheet): 5

MESSAGE: Please see the attached CMC comments regarding NDA 21-580 (Myfortic). If you have questions, please contact Yon Yu, Regulatory Project Manager at (301) 827-2127.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

NDA 50-791

Please refer to your New Drug Application (NDA) dated April 30, 2003 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Myfortic (mycophenolate sodium) Tablets, 180 mg and 360 mg.

Provided below are comments from the chemistry reviewer.

1. The DMF [redacted] mycophenolic acid, is currently inadequate. The DMF holder, [redacted] has been notified.

2. Please check and correct the denominator in the calculation formula for determining related substances contents in the intermediate mycophenolic acid as shown on p. 4-108, volume 3, of the document [redacted] It would appear that the denominator should be $PA_T + \Sigma PA_{Rsi}$ instead of $PA_T \times \Sigma PA_{Rsi}$.

3. Please include an appropriate "Residue on Ignition" acceptance criterion for the drug substance.

4. Please include appropriate drug substance release acceptance criteria to control the microbial contamination of the mycophenolate sodium or justify the absence of such testing.

5. The provided impurity data for all the clinical, registration and intended commercial drug substance batches show that the total impurities are below the LOQ value of [redacted] The provided stability data also show that the drug substance is chemically stable under storage conditions. Based on these data please tighten the total impurities and total unknown impurity acceptance criteria for the drug substance.

6. Please revise the drug substance individual and total residual solvents acceptance criteria based on the process manufacturing capability as recommended in ICH Q3C.

7. Please include in the drug substance and drug product testing monographs appropriate references to the USP general chapters for the compendial procedures along with any deviation from the compendial procedure used in the analysis of the drug substance and the drug product.

8. Please include an appropriate system suitability acceptance criteria for the [redacted] your drug substance and drug product HPLC assay methods as recommended in USP <621>.

9. Please provide detailed information about the description, composition, suitability and your quality control measures of the container closure system used to store and transport the drug substance.

10. Please note that after the re-test period the batch of the drug substance should be re-tested for compliance with the specification and then used immediately within [ ] as stated in your NDA.

11. In order to ensure that the quality of the drug substance manufactured does not change over the time, please provide a commitment to put one annual batch of the drug substance for stability studies under long-term storage conditions.

12. Please submit the room temperature stability data for the drug substance primary batch 0044030 for — time point when the data becomes available.

13. Please provide representative manufacturer/supplier's and your own certificates of analysis of all the inactive ingredients used in the production of a drug product batch.

14. Please provide a copy of the Master Batch Record for each strength that will be used for the validation and commercial batches.

15. We have noticed in the executed batch records that during the drug product manufacturing in-process controls such as appearance, thickness, weight, crushing strength, disintegration time and friability etc., for the core and coated tablets are monitored. Please provide a consolidated table that include such in-process controls and the acceptable limits for these tests.

16. You have not provided any information about the possible reprocessing of the drug product in your submission. Please note that any reprocessing of the drug product will require submission of a supplement for agency's approval.

17. We have noted your justification that the total degradants observed so far in all tested lots were less than — However, we recommend that you add an appropriate low acceptance criterion for the "total degradation product" in the drug product specification to ensure the quality of the future drug product lots.

18. You have designated [ ] as by-products. Please describe the origin [ ] and the basis for the designation as by-products. Please also provide information about [ ] present in various pre-clinical, clinical and commercial lots of the drug product.

19. Please provide drug product release HPLC chromatograms of the representative batches for assay and degradation products.

20. Please justify the absence of appropriate acceptance criteria for the microbiological attributes in the drug product specification or set appropriate acceptance criteria as per the ICH Q6A guidance.

21. Please provide experimental data to demonstrate the robustness of [ ] method for the determination of residual solvents in the drug product.

22. Please provide statement that all components used in the manufacture of [ ] comply with the appropriate FDA food additive regulations as specified in 21 CFR sections 174 –186 and cite reference to the appropriate section.

23. Please provide USP <671> moisture permeation results for all bottle/closure combinations used for packaging the drug product.

24. Please provide statement certifying that all components used in the container, closure and colorant comply with the appropriate FDA food additive regulations as specified in 21 CFR sections 174 –186 and cite reference to the appropriate section.

25. The description for only the [ ] (V.5, p. 4-67) states that tablets have beveled edges. Please confirm that the [ ] also has beveled edges and that the only difference between [ ] and commercial [ ] is that of tablet imprint

26. Please submit the [ ] time point long-term stability data for batches X049 0100 (180 mg) and X409 1299 (360 mg).

27. Please include testing at the [ ] time point during the first year in you drug product annual batch stability protocol.

28. In regards to your plan for extension of the expiration period for the drug product based on long-term stability data on the registration batches through annual report we have the following comments. The extension of expiration period through annual report can only be done based on satisfactory long-term stability data on at least three production batches in accordance with the approved stability protocol. Alternatively, the tentative expiration dating period can be extended through a prior approval supplement based on full long-term stability data on at least three pilot scale batches. The expiration period thus derived based on the pilot scale batches remain tentative until confirmed with full long-term stability data from at least three production batches.

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/s/

Yon C. Yu
10/9/03 02:01:25 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Division of Special Pathogen and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE:	7/16/03
TO:	M. Daniel Gordin Director, Regulatory Affairs
COMPANY:	Novartis
FAX NUMBER:	(973) 781-8364
RE:	NDA 21-580: 74-Day Letter
FROM:	Yon Yu, Regulatory Project Manager DSPIDP
TELEPHONE:	(301) 827-2127
FAX NUMBER:	(301) 827-2326

Number of Pages (including cover sheet): 3

MESSAGE: If you have questions, please contact Yon Yu, Regulatory Project Manager at (301) 827-2127.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 50-791

Novartis Pharmaceuticals Corporation
Attention: M. Daniel Gordin, Ph.D.
Director, Drug Regulatory Affairs
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Gordin:

Please refer to your April 30, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Myfortic® (mycophenolate sodium) delayed-release tablets, 180 mg and 360 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on June 29, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Please note the NDA number for Myfortic® has changed from [redacted] to 50-791 as communicated to you in a June 9, 2003 telephone conversation with Yon Yu of this division. The Guidance for Industry titled *Repeal of Section 507 of the Federal Food, Drug and Cosmetic Act* describes the application numbering convention that assigns a series 50,000 number to applications submitted under 505(b) on or after November 21, 1997 to which the section 125 exemptions apply.

If you have any questions, call Yon Yu, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

/S/

{See appended electronic signature page}

Ellen F. Molinaro, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Molinaro
7/11/03 04:00:34 PM
NDA 50-791

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Division of Special Pathogen and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-590
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE:	5/29/03
TO:	M. Daniel Gordin Director, Regulatory Affairs
COMPANY:	Novartis
FAX NUMBER:	(973) 781-8364
RE:	NDA 21-580
FROM:	Yon Yu, Regulatory Project Manager DSPIDP
TELEPHONE:	(301) 827-2127
FAX NUMBER:	(301) 827-2326

Number of Pages (including cover sheet): 3

MESSAGE: Please see the attached CMC request regarding NDA 21-580 (Myfortic). If you have questions, please contact Yon Yu, Regulatory Project Manager at (301) 827-2127.

NOTE: We are providing the attached information via telefacsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

We have the following requests regarding NDA —

Please confirm that the following facilities are the only sites involved in the manufacturing, testing and packaging of the drug substance and the drug product for your NDA — Please confirm that the address and the functions listed for each site are correct, and that the facilities are ready for the GMP inspection.

Site	**Function**
Novartis Pharma Schweizerhalle AG Rheinfelder Strasse CH-4133 Pratteln, Switzerland CFN # 9692042	Drug substance manufacturing and release testing
Novartis Pharma Stein AG Schaffhauserstrasse CH4332 Stein, Switzerland CFN: 9692043	Drug product manufacturing and release testing.
Novartis Pharma AG Lichtstrasse 35 CH-4056 Basle, Switzerland CFN: 9611204	Drug substance release and stability testing
Novartis Pharmaceuticals Corporation 25 Old Mill Road Suffern, NY 10901 CFN: 2416082	Drug substance release testing. Drug product release testing, stability testing and packaging.
Novartis International Pharmaceutical Ltd Branch Ireland Ringaskiddy Co. Cork, Ireland CFN: 9612715	Drug substance release and stability testing.
Novartis International Pharmaceutica SA Via Serafino Balestra 31 CH-6601 Locarno, Switzerland. CFN: 9614433	Stability testing for the drug substance. Drug product release and stability testing.
[ ] CFN: [ ]	[ ]

[ ] CFN: [ ]	[ ]

In addition, you have listed the following site for the drug product release testing. The CFN number listed for this site under drug product section (CFN [ ] does not match with the same address site listed under drug substance section (CFN 9611204). Please confirm the CFN number for this site.

Novartis Pharma AG
Lichtstrasse 35
CH-4056 Basle, Switzerland

Attendee : Steve G. Steve H. Yhcl col.
Tony B. Norm S. Ike Jang
Arthur H. Muriel B.
Marc. Avery G.

USER FEE VALIDATION SHEET

50-791

NDA # ~~X~~ Supp. Type & # N 000 UFID # 4527
(e.g., N000, SLR001, SE1001, etc.)

1. (YES) NO User Fee Cover Sheet Validated? MIS_Elements Screen Change(s):

2. (YES) NO APPLICATION CONTAINS CLINICAL DATA?
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling).

REF IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.

3. YES (NO) SMALL BUSINESS EXEMPTION

4. YES (NO) WAIVER GRANTED

5. YES (NO) NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).
If YES, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s).

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. P (S) PRIORITY or STANDARD APPLICATION?

14 May 03
PM Signature / Date

Ellen C. Frank 13 May 03
CPMS Concurrence Signature / Date

2/14/00

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

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1. APPLICANT'S NAME AND ADDRESS

Novartis Pharmaceuticals Corporation
One Health Net Plaza
East Hanover, New Jersey 07936

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 781-6940 - Vera Wolsch

3. PRODUCT NAME

Myfortic®

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4527

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See item 8, reverse side if answered YES)

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Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Vera Wolsch	Director, Planning & Administration, Drug Regulatory Affairs	April 7, 2003

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 14, 2001
Time: 3:15 p.m. – 5:30 p.m.
Location: U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
9201 Corporate Blvd., S400
Rockville, MD 20850

Sponsor: Novartis Pharmaceuticals Corporation

Type of Meeting: Pre-NDA meeting/Type B

Meeting Recorder: Matthew A. Bacho, Regulatory Project Manager

FDA Attendees, Titles, and Office/Division:

Renata Albrecht, M.D., Acting Director and Meeting Chairperson
Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader
Ekopimo Ibia, M.D., M.P.H., Medical Officer
Kenneth L. Hastings, Ph.D., Pharmacology/Toxicology Team Leader
Steve Hundley, Ph.D., Pharmacology/Toxicology Reviewer
Shukal Bala, Ph.D., Microbiology Team Leader
Karen Higgins, Sc.D., Statistics Team Leader
Qian Li, Ph.D., Statistics Reviewer
Funmilayo O. Ajayi, Ph.D., FCP, Clinical Pharmacology & Biopharmaceutics Team Leader
Kofi A. Kumi, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer
Ellen C. Frank, R.Ph., Chief, Project Management Staff
Matthew A. Bacho, Regulatory Project Manager

External Constituent Attendees and Titles:

Maria Figliomeni, Ph.D., Drug Regulatory Affairs
Michael Hall, M.D., Clinical Research
Lawrence Hauptman, Ph.D., Drug Regulatory Affairs
Peter Heining, Ph.D., Pre-Clinical Safety
Jeff Maca, Ph.D., Biostatistics
Juergen Roettele, Ph.D., Technical Research and Development
Robert Schmouder, M.D., Clinical Pharmacology
Monica Schnyder, Ph.D., Drug Regulatory Affairs
Manfred Schulz, Ph.D., Project Management

Background: Novartis Pharmaceuticals Corporation (Novartis) requested a meeting to discuss their plans for a new drug application (NDA) for Myfortic™ (mycophenolate sodium delayed-release tablets), which will also be referred to as ERL080. The investigational new drug application for Myfortic™ was submitted on September 30, 1998, and an End-of-Phase II meeting was held on November 9, 1998. The background package for this pre-NDA meeting contained questions for the FDA. A memorandum answering Novartis' questions for this pre-NDA meeting was faxed to them on December 4, 2001.

Meeting Objective: Novartis sought guidance from the FDA concerning the preclinical, clinical, and biopharmaceutical aspects of their proposed NDA for ERL080.

Discussion Points:

[Note: The statements in bold were taken from the sponsor's materials for this meeting.]

1. Novartis provided an overview of ERL080's development starting with their clinical pharmacology program, which revealed a difference in relative mycophenolic acid (MPA) exposure between mycophenolate mofetil (MMF) and ERL080. Study W152 compared the bioavailability of the final market form of enteric-coated ERL080 with MMF in 24 subjects and it showed evidence of single dose, bioequivalent MPA exposure between ERL080 720 mg and MMF 1000 mg (although there was inherent variability of MPA concentration for both drugs that precluded C_{max} bioequivalence). However, pharmacokinetic data from a subset of patients in Study B301 revealed that in the context of chronic steady-state dosing, and comparing 3 timepoints, ERL080 delivered on average 32% higher MPA exposure than MMF (p=0.004). In response to an inquiry from the FDA about the mean MPA target levels in Study B301, the sponsor noted that it was approximately 30 μg*hr/mL, although ERL080 kept most subjects above this value. *The Agency noted that this increase in MPA exposure brought to mind the 1.5-mg twice-daily dosing regimen for MMF, which was efficacious but deemed unsafe for kidney transplant recipients. The data for ERL080 seemed to mimic the upper MPA AUC levels seen with the 3-gm/day dose of MMF. The dose-dependent toxicities that were associated with this regimen might be relevant to this situation as well. The Agency also expressed concern about the high variability of the pharmacokinetic/pharmacodynamic (PK/PD) data. The FDA asked Novartis if they had any additional information regarding C_{max} and AUC for MPA and MPAG after administration of ERL080 compared to MMF.*

   Novartis stated that the C_{max} and AUC values for ERL080 would normalize over time, characteristics similar to MMF. The sponsor agreed that the PK/PD data from Study B301 was highly variable and noted that the safety aspects of a higher relative exposure to MPA would be handled in the clinical section of this meeting.

2. Novartis presented an overview of their clinical program and noted that they had satisfied the requirements stipulated by the Agency at the End-of-Phase II meeting (November 9, 1998). Novartis was asked to study at least 300 subjects with 12 months of exposure to ERL080 and they had enrolled a total of 429 patients that met these criteria [295 from the core studies B301 and B302, 107 (ex-MMF) from the extension of those studies, and 27 from Study 0107]. Novartis noted that they would have 577 patients with 6 months of ERL080 exposure. Further, Study 0107, designed to look at the relative gastrointestinal (GI) tolerability of ERL080 compared to MMF, would provide additional safety data (although it would not be finished and analyzed before submission of the proposed NDA). *The FDA inquired when Study 0107 would be finished and how many subjects Novartis planned to enroll into this trial. The Agency also pointed out this study's increased importance in light of the latest data on ERL080's relative bioavailability.*

Novartis stated that they did not know when 0107 would be finished because of the slow rate of subject enrollment. For patients to get into this study, they had to have at least 2 weeks of MMF exposure along with GI intolerance and undergo a week of dechallenge on a half-dose of MMF before being randomized to either ERL080 or MMF. Unfortunately, many of those who were eligible from studies B301 and B302 were not caught in time and the competing interests of other clinical trials also limited the pool of eligible patients. Novartis planned to enroll 75 subjects per arm and had only a total of 110. The sponsor reiterated their intention of including the safety data from this trial with their NDA. *The Agency noted that the proposed NDA appeared fileable but the original assumptions concerning ERL080's safety profile have to be put aside and the pivotal studies, B301 and B302, might be underpowered to detect a clinically significant difference in toxicity between Novartis' drug product and MMF. This issue would not preclude filing but might affect the action made after a thorough review of the application. The FDA would certainly welcome other sources of safety data besides Study 0107, although papers from the literature usually do not provide the types of information the Agency requires for review.*

Novartis acknowledged these comments, and they presented the preliminary safety data that had been collected so far. For Study B301, there was a greater proportion of patients with longer cold ischemia times and poorer panel reactive antibodies in the ERL080 arm. Comparable efficacy was seen in both treatment arms as well as a similar incidence of adverse events, including infections and neoplasms. There were similar hematologic values between both treatments. More MMF-treated patients discontinued or underwent dose reduction because of GI intolerance. As for Study B302, the 12-month datasets had just been locked and Novartis' initial look had established that the results were very similar to those stated above for B301. *The Agency noted that the patient populations for these two studies were different in composition (B302 only enrolled subjects who were tolerant to MMF). Also, the data did not indicate that ERL080 had a statistically significant advantage in terms of GI tolerance over MMF. The FDA then asked about the quantity and quality of the data Novartis had comparing safety and efficacy between African-Americans and Caucasians. The Agency further asked if Novartis had any information on the pharmacokinetic differences between these two ethnic groups.*

Novartis agreed with the Agency's statements and noted that these pivotal studies were not adequately designed to detect a difference in the frequency of GI effects associated with these drug products. Novartis expressed their hope that Study 0107 would provide more information on this important safety parameter. As for the ethnic groups mentioned above, Novartis stated their disappointment that certain centers did not enroll as many African-Americans as they had originally promised (there were a total of 92 such subjects in B301 and B302). A 16-subject, food-effect study was conducted in Sao Paulo, Brazil, but Novartis was not sure that these individuals were in the same ethnic group as African-Americans. Novartis pledged to do the necessary subgroup analyses using the data available on these different ethnic groups. *The Agency suspected true differences in MPA pharmacokinetics, safety, and efficacy not only between different ethnic groups, but also across age groups and genders. The FDA then inquired about the protein binding characteristics of ERL080.*

Novartis noted it would be difficult to elucidate any of these important differences (ethnicity, age, and gender) with the paucity of data on hand. They stated that a great deal of experience with marketed MMF had already been accumulated before the ERL080 development program began. As for the protein binding characteristics, the sponsor stated that ERL080 was usually around 95 – 97% protein bound at therapeutic levels (this data would be available in the NDA). Novartis then asked if using free MPA as a marker to track differences in these various subpopulations would be useful to review. *The Agency was not certain how useful it would be to track free MPA levels in the subjects treated with ERL080 and MMF but any submitted analyses based on this marker would not be turned down (however, its relevance would have to be substantiated). The FDA then inquired if any studies using this method been initiated.*

Novartis noted that they have not started any such studies but [ ] published research using free MPA in this manner.

3. Novartis [ ] The side effects associated with both drugs were very similar; however, GI toxicities forced them to terminate the study at Week 3. While this study did not look at the highest dosage level administered to patients (2x 360-mg tablets), the results were similar to those from a Hoffmann-LaRoche study involving MMF. Novartis stated that they believe the result of the p53± assay will support approval of ERL080, despite a negative result in the benzene positive control group, Novartis felt that the data supported ERL080's registration. *The FDA asked where the p53± assay was performed; they noted information on this assay indicated that 100 mg/kg PO was not enough benzene for a positive control). They stated that this drug product would be labeled as a carcinogen whether the study is repeated or not. If Novartis decided to perform the p53± assay again, the Agency recommended that they submit the protocol to the Executive CAC for review. Novartis was asked to submit the complete, audited study report for the p53± assay and the standard rat carcinogenicity assay prior to submission of the NDA (both studies will need to be reviewed by the Executive CAC).*

   Novartis noted that their Basel, Switzerland, group had performed this assay and they knew about the limitations of the "ILSI Protocol." They agreed with the possibility that not enough benzene had been used in the positive control animal group and noted that there were no historical data on how much should be used. Novartis agreed to submit the final study report from the performed assay.

4. Novartis summarized the outcome of their *in vitro* dissolution profile study for ERL080 and noted that it had failed the F_2 similarity factor at rpm in this evaluation (as well as the average difference per time point). At the FDA's inquiry, Novartis stated they would recommend a 50-rpm dissolution speed for this drug product. The sponsor described [ ] noted that this could lead to a difference in the release characteristics of the two tablet strengths, 180 and 360 mg, which were different shapes and sizes. Novartis inquired as to whether the FDA accepted the current data

for a biowaiver application for the 180-mg tablets even though not all of the criteria were met. *The Agency stated that this would be a review issue. The FDA inquired as to whether all the data points were used in their calculation of the F_2 calculations. The Agency stated that not more than one data point after reaching — dissolution may be used in the calculation of F_2 for both test and reference product. The FDA also asked that the sponsor re-evaluate* [redacted]

Novartis noted that even if these changes were made to the analysis, the F_2 similarity factor would only change by — Novartis then asked the Agency for any other advice, technical or otherwise, that could help solve this problem. *Although the 360-mg tablet could be used as a reference, the FDA advised Novartis to look at the Immediate Release Guidance document and focus on the estimated method of calculating F_2. They noted that the sponsor already had a number of data points for the 180-mg tablet and although the Agency could not commit to granting a biowaiver for this strength, Novartis had enough data to help the Division make this determination as long as the sponsor completed the statistical analysis. The Agency suggested using* [redacted]

Novartis acknowledged the FDA's advice. The sponsor also noted [redacted]; however, they would consider using it in an attempt to resolve the F_2 problem.

5. **Does the FDA agree that the sources of data described in the clinical pharmacology section (both Novartis studies and data from other sources) support the content of the clinical pharmacology component of the U.S. package insert?**

Novartis elaborated on this question from their background package by asking if there were any "inappropriate" sources of data that they should avoid. *The Agency noted that they were not aware of any such data sources, although a better question would be whether the initial submission would be fileable or not. Novartis was then asked to provide a summary of each "Clinical Pharmacology" subsection (e.g., references Novartis planned to use for hepatic insufficiency), which would help the Division answer this question.*

Novartis agreed to provide this information.

6. **Does the Agency agree that the clinical development program is sufficient to support the registration of Myfortic™?**

Novartis asked whether their proposed marketing application could be filed and specifically asked about the adequacy of the overall number of subjects treated with ERL080 as well as the adequacy of the various patient subpopulations. *The FDA stated that the proposed NDA could be filed. However, the differences in MPA exposure between ERL080 and MMF, which were not addressed in Study B302, were a major concern for the Agency. It was difficult to predict if the sponsor would be able to provide enough data on a sufficient number of patients to convincingly*

establish the safety of this drug. It would behoove Novartis to submit any and all data on the long-term effects of exposing patients to such high levels of MPA, especially given the inadequate amount of PK/PD data on ERL080 (due in part to the high variability seen in what Novartis had provided so far). The FDA was also concerned about differences in MPA exposure in various subpopulations.

Novartis mentioned the normally high variability in MPA exposures in patients treated with 1 gram twice daily of MMF. Dr. Van Gelder has published data that indicated a mean $AUC_{(0\text{-}12h)}$ closer to 50 μg*hr/mL, not the usual 30-40 μg*hr/mL, with an upper limit close to 70 μg*hr/mL. *The FDA noted that Dr. Van Gelder's study would differ from Novartis' studies in patient selection, dosage adjustment, and assays. Additionally, the raw data supporting such a finding would have to be reviewed before it could be accepted as valid. The Agency would also want to see an analysis of acute rejections and PK/PD based on Dr. Van Gelder's data.*

Novartis asked if they could use the graft loss and death endpoint without incorporating the data from those individuals who were lost to follow-up. They stated that this point had been agreed upon by the Division at the End-of-Phase II meeting and was acceptable to the European authorities. *The FDA asked Novartis to include the patients who were lost to follow-up as failures for the primary endpoint of graft loss and death since it is the FDA's usual practice to always consider these individuals as failures in the intent-to-treat analysis.*

Novartis said that they would like to focus on the real cases of graft loss and death worldwide when composing this primary endpoint but include those subjects lost to follow-up as part of a secondary analysis. *The Agency strongly urged all sponsors to include these individuals in their primary endpoint of graft loss and death. This is consistent with the advice that the Agency has provided on clinical trials for other products in transplantation.*

[Post-Meeting Note: There was no discussion on how to treat patients who were lost to follow-up at the End-of-Phase II meeting. Please see our November 9, 1998 minutes for this meeting.]

7. **Does the Agency agree with the adequacy of the proposed format and content of the Clinical portion of the NDA?**

Novartis elaborated on this question by pointing out that not all case report forms (CRFs) for serious adverse events would be submitted for review. [redacted], but since this would be a 505(b)(2) application, they felt these CRFs would not be necessary. Novartis pledged to provide a detailed comparative safety profile, along with the SAE incidence rates by body system, for review. They also noted that the data from Studies 301 and 302 would not be pooled. *While reiterating their concerns about the difference in MPA exposure between ERL080 and MMF, the FDA noted that these CRFs were necessary for a thorough review. In general, these subjects have very complicated medical histories and it will be important to have all of the details on those individuals who experienced SAEs.*

Novartis asked if they could provide specific CRFs whenever the medical officer required them instead of making them all available at the time of submission. After their receipt, the sponsor noted that it would take them approximately 1 – 2 weeks to submit this information. *The Agency was not certain this would be an adequate solution and sought reasons for Novartis' inability to make all SAE CRFs available from the start.*

Novartis stated that they did not have the resources to accomplish this task. Novartis then noted that 50% of the SAE CRFs and 20% of the CRFs involving an infectious disease were currently in their electronic database. The sponsor inquired about the possibility of making their proposed NDA a "rolling submission" so that there would be enough time to enter the rest of the necessary CRFs into their database. *The FDA noted that the PDUFA goal dates were virtually immovable and there was only so much time for waiting on information that should already be in the NDA. The Agency then stated that they would consider Novartis' "rolling submission" proposal and get back to them later on this issue.*

Novartis noted that they would explore various solutions to the problem and agreed to return to this issue later.

[Post-Meeting Note: The term "rolling submission" in this context was not a reference to the guidance on Fast Track Designation or the regulations concerning drugs intended to treat life-threatening and severely-debilitating diseases.]

8. **Does the FDA agree with the wording of the indication as follows: '**

Novartis wished to have more feedback from the Agency on the adequacy of their proposed indication. *The FDA noted that the term* *was incorrect and in its place Novartis should use "cyclosporine." In general, the specific wording of an indication would be worked out along with the rest of the label during the review. However, the Agency stated that the* *phrase had not been previously used in any other immunosuppressant labels, and they would have to carefully consider whether it would be warranted in this instance.*

Novartis acknowledged these statements.

9. The Agency requested that Novartis include all of the raw data in their proposed NDA along with the derived datasets. Additionally, the FDA reminded Novartis that ERL080/Myfortic™ would be considered an "old antibiotic" and that the guidance entitled, "Repeal of Section 507 of the Federal Food, Drug, and Cosmetic Act (May 1998)" should be consulted if the sponsor has any questions about how this affected their marketing application. *Novartis agreed to the request for raw data and acknowledged the Agency's remarks regarding the "old antibiotic" issue. Finally,*

Novartis asked the FDA if there was a chance that their application would be presented to an Advisory Committee.

The Agency noted that this issue would be addressed at the time of filing the sponsor's NDA.

Action Items:

1. Novartis agreed to provide a summary of the data and references that would be used to write the "Clinical Pharmacology" section.
2. Both Novartis and the FDA agreed to revisit the issue of SAE CRFs.
3. Novartis agreed to include all of the raw data in their NDA.
4. Novartis agreed to submit the final study report for the performed p53± assay.

Meeting Chairperson: *{See appended electronic signature page}*

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF MEETING MINUTES

Meeting Date: November 9, 1998

Time: 1:00 p.m.

Location: Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
9201 Corporate Blvd., S400
Rockville, MD 20850

Application: IND 57,005 (Serial No. 000)

Type of Meeting: End-of-Phase II (Type B)

Meeting Chair: Mark Goldberger, M.D., M.P.H., Director, DSPIDP

Meeting Recorder: D. Laurie Bernato, R.N., MN, Regulatory Project Manager

FDA Attendees, Titles, and Office/Division:

Thomas Hassall, RPh., Assistant Director of Regulatory Affairs, ODE IV
Renata Albrecht, M.D., Deputy Director, DSPIDP
Marc Cavaillé-Coll, M.D., Ph.D., Medical Team Leader
Joyce Korvick, M.D., Medical Officer
Kenneth Hastings, Ph.D., Pharmacology/Toxicology Team Leader
Stephen Hundley, Ph.D., Pharmacology/Toxicology Reviewer
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Nancy Silliman, Ph.D., Statistical Team Leader
Karen Higgins, Ph.D., Statistical Reviewer
Norman Schmuff, Ph.D., Chemistry Team Leader
Ellen C. Frank, R.Ph., Chief, Project Management Staff
Matthew Bacho, Project Manager

External Constituent Attendees and titles:

Somesh Choudhury, Ph.D., Clinical Pharmacokinetist
Michael C. Hall, M.D., Director, Clinical Research
Lawrence Hauptman, Ph.D., Director, Regulatory Expert
Peter Heining, Ph.D., Head of Clinical Laboratories
Daniel Lapadula, Ph.D. Director, General Toxicology

IND 57,005
End of Phase 2 Meeting
November 9, 1998
Walter Kremers, Ph.D., Project Statistician
Edgar Mueller, M.D., Senior Clinical Research Physician
Jutta Riedl, Ph.D., Technical R&D
Robert Schmouder, M.D., Clinical Pharmacology Physician
Manfred Schulz, Ph.D., Project Manager
Henry Weidmuller, R.Ph., Assistant Director, Drug Regulatory Affairs
Sharon Olmstead, Assistant Director, Regulatory Liaison

Background: Novartis Pharmaceuticals Corporation requested a pre-IND consultation regarding ERL080A on April 24, 1998. FDA provided advice via letter dated August 5, 1998. This enabled Novartis to make substantive changes to the drug's development program and harmonize it with their efforts in Europe. The subsequent IND for this compound for prophylaxis of acute transplant rejection in patients receiving allogenic renal transplants was submitted for review on October 1, 1998. Novartis requested an End-of-Phase II meeting in this original IND submission.

Meeting Objectives:

1. Novartis proposed an abbreviated clinical and toxicological program for ERL080A that would be supported by published literature.

2. Novartis wanted to discuss the additional data involving tolerability, a demonstration of bioequivalent exposure between the active and inactive moieties (mycophenolic acid and MPA glucuronide), and the bioequivalent Cmax of MPA glucuronide.

3. Ultimately, Novartis was seeking FDA approval of its development program, which would be used to obtain marketing authorization for ERL080A.

Discussion Points:

CLINICAL PROGRAM

1. Novartis proposed two Phase III clinical studies (i.e., one conversion study and one study in *de novo* renal transplant recipients) for obtaining NDA approval of ERL 080A for the indication "prophylaxis of acute transplant rejection in-patients receiving allogenic renal transplants". They intend to enter Phase III without prior dose-finding studies and will refer to published CellCept® data for dose and dosing interval to be used in the Phase III trials. This is based upon the results of their study ERLW /152 which showed that ERL080A and CellCept® deliver bioequivalent exposure (AUC) of both the active moiety, mycophenolic acid (MPA), and the solitary metabolite, mycophenolic acid glucuronide (MPAG).

It is acceptable to FDA to proceed as outlined above. Given the experience with mycophenolic acid moiety, there is little reason to expect a difference in efficacy. However, it is important to study a large enough to document similar efficacy and especially safety of this product.

2. Novartis proposed the combined endpoint of incidence of acute biopsy proven rejection graft loss or death at six months following transplantation as the primary efficacy endpoint

FDA noted that this is generally acceptable; however, demonstration of equivalence with CellCept® at 6 months is contingent upon demonstration that death and graft loss at 12 months is also similar between treatment arms. This suggests a co-primary endpoint.

3. Novartis proposed that the therapeutic equivalence between ERL080A and CellCept® be defined as the same incidence of acute biopsy proven rejection, graft loss or death at six months (CI+ 12%, 85% power) with comparable safety protocol.

FDA noted that this is clinically acceptable given the expected incidence rate for the primary endpoint. Sample sizes similar to that proposed are obtained when the CI and power are varied to 10% and 90%, respectively.

4. Novartis stated [redacted]

Since Study B 302 has safety as its primary endpoint, this study would be viewed as being able to define the statistically significant difference in GI toxicity. Study B 301 would be supportive, and because of the multiplicity of safety endpoints, no statistical value would be able to be placed upon the difference. This would be a qualitative finding.

5. Narratives will be written according to FDA guidelines for clinically significant lab abnormalities or adverse events as defined in the study protocols. Novartis proposed that no narratives would be written for deaths and SAEs definitely unrelated to study medications and for trivial adverse event dropouts. In addition, they also proposed that no narratives be written for rejection episodes because this is a common SAE for this indication and drug class. Novartis requested FDA feedback on their proposal for handling patient narratives.

FDA stated that they would like to receive narratives for death and SAEs including rejection. It was noted that it is very difficult to ensure that potential bias regarding relatedness of an event does not obscure important safety issues.

TOXICOLOGY PROGRAM

6. Novartis inquired whether they could avoid performing any regulatory acute or chronic animal toxicity studies with ERL080A.

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End of Phase III Meeting
November 9, 1998

FDA agreed that this would be possible. However, FDA suggested a study using a non-rodent model (e.g. dogs for nine months) comparing the proposed formulation (enteric coated capsules) with CellCe pt® to look at GI toxicity. This data could then be used to support clinical results.

7. Novartis stated that they feel that no teratogenic rabbit studies would be required because of the clear results in rats and the available literature on this subject. They requested FDA agreement.

   FDA agreed.

8. Novartis asked whether the same carcinogenicity and/or genotoxicity wording in the current CellCept ® label could be used for ERL080A if carcinogenicity and genotoxicity study results are identical.

   FDA stated that only Novartis study results should be put into any future label.

9. Novartis noted that conflicting data are available for genotoxicity of MMF and MPA. They requested FDA comments on this issue.

   The FDA and Novartis agreed that the results from the Mouse Lymphoma Assay (L5178Y cells-Thymidine Kinase (tk) locus) indicated metabolic activation was required for genotoxicity. The current understanding of mycophenolate metabolism is inconsistent with metabolic activation as a requisite for genotoxic activity. There was general agreement that Novartis should explore the metabolic profile for mycophenolate produced by the rodent liver S-9 activation system that is commonly used in genotoxicity assays. The goal is to identify the metabolite responsible for genotoxicity. An additional comparison between the mycophenolate metabolite pattern from the S-9 activation system and human liver slices would be beneficial in assessing the relevance of the Mouse Lymphoma genotoxicity results.

10. Novartis inquired whether a submission of the carcinogenicity studies after the NDA is sent in (i.e. as a Phase IV commitment) would be acceptable.

    FDA noted that this would be acceptable and reminded Novartis that the protocol(s) would have to be reviewed and passed by the CAC. The transgenic model proposal would also have to go before the same committee (since the genotoxicity data is equivocal this plan would probably be acceptable). Both protocols SN003 and SN 006 will need to go before the CAC.

11. Novartis proposed to do the following to assess the reproductive toxicology of ERL080A:

    a. A study on embryo-fetal development in rats

    b. A 13-week toxicity study in rats (histopathology of reproductive organs to assess effects on male fertility)

c. A combined study on male and female fertility.

FDA noted that the above would be sufficient.

CLINICAL PHARMACOLOGY PROGRAM

12. Novartis noted that they plan to proceed to the Phase III study of ERL080A utilizing the 360 mg. enteric coated formulation.

FDA noted that it would be acceptable to use the 720-mg. dose in Phase III.

13. Novartis proposed that the published data on the distribution, metabolism, and excretion of MPA be sufficient to support the further development of ERL080A.

FDA accepted the equivalency of ERL080A and MMF metabolism that is demonstrated by bioequivlaent MPAG pharmacokinetics. In order to use the published data to further support ERL080A labeling, the raw data from these studies would be required.

14. Norvartis noted that they plan to forego studies on the use of ERL080A in patients with renal insufficiency since a large body of information is available on the pharmakokinetics of plasma mycophenolic acid in patients with different degrees of renal insufficiency. They plan to present adequate interpretation of these studies to ERL080A. They inquired whether this is acceptable to the FDA.

FDA agreed to accept the published MMF data on renal/hepatic insufficiency but requested that Novartis submit a plan for providing raw data from these studies for review. If the FDA does not find this data acceptable, they would need to consider conducting a study in these populations.

15. Novartis noted that they do not plan to study the use of ERL080A in patients with hepatic insufficiency since there are several clinical studies that have measured the pharmakokinetics of plasma mycophenolic acid in this population. They inquired whether this was acceptable to the FDA

Again, the FDA requested the raw data from these studies. If this data were found not to be acceptable, Novartis would need to consider conducting a study in both the renal and hepatic insufficiency groups.

16. Novartis proposed that previous data has shown dose proportional exposure of plasma mycophenolic acid after oral administration of mycophenolic acid. Also, the data obtained from ERLW151 and ERLW152 demonstrates that ERL080A (400mg. dose vs. 720mg, respectively) manifests dose proportionality of C max and AUC. This comparison is quite similar to that of MMF (500mg vs.1000mg, repectively). The sponsor proposes that these data are sufficient to

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support ERL080A dose proportionality.

The FDA agreed with this proposal.

17. In order to characterize the pharmakokinetics of ERL080A in pediatric renal transplant patients, Novartis requested FDA guidance regarding the use of these compounds in this patient group.

    In order to characterize the pharmacokinetics of ERL080A in renal pediatric transplant patients, the FDA requested a single dose study in two parallel groups (ages 5-10 and 10-16). This study would include appropriate numbers of patients in each age range (i.e., 12-16 per age group). It was agreed that the study should include a reasonable representation of age mix within these two groups.

18. FDA expressed concern about the amount of sodium that patients might receive, especially if they have to receive high doses. Novartis indicated they would consider this issue and examine patients, especially those on high doses, to determine whether sodium levels are elevated and any significance.

19. FDA recommended to the sponsor that a dissolution specification and method be established at this stage in the development of ERL 080A.

CHEMISTRY

20. Novartis agreed to obtain comparative dissolution data [
    ]

22. Novartis proposed and FDA agreed that the use of locking capsules would sufficiently discourage opening of the capsules and aid in maintaining blind.

23. Novartis agreed [
    ]

Mark Goldberger, M.D., MPH, Div. Director DSPIDP

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cc:
Div. File
Original File IND 57,005
HFD-590/Div.Dir./Goldberger
HFD-590/MO/Korvick ✓
HFD-590/BioPharm/Meyer
HFD-590/CPMS/Frank
HFD-590/PM/Drafter/Bernato
HFD-590/PM/Drafter/Bacho

Distribution:
HFD-590/MO/Korvick ✓
HFD-590/Stat.TL/Silliman
HFD-590/Stat/Higgins
HFD-590/BioPharm.TL/Ajayi
HFD-590/BioPharm/Kumi
HFD-590/Chem.TL/Schmuff
HFD-590/Chem./Seggel
HFD-590/PharmToxTL/Hastings
HFD-590/PharmTox/Hundley
HFD-590/PM/Bacho ✓
HFD-590/PM/Bernato ✓

9 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling