

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**50-791**

**Chemistry Review(s)**

**NDA 50-791**

**Myfortic (mycophenolic acid) Delayed-Release Tablets**

**Novartis Pharmaceutical Corporation**

**Ramesh Sood, Ph.D.  
Division of Special Pathogen and Immunological Drug  
Products, HFD-590**

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# Chemistry Review Data Sheet

1. NDA 50-791
2. REVIEW #: 2
3. REVIEW DATE: January 14, 2004
4. REVIEWER: Ramesh Sood, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	30-Apr-2003
Amendment	23-Jun-2003

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	8-Oct-2003
Amendment	26-Nov-2003
Amendment	11-Dec-2003
Amendment	17-Dec-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation  
Address: One Health Plaza  
East Hanover, NJ 07936-1080  
Representative: M. Daniel Gordin, Ph.D.

## CHEMISTRY REVIEW

### Chemistry Review Data Sheet

Telephone: 862-778-4784

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Myfortic
- b) Non-Proprietary Name (USAN): Mycophenolate sodium
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 2
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: The listed drug that forms the basis of this 505(b) application is Roche Pharmaceuticals Inc's drug CellCept (mycophenolate mofetil) Tablets, 500 mg, NDA 50-723. The listed drug is an immediate release formulation of mycophenolate mofetil compared to the current application where the formulation is delayed release and the active moiety is sodium salt of mycophenolate.

10. PHARMACOL. CATEGORY: Immunosuppressant. For the prophylaxis of organ rejection in patients receiving allogenic renal transplants.

11. DOSAGE FORM: Delayed release tablets

12. STRENGTH/POTENCY: 180 mg and 360 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

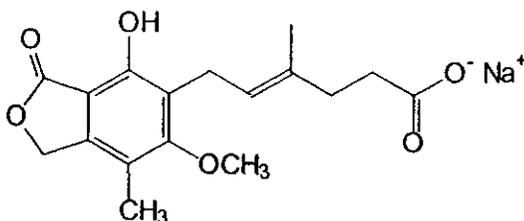
### 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

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

CAS Registry: 24280-93-1 (free acid).

Molecular Formula: C<sub>17</sub>H<sub>19</sub>O<sub>6</sub>Na

Molecular Weight: 342.32



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II			1	Adequate	12/22/03	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

7 - Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	57,005	
NDA	50-722	CellCept 250 mg capsules, Roche, approved May 3, 1995
NDA	50723	CellCept 500 mg tablets, Roche, approved June 19, 1997.
NDA	50-758	CellCept 500 mg, injection, Roche, approved August 12, 1998.
NDA	50-759	CellCept suspension, 200 mg, Roche, approved Oct 1, 1998.

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/a		
EES	Acceptable	10/2/03	
Pharm/Tox	N/a		
Biopharm	N/a		
LNC	N/a		
Methods Validation	To be submitted		
DMETS			
EA	N/a		
Microbiology	N/a		

## The Chemistry Review for NDA 50-791

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, the NDA is recommended for approval. The firm has satisfactorily responded to all the comments provided by the Agency in their October 9, 2003 letter.

##### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

#### II. Summary of Chemistry Assessments

##### A. Description of the Drug Product(s) and Drug Substance(s)

**Drug Substance:** Mycophenolate sodium is semisynthetic drug substance. The manufacturing of [ ] mycophenolic acid [ ] is described in DMF [ ] The DMF was found to be deficient and the comments were sent to the DMF holder. The [ ] product is then [ ] by the NDA holder. The sodium salt is white to off-white, crystalline powder. The drug substance [ ]

[ ] quality of the drug substance is ensured through specification that include acceptance criteria for assay, impurities, identification and particle size. The drug substance is chemically very stable under storage conditions. However, it is susceptible to degradation when exposed to light and it is also sensitive to moisture. The drug substance is stored protected from light and moisture. The requested and granted re test period for the drug substance is [ ]

*In the second review cycle, we were able to tighten the limit for total impurities and include limit for microbial contamination to improve the quality of the drug substance. The HPLC assay and impurity procedure was also improved by adding additional system suitability criterion.*

**Drug Product:** Myfortic is delayed-release tablets that are formulated in 180 mg and 360 mg strengths. The inactive ingredients are colloidal silicon dioxide, crospovidone, lactose, starch, magnesium stearate and povidone. The drug product manufacturing [ ]

## CHEMISTRY REVIEW

### Executive Summary Section

]. The acidic phase dissolution acceptance criterion of NMT — dissolved in 120 minutes ensures that the tablets stay intact in stomach. The final commercial formulation is same as used during clinical studies. The drug product was found to be stable when exposed to light, however, it still needs to be protected from moisture.

*For the drug product as well in the second review cycle, we were able to convince the firm to add a limit for total impurities and include limit for microbial contamination to improve the quality of the drug product.*

#### **B. Description of How the Drug Product is Intended to be Used**

Myfortic is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids. The recommended dose is 720 mg administered twice daily taken with or without food. There are no dose adjustments prescribed for patients with renal or hepatic impairments. The drug is being supplied in 360 and 180 mg strengths. It appears that the lower strength of 180 mg is being supplied for dose adjustment that may be needed to manage some side effects. Limited pharmacokinetic data are available for pediatric renal transplant patients but no dose adjustment for any special population has been proposed. The product will be supplied in the USA in [ ] bottles with [ ] CRC plastic caps ( 120 tablets of 180 mg strength) and in [ ] bottles with [ ] CRC plastic caps (120 tablets of 360 mg strength). The requested expiration period of 36 month is supported by the stability data, however, the firm was been asked to provide missing [ ] time point data for one batch of each strength. The requested data was submitted by the firm in their later amendment. The stability data show that the drug is stable under storage conditions without any increase in degradation products over the storage period. The product is stored at 25° C protected from moisture and dispensed in tight containers.

#### **C. Basis for Approvability or Not-Approval Recommendation**

The firm has adequately addressed all the CMC deficiencies communicated to them on October 9, 2003.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Chemist: Ramesh Sood, Ph.D./ January 14, 2004  
ChemistryTeamLeader: Norman Schmuff, Ph.D.  
ProjectManager: Rebecca Saville

#### **C. CC Block**

19 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Ramesh Sood  
2/23/04 03:03:18 PM  
CHEMIST

Norman: Here is the final review for Myfortic.

Norman Schmuff  
2/26/04 06:33:08 AM  
CHEMIST

**NDA 50-791**

**Myfortic (mycophenolate sodium) Delayed-Release Tablet**

**Novartis Pharmaceutical Corporation**

**Ramesh Sood, Ph.D.  
Division of Special Pathogen and Immunological Drug  
Products, HFD-590**



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1. NDA 50-791
2. REVIEW #: 1
3. REVIEW DATE: July 10, 2003
4. REVIEWER: Ramesh Sood, Ph.D.
5. PREVIOUS DOCUMENTS: N/A

Previous Documents

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original Submission

30-Apr-2003

Amendment

23-Jun-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Address: One Health Plaza  
East Hanover, NJ 07936-1080

Representative: M. Daniel Gordin, Ph.D.

Telephone: 862-778-4784

8. DRUG PRODUCT NAME/CODE/TYPE:

## CHEMISTRY REVIEW

### Chemistry Review Data Sheet

- a) Proprietary Name: Myfortic
- b) Non-Proprietary Name (USAN): Mycophenolate sodium
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 2
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: The listed drug that forms the basis of this 505(b) application is Roche Pharmaceuticals Inc's drug CellCept Tablets, 500 mg, NDA 50-723. The listed drug is an immediate release formulation of mycophenolate mofetil compared to the current application where the formulation is delayed release and the active moiety is sodium salt of mycophenolate.

10. PHARMACOL. CATEGORY: Immunosuppressant. For the prophylaxis of organ rejection in patients receiving allogenic renal transplants.

11. DOSAGE FORM: Delayed release tablets

12. STRENGTH/POTENCY: 180 mg and 360 mg.

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

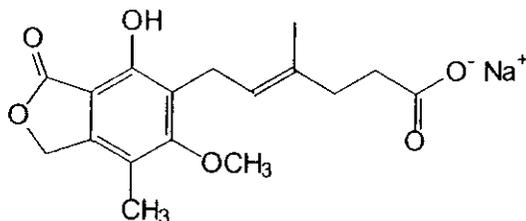
(E)-6-(4-hydroxy-6-methoxy-7-methyl-3-oxo-1,3-dihydroisobenzofuran-5-yl)-4-methylhex-4-enoic acid sodium salt  
CAS Registry: 24280-93-1 (free acid).

# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

Molecular Formula: C<sub>17</sub>H<sub>19</sub>O<sub>6</sub>Na

Molecular Weight: 342.32



### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate	7/10/03	
	III			7	N/A		See deficiencies
	III			7	N/A		See deficiencies
	III			7	N/A		See deficiencies
	III			7	N/A		See deficiencies
	III			7	N/A		See deficiencies

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

#### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
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# CHEMISTRY REVIEW

## Chemistry Review Data Sheet

IND	57,005	
NDA	50-722	CellCept 250 mg capsules, Roche, approved May 3, 1995
NDA	50723	CellCept 500 mg tablets, Roche, approved June 19, 1997.
NDA	50-758	CellCept 500 mg, injection, Roche, approved August 12, 1998.
NDA	50-759	CellCept suspension, 200 mg, Roche, approved Oct 1, 1998.

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/a		
EES	Pending		
Pharm/Tox	N/a		
Biopharm	N/a		
LNC			
Methods Validation	Pending		
DMETS			
EA			
Microbiology			

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# The Chemistry Review for NDA 50-791

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, the NDA is recommended as approvable pending satisfactory resolution of the CMC-related deficiencies. The application has many deficiencies with respect to the drug substance and the drug product. It is expected that the firm will be able to address these deficiencies in a satisfactory manner.

#### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Mycophenolate sodium is a semisynthetic drug substance. The manufacturing of [ ] mycophenolic acid [ ] is described in DMF [ ] The DMF was found to be deficient and the comments have been sent to the DMF holder. The [ ] product is then [ ] by the NDA holder. The sodium salt is white to off-white, crystalline powder. The drug substance [ ]

[ ] quality of the drug substance is ensured through specifications that include acceptance criteria for assay, impurities, identification and particle size. The drug substance is chemically very stable under storage conditions. However, it is susceptible to degradation when exposed to light and it is also sensitive to moisture. The drug substance is stored protected from light and moisture. The requested and granted retest period for the drug substance is [ ] [ ]

Drug Product: Myfortic is delayed-release tablets that are formulated in 180 mg and 360 mg strengths. The inactive ingredients are colloidal silicon dioxide, croscopolone, lactose, starch, magnesium stearate and povidone. The drug product manufacturing [ ]

[ ] The acidic phase dissolution acceptance criterion of NMT — dissolved in 120 minutes ensures that the tablets stay intact in stomach. The final commercial formulation is

## CHEMISTRY REVIEW

### Executive Summary Section

same as used during clinical studies. The drug product was found to be stable when exposed to light, however, it still needs to be protected from moisture.

#### **B. Description of How the Drug Product is Intended to be Used**

Myfortic is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids. The recommended dose is 720 mg administered twice daily taken with or without food. There are no dose adjustments prescribed for patients with renal or hepatic impairments. It is not clear why the drug is being supplied in 360 and 180 mg strengths. The 360 mg strength should be able to provide the required dose. Limited pharmacokinetic data are available for pediatric renal transplant patients but no dose adjustment for any special population has been proposed. The product will be supplied in the USA in 1 bottle with 1 CRC plastic caps (120 tablets of 180 mg strength) and in 1 bottle with 1 CRC plastic caps (120 tablets of 360 mg strength). The requested expiration period of 36 months is supported by the stability data, however, the firm has been asked to provide missing 1 time point data for one batch of each strength. The stability data show that the drug is stable under storage conditions without any increase in degradation products over the storage period. The product is stored at 25° C protected from moisture and dispensed in tight containers.

#### **C. Basis for Approvability or Not-Approval Recommendation**

The application is approvable because of several deficiencies related to the manufacturing of the drug substance and the drug product. The respective deficiencies are being communicated to the DMF holder and the applicant.

### **III. Administrative**

#### **A. Reviewer's Signature**

#### **B. Endorsement Block**

Chemist: Ramesh Sood, Ph.D./ July 10, 2003  
ChemistryTeamLeader: Norman Schmuff, Ph.D  
ProjectManager: Yon Yu

#### **C. CC Block**

46 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Ramesh Sood  
2/25/04 11:04:18 AM  
CHEMIST

Norman: Review # 1 was never put in DFS. So here it is.

Norman Schmuff  
2/26/04 06:42:07 AM  
CHEMIST