CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-722/S-007

50-723/S-004

50-759/S-005

CORRESPONDENCE

April 20, 2000

NDA PUBLIC ASSESSMENT

Pharmaceuticals

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

SE5-007 BM

SUBJECT: **NDA 50-722 / S-007 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Pediatric Use Supplement
Response to FDA Request for Information Dated April 13, 2000

Dear Reviewers:

We are acknowledging receipt of your telefacsimile correspondence dated April 13, 2000 and are herein responding to the request for information regarding the pediatric use supplement.

For ease of review, we have reproduced your comments (*in italics*) with our response following:

1. *Please provide us with the date of submission and location within the supplemental NDA of the pilot study MYC2190.*

Study IID/MYC2190/USA was filed in NDA 50-758 for CellCept Intravenous on August 28, 1997 and was included in the pediatric use supplement by cross-reference. Please note that the summary for this study is included in Section 8, Volume 19, Page 7 of this supplement. As discussed with the FDA on January 21, 1999 and summarized in a proposal by Roche on February 1, 1999, a list of all Roche studies incorporated by cross-reference into this supplement are listed on the "Table of Cross-Referenced Roche Studies" located in Volume 7, Page 276, as well as in Volume 19, Page 3.

2. *Could you provide the meaning behind "Master Reference Number" and whether we can use this information to locate specific pieces of information?*

The Master Reference Number, or MRN, is a unique 4-digit number assigned to all Roche documents and published literature references to identify those documents within the dossier. Please note that the Reviewers' Guide which is included in the supplement provides further explanations and examples of how the MRN is used. Furthermore, the Index in Volume 1 lists all studies, summaries, and literature references included in the submission with their respective MRN (example: Section 6, Pharmacokinetics References, Volume 7, Page 297).

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Global Development-Palo Alto
a Division of Syntex (U.S.A.) Inc.

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3. *Please send a data set that includes the outcome/efficacy of CellCept® in pediatric kidney transplant patients in study MYCS2675. Review of the current SAS transport sets does not reveal an "efficacy" file. Although this study is not powered to describe the efficacy of CellCept® in pediatric patients, it is important for us to review outcomes to ensure that the rejection rates are no worse that[than] that which would be expected in this group of patients.*

As requested, we are herein submitting a diskette providing two SAS transport files for efficacy and treatment of rejection. The descriptor files and case report forms with annotations corresponding to the descriptor files are also included on the diskette. The diskette is provided in Attachment 1. A paper copy of the descriptor files and annotated case report forms are provided in Attachments 2 and 3, respectively. Please note that the efficacy outcome of study MYCS2675 is described and discussed in the study report and appendices, as well as in the Application Summary of this supplement.

We appreciate your continued interest and support for the CellCept pediatric program and look forward to working with the Division during the review process of this important label revision for CellCept. Should you have any questions during the course of the review period, please do not hesitate to contact me by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

Carmen R. Rodriguez

Carmen R. Rodriguez, M.Sc.
Regulatory Program Director for CellCept/Zenapax
Roche Global Development

Attachment 1: Diskette
Attachment 2: Paper copy of descriptor files
Attachment 3: Paper copy of annotated case report forms

Cover letter by fax to Mr. Matthew Bacho
Desk copy (1): Mr. Matthew Bacho
Reviewers copies (2)
Archival copy (1)

Via: Fed-Ex

June 16, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd.. 4th Floor
Rockville, MD 20850

NDA SUPPLEMENT
SU
S-007

SUBJECT: **NDA 50-722 / S-007 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Pediatric Use Supplement
Integrated Safety Summary - 4-month Update

Dear Reviewers:

In accordance with 21 CFR 314.50(d)(5), we are providing a safety update for NDA 50-722/ S-007. This update includes data from the pivotal pediatric study MYCS 2675 that supported the supplemental application, and from 2 pediatric patients that were enrolled in the hepatic study MYCS2646. The cut-off date for the database was March 10, 2000.

Copies of the Case Report Forms for patients who died or terminated prematurely for safety related reasons since the cut-off date for the original pediatric ISS (September 20, 1999) and the cut-off date for the 4-month safety update (March 10, 2000) are provided on a CD-ROM accompanying this submission. Within this time period, one patient terminated for a safety related reason (Patient 53061).

Should you have any questions during the course of the review period, please do not hesitate to contact me by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

Carmen R. Rodriguez

Carmen R. Rodriguez. M.Sc.
Regulatory Program Director
CellCept/Zenapax Program

2 desk copies (1 w/CD. 1 w/o CD): Mr. Matthew Bacho via Fed Ex
Archival copy (1): NDA 50-722/S-007
Reviewer copy (1 each): Biopharmaceutics. Clinical. Statistical
Cover letter by fax to Mr. Matthew Bacho

Global Development-Palo Alto
a Division of Syntex (U.S.A.) Inc.

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California 94304-1397

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Roche

NDA [illegible] DMENT

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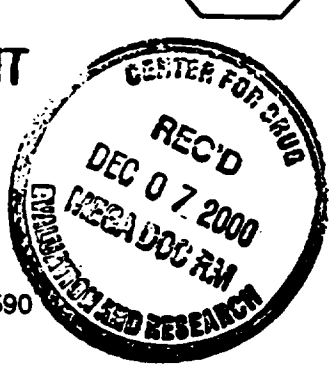
SES-004



Pharmaceutical

December 6, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

SUBJECT: [redacted] **CellCept® 500 mg Tablets (mycophenolate mofetil)**
NDA 50-759/S-005 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)
Response to FDA Request for Study MYCS2675 Rejection Episodes Information

Dear Reviewers:

As requested by Mr. Matthew Bacho via telephone today, we are hereby submitting a copy of the submission to NDA 50-722/S-007, November 30, 2000, to NDA 50-723/S-004 and NDA 50-759/S-005. This submission was in response to the Division's request for Study MYCS2675 rejection episodes information.

Should you have any questions, please do not hesitate to contact me by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

Also for Carmen R. Rodriguez

Carmen R. Rodriguez, M.Sc.
Regulatory Program Director
CellCept/Zenapax Program

Desk copy (1): Mr. Matthew Bacho
Archival copy: NDA 50-723/S-004 (1 copy) and NDA 50-759/S-005 (1 copy)
Cover letter by fax to Mr. Matthew Bacho

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Roche

Pharmaceuticals

December 6, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

NDA S[redacted]ENDMENT

BM
SBS-005

SUBJECT: **NDA 50-723/S-004 - CellCept® 500 mg Tablets (mycophenolate mofetil)**
NDA 50-759/S-005 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)
Response to FDA Request for Study MYCS2675 Rejection Episodes Information

Dear Reviewers:

As requested by Mr. Matthew Bacho via telephone today, we are hereby submitting a copy of the submission to NDA 50-722/S-007, November 30, 2000, to NDA 50-723/S-004 and NDA 50-759/S-005. This submission was in response to the Division's request for Study MYCS2675 rejection episodes information.

Should you have any questions, please do not hesitate to contact me by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

Alice J Lai for Carmen R. Rodriguez

Carmen R. Rodriguez, M.Sc.
Regulatory Program Director
CellCept/Zenapax Program

Desk copy (1): Mr. Matthew Bacho
Archival copy: NDA 50-723/S-004 (1 copy) and NDA 50-759/S-005 (1 copy)
Cover letter by fax to Mr. Matthew Bacho

Global Development-Palo Alto
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Phone: (415) 855-5050

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NDA SUPPL FOR

Roche

Pharmaceuticals

NDA NO. 50-722 REF. NO. 007/el

NDA SUPPL FOR SES 1

December 12, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

SUBJECT: **NDA 50-722 / S-007 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
NDA 50-723 / S-004 - CellCept® 500 mg Tablets (mycophenolate mofetil)
NDA 50-759 / S-005 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

Response to FDA Comments on Proposed CellCept Pediatric Labeling

Dear Reviewers:

We acknowledge receipt of your telefacsimile correspondences dated December 6, 2000 and December 8, 2000 with comments from the clinical pharmacology and medical reviewers on the labeling revisions to the proposed CellCept pediatric USPI. Following are our comments to the reviewers' proposals. For ease of review, a copy of the proposed pediatric label in revision mode is included in Attachment 1.

CLINICAL PHARMACOLOGY: *Pharmacokinetics*: Pediatrics

On December 6, 2000, the clinical pharmacologist proposed revisions to the text (underlined) and the addition of a table as follows:

The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging in age from 1 year to 18 years) receiving CellCept oral suspension at a dose of 600 mg/m2 bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in the following table:

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Mean Computed Pharmacokinetic Parameters for MPA by Age and Time after Allogeneic Renal Transplantation

Age Group (n)	Time	T_{max} (h)	C_{max} (µg/mL)[a]	$AUC_{(0-12)}$ (µg·h/mL)[a]
<2 yrs[b] (6)	Early (Day 7)	3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
< 6yr (17)		1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 – < 12 yrs (16)		0.94 (1.55)	13.1 (6.30)	33.2 (12.1)
12 – 18 yrs (21)		1.16 (0.83)	11.7 (10.7)	26.3 (9.14)
<2 yrs[b] (4)	Late (Month 3)	0.72 (0.28)	23.8 (13.4)	47.4 (14.7)
< 6yrs (15)		0.99 (0.51)	22.7 (10.1)	49.7 (18.2)
6 – < 12 yrs (14)		1.21 (0.53)	27.8 (14.3)	61.9 (19.6)
12 – 18 yrs (21)		0.98 (0.48)	17.9 (9.57)	53.6 (20.3)
<2 yrs[b] (4)	Late (Month 9)	0.60 (0.21)	25.6 (4.25)	55.8 (11.6)
< 6yrs (12)		0.87 (0.48)	30.4 (9.16)	61.0 (10.7)
6 – < 12 yrs (11)		1.12 (0.46)	29.2 (12.6)	66.8 (21.2)
12 – 18 yrs (14)		1.09 (0.52)	18.1 (7.29)	56.7 (14.0)

[a] C_{max} and AUC were adjusted to a dose of 600 mg/m^2
[b] The <2 years is a subset of the <6 year

The studied CellCept oral suspension dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) achieved MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving CellCept capsules at a dose of 1 g bid in the early post-transplant period. There was wide variability in the data, especially in the <2 year-old patients. As observed in adults, early post-transplant MPA AUC values were approximately 45-53% lower than those observed in the later post-transplant period (> 3 months). MPA AUC values were similar in the early and late post-transplant period across the 1-18 year age range.

Roche agrees with the addition of the table and proposes the following revisions to the table and text, as shown on page 8 in Attachment 1:

- Add (±SD) to the title of the table after the word "Mean". Furthermore, add "±" to the standard deviation values already included within the table.
- For clarity, add the lower limit of the age range to the two youngest age groups (i.e. 3 mo-<2 years and 3 mo-<6 years).
- Provide all T_{max}, C_{max}, and AUC values using 3 significant digits.
- Correct the following typographical errors:
  - The number of patients in the Age Group 12-18 years, Late (Month 3) timepoint should be 17 not 21.
  - The standard deviation for T_{max}, Early (Day 7) timepoint, Age Group 6-<12 years should be ±0.546 not 1.55.

We propose to remove the word "studied" from the sentence "The studied CellCept oral suspension dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) achieved MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving CellCept capsules at a dose of 1 g bid in the early post-transplant period."

In reference to the proposed statement "There was wide variability in the data, especially in the <2 year-old patients", Roche wishes to make the following comment:

The extent of variability (%CV) of the pharmacokinetic parameters in pediatric patients appears to be within the range of that observed in other patient populations (i.e. generally 20-50% for AUC and 30-60% for C_{max}). Furthermore, despite the smaller sample size, it is not apparent that the 3 mo-<2 years old patient exhibited greater variability compared to children in the other age groups. Thus, we prefer that the above recommended statement not be included in the label.

On December 8, 2000, the clinical reviewer proposed the following labeling revisions:

CLINICAL STUDIES: Pediatrics

The reviewer asked for Roche to specify the rates of graft loss and death at 12 months in the sentence "The overall biopsy-proven rejection rate at 6 months and the combined incidence of graft loss and patient death at 12 months posttransplant were similar to the rates observed in adult renal transplant patients."

Roche agrees with the inclusion of the rejection rates and proposes the following wording on page 12 in Attachment 1:
The overall biopsy-proven rejection rate at 6 months was comparable to adults. The combined incidence of graft loss (5%) and patient death (2%) at 12 months posttransplant was similar to that observed in adult renal transplant patients.

ADVERSE EVENTS: Pediatrics

a) The Division noted that the rate of leukopenia (24%) appears to be the same as that seen in renal transplant patients in the United States (23.2%).

Roche agrees with this assessment and proposes to remove leukopenia from the list of adverse events which occurred at a higher frequency in the pediatric population as compared to adults.

b) The Division provided the comment "In addition to the 4 events listed in the proposed labeling, we noted that pain, abdominal pain, fever, infection, sepsis, hypertension, vomiting, respiratory tract infection, and pharyngitis were also seen in a higher proportion of pediatric patients."

Roche agrees with the addition of the following adverse events: pain, abdominal pain, fever, infection, hypertension, vomiting, respiratory tract infection, and pharyngitis. We propose to list them by body system as follows (page 28 in Attachment 1):
The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with CellCept oral suspension 600 mg/m^2 bid (up to 1 g bid) were generally similar to those observed in adult patients dosed with CellCept capsules at a dose of 1 g bid with the exception of abdominal pain, fever, infection, pain, sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension, and anemia, which were observed in a higher proportion in pediatric patients.

c) The Division indicated that a comment should be made regarding the occurrence of malignancies in the pediatric studies.

Roche agrees with the recommendation and proposes to add the following wording in **WARNINGS** (page 14 in Attachment 1) and **ADVERSE REACTIONS: *CellCept Oral*** (page 25 in Attachment 1):
In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed.

d) The Division stated "the rate of gastrointestinal hemorrhage should be added to the **PRECAUTIONS: *General*** section."

Roche agrees with the recommendation and proposes the following wording on page 15 in Attachment 1:
In pediatric renal transplant patients, 5/148 cases of gastrointestinal bleeding (requiring hospitalization) were observed.

In addition to the revisions discussed above, we propose the following additional minor changes:
- In **CLINICAL PHARMACOLOGY: Pharmacokinetics:** *Geriatric Use*, we propose to change the heading *Geriatric Use* to *Geriatrics*. Due to the addition of the heading *Pediatrics* in this section, we would like to revise the geriatrics heading accordingly. This revision can be found on page 9 in Attachment 1.
- In **PRECAUTIONS: *Pediatric Patients***, we propose to change the heading **Pediatric Patients** to **Pediatric Use**. This is in accordance with 21CFR201.57(f)(9). In addition, we propose to add "or hepatic" to the revised statement "Safety and effectiveness in pediatric patients receiving allogeneic cardiac or hepatic transplants have not been established." Both revisions can be found on page 20 in Attachment 1.
- In **DOSAGE AND ADMINISTRATION: CellCept Capsules, Tablets, and Oral Suspension:** *Geriatric Use*, we propose to change the heading *Geriatric Use* to *Geriatrics*. Due to the addition of the heading *Pediatrics* in the **DOSAGE AND ADMINISTRATION: *RENAL TRANSPLANTATION*** section, we would like to revise the geriatrics heading accordingly. This revision can be found on page 30 in Attachment 1.

Also enclosed, please find a clean version of the revised labeling proposal for CellCept in Attachment 2. Electronic copies of both the revision version and clean version are provided on the diskette in Attachment 3.

We appreciate your continued support of the CellCept program. Should you have any further questions during the course of the review period, please do not hesitate to contact me by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

Carmen R. Rodriguez

Carmen R. Rodriguez, M.Sc.
Regulatory Program Director
CellCept/Zenapax Program

Reviewer copies w/o diskette: Biopharmaceutics (1), Clinical (1)
4 desk copies (1 w/diskette): Mr. Matthew Bacho
Archival copies (w/diskette): NDA 50-722/S-007 (1), NDA 50-723/S-004 (1), and NDA 50-759/S-005 (1)
Cover letter by fax to Mr. Matthew Bacho

NDA NO. N-722 REF. NO. 0041

NDA SUPPL FOR SE5

Roche

Pharmaceuticals

December 12, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

SUBJECT: **NDA 50-722 / S-007 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
[redacted]- CellCept® 500 mg Tablets (mycophenolate mofetil)
NDA 50-759 / S-005 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

Response to FDA Comments on Proposed CellCept Pediatric Labeling

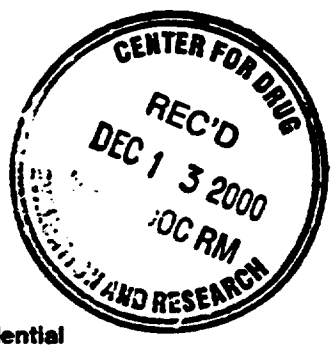
Dear Reviewers:

We acknowledge receipt of your telefacsimile correspondences dated December 6, 2000 and December 8, 2000 with comments from the clinical pharmacology and medical reviewers on the labeling revisions to the proposed CellCept pediatric USPI. Following are our comments to the reviewers' proposals. For ease of review, a copy of the proposed pediatric label in revision mode is included in Attachment 1.

CLINICAL PHARMACOLOGY: *Pharmacokinetics*: Pediatrics

On December 6, 2000, the clinical pharmacologist proposed revisions to the text (underlined) and the addition of a table as follows:

The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging in age from 1 year to 18 years) receiving CellCept oral suspension at a dose of 600 mg/m2 bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in the following table:



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Phone: (415) 855-5050

NDA NO 50-759 REF. NO. 005/BL

NDA SUPPL FOR SES

Roche

Pharmaceuticals

December 12, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

SUBJECT: **NDA 50-722 / S-007 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
NDA 50-723 / S-004 - CellCept® 500 mg Tablets (mycophenolate mofetil)
[redacted] S-005 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)

Response to FDA Comments on Proposed CellCept Pediatric Labeling

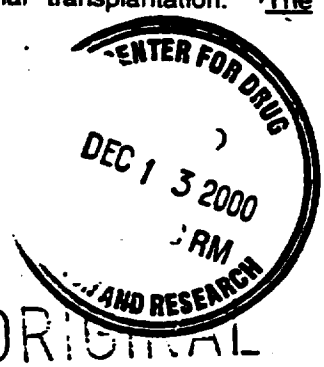
Dear Reviewers:

We acknowledge receipt of your telefacsimile correspondences dated December 6, 2000 and December 8, 2000 with comments from the clinical pharmacology and medical reviewers on the labeling revisions to the proposed CellCept pediatric USPI. Following are our comments to the reviewers' proposals. For ease of review, a copy of the proposed pediatric label in revision mode is included in Attachment 1.

CLINICAL PHARMACOLOGY: *Pharmacokinetics*: Pediatrics

On December 6, 2000, the clinical pharmacologist proposed revisions to the text (underlined) and the addition of a table as follows:

The pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging in age from 1 year to 18 years) receiving CellCept oral suspension at a dose of 600 mg/m2 bid (up to a maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in the following table:



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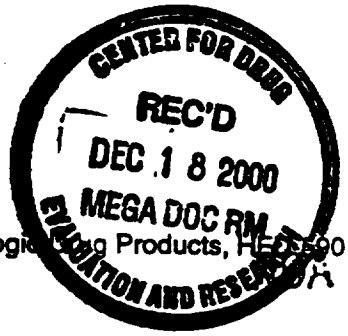
Roche

Pharmaceuticals



December 14, 2000

Division of Special Pathogens and Immunologic [illegible]g Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

BL
SE5-007

SUBJECT: **NDA 50-722 / S-007 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
NDA 50-723 / S-004 - CellCept® 500 mg Tablets (mycophenolate mofetil)
NDA 50-759 / S-005 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)
Pediatric Use Supplement - Final CellCept Labeling

Dear Reviewers:

We acknowledge receipt of your telefacsimile correspondence dated December 14, 2000 with comments from the Division on the labeling revisions to the proposed CellCept pediatric USPI. We agree with the clinical pharmacologist's proposals as detailed in points 1 to 3 of the telefacsimile. These changes have been incorporated in the attached revision and clean versions of the label. (Attachments 1 and 2, respectively.)

In addition, we have also incorporated the following minor revisions to the label.

1. The word "adult" was added to the following sections:
   - **CLINICAL STUDIES:**
     "The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in randomized, double-blind, multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult transplant patients."
     This revision can be found on page 9 of Attachment 1.
   - **DOSAGE AND ADMINISTRATION: *CARDIAC TRANSPLANTATION***
     "A dose of 1.5 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult cardiac transplant patients."
     This revision can be found on page 30 of Attachment 1.
   - **DOSAGE AND ADMINISTRATION: *HEPATIC TRANSPLANTATION***
     "A dose of 1 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult hepatic transplant patients."
     This revision can be found on page 30 of Attachment 1.
2. The revision date of the label (page 35 of Attachment 1) has been updated to December 2000.

Also enclosed, please find electronic copies of both the revision version and clean version on the diskette in Attachment 3.

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a Division of Syntex (U.S.A.) Inc.

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We trust that having reached agreement on the CellCept USPI, no further discussions between Roche and the Division will be necessary and therefore, the teleconference originally scheduled for tomorrow will not be necessary.

We would like to take this opportunity to express our appreciation for your continued support to the CellCept program. Should you have any further questions, please do not hesitate to contact me by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

Carmen R. Rodriguez, M.Sc.
Director of Regulatory Affairs
CellCept/Zenapax Program

Reviewer copies w/o diskette: Biopharmaceutics (1), Clinical (1)
4 desk copies (1 w/diskette): Mr. Matthew Bacho
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Cover letter by fax to Mr. Matthew Bacho

Roche

Pharmaceuticals

December 14, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

NDA S[illegible]ENDMENT
BL
SE5-004

SUBJECT: **NDA 50-722 / S-007 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
NDA 50-723 / S-004 - CellCept® 500 mg Tablets (mycophenolate mofetil)
NDA 50-759 / S-005 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)
Pediatric Use Supplement - Final CellCept Labeling

Dear Reviewers:

We acknowledge receipt of your telefacsimile correspondence dated December 14, 2000 with comments from the Division on the labeling revisions to the proposed CellCept pediatric USPI. We agree with the clinical pharmacologist's proposals as detailed in points 1 to 3 of the telefacsimile. These changes have been incorporated in the attached revision and clean versions of the label. (Attachments 1 and 2, respectively.)

In addition, we have also incorporated the following minor revisions to the label.

1. The word "adult" was added to the following sections:
   - **CLINICAL STUDIES:**
     "The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in randomized, double-blind, multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult transplant patients."
     This revision can be found on page 9 of Attachment 1.
   - **DOSAGE AND ADMINISTRATION: *CARDIAC TRANSPLANTATION***
     "A dose of 1.5 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult cardiac transplant patients."
     This revision can be found on page 30 of Attachment 1.
   - **DOSAGE AND ADMINISTRATION: *HEPATIC TRANSPLANTATION***
     "A dose of 1 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult hepatic transplant patients."
     This revision can be found on page 30 of Attachment 1.
2. The revision date of the label (page 35 of Attachment 1) has been updated to December 2000.

Also enclosed, please find electronic copies of both the revision version and clean version on the diskette in Attachment 3.

Roche Confidential

Global Development-Palo Alto
a Division of Syntex (U.S.A.) Inc.

3401 Hillview Avenue
Palo Alto
California 94304-1397

Phone: (650) 855-5050

ORIGINAL

We trust that having reached agreement on the CellCept USPI, no further discussions between Roche and the Division will be necessary and therefore, the teleconference originally scheduled for tomorrow will not be necessary.

We would like to take this opportunity to express our appreciation for your continued support to the CellCept program. Should you have any further questions, please do not hesitate to contact me by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

Carmen R. Rodriguez, M.Sc.
Director of Regulatory Affairs
CellCept/Zenapax Program

Reviewer copies w/o diskette: Biopharmaceutics (1), Clinical (1)
4 desk copies (1 w/diskette): Mr. Matthew Bacho
Archival copies (w/diskette): NDA 50-722/S-007 (1), NDA 50-723/S-004 (1), and NDA 50-759/S-005 (1)
Cover letter by fax to Mr. Matthew Bacho

Roche

Pharmaceuticals

December 14, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
9201 Corporate Blvd., 4th Floor
Rockville, MD 20850

NDA [illegible]MENT
BL
505-005

SUBJECT: **NDA 50-722 / S-007 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
NDA 50-723 / S-004 - CellCept® 500 mg Tablets (mycophenolate mofetil)
NDA 50-759 / S-005 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)
Pediatric Use Supplement - Final CellCept Labeling

Dear Reviewers:

We acknowledge receipt of your telefacsimile correspondence dated December 14, 2000 with comments from the Division on the labeling revisions to the proposed CellCept pediatric USPI. We agree with the clinical pharmacologist's proposals as detailed in points 1 to 3 of the telefacsimile. These changes have been incorporated in the attached revision and clean versions of the label. (Attachments 1 and 2, respectively.)

In addition, we have also incorporated the following minor revisions to the label.

1. The word "adult" was added to the following sections:
   - **CLINICAL STUDIES:**
     "The safety and efficacy of CellCept in combination with corticosteroids and cyclosporine for the prevention of organ rejection were assessed in randomized, double-blind, multicenter trials in renal (3 trials), in cardiac (1 trial), and in hepatic (1 trial) adult transplant patients."
     This revision can be found on page 9 of Attachment 1.
   - **DOSAGE AND ADMINISTRATION: *CARDIAC TRANSPLANTATION***
     "A dose of 1.5 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult cardiac transplant patients."
     This revision can be found on page 30 of Attachment 1.
   - **DOSAGE AND ADMINISTRATION: *HEPATIC TRANSPLANTATION***
     "A dose of 1 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5 g bid oral (daily dose of 3 g) is recommended for use in adult hepatic transplant patients."
     This revision can be found on page 30 of Attachment 1.
2. The revision date of the label (page 35 of Attachment 1) has been updated to December 2000.

Also enclosed, please find electronic copies of both the revision version and clean version on the diskette in Attachment 3.

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ORIGINAL

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We would like to take this opportunity to express our appreciation for your continued support to the CellCept program. Should you have any further questions, please do not hesitate to contact me by phone at (650) 354-2370 or by fax at (650) 852-1861.

Sincerely,

Carmen R. Rodriguez, M.Sc.
Director of Regulatory Affairs
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Cover letter by fax to Mr. Matthew Bacho

NDA 50-722/S-007
NDA 50-723/S-004
NDA 50-759/S-005

Dear Ms. Rodriguez:

Please refer to your supplemental new drug applications for CellCept® Capsules, Tablets, and Oral Suspension of February 18 and May 19, 2000. Our reviewing clinical pharmacologist would like to make the following changes to your proposed package insert for these drug products (pediatric section of the annotated label, page 2-61):

1) With regard to the table on page 8 of the draft label, we recommend that you eliminate the "±" symbols so that this table appears less busy.

2) In the paragraph following this table on pages 8 and 9, we would still like to see a statement about the wide variability in the data and add the word "mean" in front of "MPA AUC":

   "The CellCept oral suspension dose of 600 mg/m^2 bid (up to a maximum of 1 g bid) achieved mean MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving capsules at a dose of 1 g bid in the early posttransplant period. There was wide variability in the data."

3) All of the other changes were acceptable.

Please let us know if you would like to have a teleconference with the Division (Friday, December 15, 2000 @ 2:30 p.m. EST) to discuss the issues stated above.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

NDA 50-722/S-007
NDA 50-723/S-004
NDA 50-759/S-005

Dear Ms. Rodriguez:

Please refer to your supplemental new drug applications for CellCept® Capsules, Tablets, and Oral Suspension of February 18 and May 19, 2000. Our reviewing medical officer would like to make the following changes to your proposed package insert for these drug products:

1. **CLINICAL STUDIES** ***Pediatrics:***

   One open-label, safety and pharmacokinetic study of CellCept oral suspension 600 mg/m^2 bid (up to 1g bid) in combination with cyclosporine and corticosteroids was performed at centers in the US (9), Europe (5) and Australia (1) in 100 pediatric patients (3 months to 18 years of age) for the prevention of renal allograft rejection. CellCept was well-tolerated in pediatric patients (see ADVERSE REACTIONS), and the pharmacokinetics profile was similar to that seen in adult patients dosed with 1g bid CellCept capsules (see CLINICAL PHARMACOLOGY: Pharmacokinetics). The rate of biopsy-proven rejection was similar across the age groups (3 months to <6 years, 6 to <12 years, 12 to 18 years). The overall biopsy-proven rejection rate at 6 months and the combined incidence of graft loss and patient death at 12 months posttransplant were similar to the rates observed in adult renal transplant patients.

   Please specify the rates of graft loss and death at 12 months in the last sentence above.

2. **PRECAUTIONS** ***Pediatric Use:***

   Based on pharmacokinetic and safety data in pediatric patients after renal transplantation, the recommended dose of CellCept oral suspension is 600 mg/m^2 bid (up to maximum of 1 g bid). Also see CLINICAL PHARMACOLOGY; CLINICAL STUDIES; ADVERSE REACTIONS; and DOSAGE AND ADMINISTRATION.

   Safety and effectiveness in pediatric patients receiving allogeneic cardiac transplants have not been established.

   We find these statements acceptable.

3. **ADVERSE EVENTS** ***Pediatrics:***

   The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with CellCept oral suspension 600 mg/m^2 bid (up to 1g bid) were generally similar to those observed in adult patients dosed with CellCept

capsules at a dose of 1 g bid with the exception that pediatric patients had a higher proportion of diarrhea, anemia, leukopenia and sepsis.

Upon review, we noted that the rate of leukopenia (24%) appears to be the same as that seen in renal transplant patients in the United States (23.2%).

We recommend that you expand the information regarding adverse events in pediatric patients because it is important information for any physician managing a renal transplant recipient. In general, the types of adverse events experienced by children were similar to those seen in adults; however, the frequencies were significantly higher in the former. In addition to the 4 events listed in the proposed labeling, we noted that pain, abdominal pain, fever, infection, sepsis, hypertension, vomiting, respiratory tract infection, and pharyngitis were also seen in a higher proportion of pediatric patients.

A comment should be made regarding the occurrence of malignancies in the pediatric studies.

*The rate of gastrointestinal hemorrhage should be added to the **PRECAUTIONS/ General** section.*

4. **DOSAGE AND ADMINISTRATION** ***Renal Transplantation:*** *Pediatrics*

The recommended dose of CellCept oral suspension is 600mg/m^2 administered twice daily (up to a maximum daily dose of 2 g/10 mL oral suspension). Patients with a body surface area of 1.25 to 1.5 m^2 may be dosed with CellCept capsules at a dose of 750 mg twice daily (1.5 g daily dose). Patients with a body surface area >1.5 m^2 may be dosed with CellCept capsules or tablets at a dose of 1 g twice daily (2 g daily dose).

We find these statements acceptable.

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

NDA 50-722/S-007
NDA 50-723/S-004
NDA 50-759/S-005

Dear Ms. Rodriguez:

Please refer to your supplemental new drug applications for CellCept® Capsules, Tablets, and Oral Suspension of February 18 and May 19, 2000. Our reviewing clinical pharmacologist would like to make the following changes to your proposed package insert for these drug products (pediatric section of the annotated label, page 2-61):

The Pharmacokinetic parameters of MPA and MPAG have been evaluated in 55 pediatric patients (ranging in age from 1 year to 18 years) receiving CellCept oral suspension at a dose of 600 mg/m^2 bid (up to maximum of 1 g bid) after allogeneic renal transplantation. The pharmacokinetic data for MPA is provided in the following table:

Mean Computed Pharmacokinetic Parameters for MPA by Age and Time after Allogeneic Renal Transplantation

Age Group (n)	Time	T_{max} (h)	C_{max} (μg/mL)[a]	AUC $_{(0-12)}$ (μg*h/mL)[a]
< 2 yrs[b] (6)	Early (Day 7)	3.03 (4.70)	10.3 (5.80)	22.5 (6.66)
< 6 yrs (17)		1.63 (2.85)	13.2 (7.16)	27.4 (9.54)
6 – <12 yrs (16)		0.94 (1.55)	13.1 (6.30)	33.2 (12.1)
12 – 18 yrs (21)		1.16 (0.83)	11.7 (10.7)	26.3 (9.14)
< 2 yrs[b] (4)	Late (Month 3)	0.72 (0.28)	23.8 (13.4)	47.4 (14.7)
< 6 yrs (15)		0.99 (0.51)	22.7 (10.1)	49.7 (18.2)
6 – <12 yrs (14)		1.21 (0.53)	27.8 (14.3)	61.9 (19.6)
12 – 18 yrs (21)		0.98 (0.48)	17.9 (9.57)	53.6 (20.3)
< 2 yrs[b] (4)	Late (Month 9)	0.60 (0.21)	25.6 (4.25)	55.8 (11.6)
< 6 yrs (12)		0.87 (0.48)	30.4 (9.16)	61.0 (10.7)
6 – <12 yrs (11)		1.12 (0.46)	29.2 (12.6)	66.8 (21.2)
12 – 18 yrs (14)		1.09 (0.52)	18.1 (7.29)	56.7 (14.0)

[a] C_{max} and AUC were adjusted to a dose of 600 mg/m^2
[b] The <2 years is a subset of the < 6 year

The studied CellCept oral suspension dose of 600 mg/m^2 bid (up to maximum of 1 g bid) achieved MPA AUC values in pediatric patients similar to those seen in adult renal transplant patients receiving CellCept capsules at a dose of 1 g bid in the early post-transplant period. There was wide variability in the data, especially in the < 2-year-old patients. As observed in adults, early post-transplant MPA AUC values were approximately 45- 53% lower than those

observed in the later post-transplant period (> 3 months). MPA AUC values were similar in the early and late post-transplant period across the 1 – 18 year age range.

(Note: The changes under Dosage and Administration, page 2-87 of the annotated label, are acceptable.)

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at (301) 827-2127 if you have any questions regarding the contents of this transmission.

Sincerely yours,

Matthew A. Bacho
Regulatory Project Manager
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
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