CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

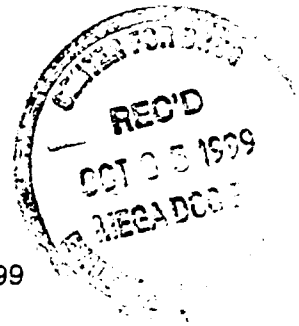
50-722/S-005

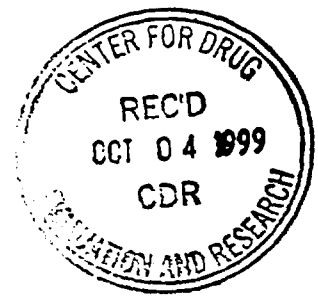
50-723/S-005

50-758/S-004

50-759/S-006

CORRESPONDENCE





Roche

October 1, 1999

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 / S00X - CellCept® 250 mg Capsules (mycophenolate mofetil) Supplement for Hepatic Indication**

Dear Reviewers:

On behalf of [redacted] and pursuant to Section 21CFR314.70(b), we are herewith submitting a Supplemental New Drug Application for extending the current indication of CellCept (mycophenolate mofetil) to the prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants.

Approvals of CellCept for the prophylaxis of organ rejection in patients receiving allogeneic renal (CellCept 250 mg capsules, NDA 50-722) and cardiac (NDA 50-722/S002) transplants, were granted on May 3, 1995 and February 12, 1998, respectively. In addition to the capsule formulation, other approved pharmaceutical forms of CellCept are: CellCept tablets (NDA 50-723) approved on June 19, 1997, CellCept Intravenous (NDA 50-758) approved on August 12, 1998, and CellCept oral suspension (NDA 50-759) approved on October 1, 1998. This supplement is being submitted in full to NDA 50-722; letters of cross-reference will be sent to the NDAs for the tablet, intravenous and suspension formulations, to seek approval for the use of these dosage forms in hepatic transplantation.

The basis of this supplemental application is the primary hepatic study MYCS2646. This study compared the safety and efficacy of mycophenolate mofetil (capsules and intravenous) to azathioprine, both administered in conjunction with cyclosporine and corticosteroids. Other studies including transplant patients are in this supplement as supportive data.

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

Roche Confidential
3401 Hillview Avenue
Palo Alto
California 94304-1397

Phone: (415) 855-5050

The organization and content of this supplement was discussed and agreed on with the Division at the Pre-NDA meeting on March 12, 1999. An outline of the organization is presented below.

NDA Section		Volume	Reviewers
I.	Application Forms and Index	1	All
II.	Application Summary	2	All
III.	Chemistry, Manufacturing and Controls	2	Technical
VI.	Human Pharmacokinetics/Bioavailability	3-15	Biopharma-ceutics
VIII.	Clinical Data	16-42	Medical
X	Statistical Data	43-55	Statistical
XI.	Patient Listings	*CD -ROM* CRTs Domain listings for all studies in the supplement in .pdf format CRTs Patient profiles for study MYCS2646 in .pdf format	N/A
XII.	Case Report Forms	*CD-ROM* electronic copies of deaths, terminations due to AEs plus a random 10% sample in .pdf format	N/A

Furthermore, as agreed with the Division, an electronic copy of this supplement will be submitted in the form of a Reviewers' Aid by October 22, 1999.

In accordance with 21.CFR 314.50 (d)(5), a safety update will be provided during the review period. In agreement with Roche's proposal (letter dated September 2, 1999) the update will include tabulation of malignancies, graft loss (re-transplantation or death) and AEs leading to study termination for all patients in both treatment arms in study MYCS2646. It will also include narratives for patients treated with MMF for malignancies, graft loss (re-transplantation or death) and AEs leading to study termination in study MYCS2646 and in the other two on-going hepatic studies (NR15714 and NR15715). The Division verbally endorsed this proposal on September 28, 1999.

As agreed with Mr. Matt Bacho, the archival copy of this NDA supplement is being sent to the Central Document Room for CDER. Reviewer's copies and desk copies are being sent to the Document Control Room for the Division, to the attention of Mr. Bacho.

Roche appreciates the continuous support the Division has provided on the development program for CellCept; we look forward to extending this long-standing collaboration to the review of this supplement.

Should you have any questions during the course of the review period, please do not hesitate to contact Dr. Sabine Geisel or me by phone at (650) 855-5923 or (650) 354-2370, respectively, or by fax at 650-852-1861.

Sincerely,

Carmen R. Rodriguez

Carmen R. Rodriguez, M.Sc.
Regulatory Program Director
Roche Global Development

Archival Copy:
CDER Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852

Reviewers/Desk Copies:
Division of Special Pathogens and Immunologic Drug Products
Document Control Room (Attn: Mr. Matt Bacho)
9201 Corporate Blvd. 4th Floor
Rockville, MD 20852

Mail via Fed-Ex

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-722/S-005

OCT 7 1999

Syntex (U.S.A.) Inc.
3401 Hillview Avenue
Palo Alto, California 94303

Attention: Carmen R. Rodriguez, M.Sc. Regulatory Program Director, Global Development

Dear Ms. Rodriguez:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: CellCept® 250 mg Capsules (mycophenolate mofetil)

NDA Number: 50-722

Supplement Number: S-005

Date of Supplement: October 1, 1999

Date of Receipt: October 4, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on December 3, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

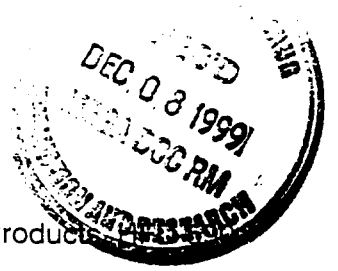
Sincerely,

/S/

Ellen C. Frank, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Roche

December 7, 1999



Division of Special Pathogens and Immunologic Drug Product
Food and Drug Administration
Center for Drug Evaluation and Research
1201 Corporate Blvd., 4th Floor
Rockville, MD 20850

SUBJECT: **NDA 50-722 / S-005 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Supplement for Hepatic Indication
Response to Comments Received by Voicemail on November 23, 1999

Dear Reviewers:

On November 23, 1999, we received a voicemail from Mr. Matthew Bacho with comments regarding NDA 50-722 / S-005, and we are responding in this submission.

Please find below our responses to the comments.

[redacted]

2. *Please indicate the location of the Declaration of Helsinki in the supplement.*

Please see Attachment 2 for a listing of the location of the Declaration of Helsinki within the study reports for all studies included in this supplemental NDA, except for study MYCS2378. MYCS2378 was conducted in the US pursuant to 21CFR 50 and 56.

3. *Please provide copies of all approved international labels of CellCept.*

As discussed on the phone on December 2, 1999 with Mr. Bacho, we look forward to receiving additional information on this request as we had not been asked in previous filings to provide copies of all approved CellCept labels. CellCept is approved in over 60 countries worldwide and we are currently in the process of retrieving printed labels of some major English-speaking markets. Furthermore, following a telephone discussion between Mr. Bacho and Carmen Rodriguez on December 7, 1999, we will be submitting the approved English versions of the labels for UK, Canada, and Australia in the near future.

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Phone (415) 855-5050

4. *Is this sNDA being supported by any preclinical or nonclinical studies from other applications and if yes, where can the statements regarding GLP be found?*

There was no new preclinical or nonclinical information included in this supplemental NDA. All preclinical and nonclinical information has already been submitted with the previous filings for CellCept in renal (NDA 50-722) and cardiac transplantation (NDA 50-722/S-002).

5. *Have marketing applications for the liver indication been submitted in any other countries?*

Marketing applications for CellCept in hepatic transplantation have been submitted in the following countries:

[redacted]

We believe the above will adequately address your comments. Should you have any further questions, please do not hesitate to contact either Ms Carmen Rodriguez or me by phone at (650) 354-2370 or (650) 855-5923, respectively, or by fax at (650) 852-1861. Thank you very much for your continued support of the CellCept program.

Sincerely,

Mae J Lai for Dr. Sabine Geisel

Sabine Geisel, Ph.D.
Sen. Regulatory Program Manager
Roche Global Development

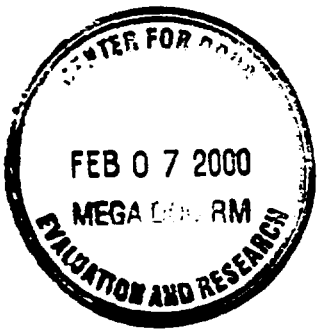
Desk copies (2): Mr. Matthew Bacho via FedEx
Cover Letter by Fax to Mr. Bacho

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Roche

SE1 005/BM

February 4, 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-005 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Supplement for Hepatic Indication
Modified Datasets and Roche's Internal Minutes of Teleconference
on January 21, 2000

Dear Reviewers:

As discussed and agreed during our teleconference on January 21, 2000, we are herein submitting the modified datasets pertaining to adverse events, efficacy and laboratory data for study MYCS2646 on CD ROM. To launch the datasets table of contents, please double-click on [redacted]

In addition, we are providing Roche's internal meeting minutes for the above described teleconference for your information.

We appreciate your continued support of the CellCept program. Should you have any further questions. please do not hesitate to contact either Ms. Carmen Rodriguez or me by phone at (650) 354-2370 or (650) 855-5923, respectively, or by fax at (650) 852-1861.

Sincerely,

Sabine Geisel, Ph.D.
Sr. Regulatory Program Manager
Roche Global Development

Desk copies (4) Attn. Mr. Matthew Bacho
via: FedEx

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

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Roche

March 20, 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 SUBMISSION
SE1-005 6m

SUBJECT: **NDA 50-722 / S-005 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Supplement for Hepatic Indication
Response to FDA Request for Information of March 13, 2000
Dataset for Selected Key Baseline Characteristics

Dear Reviewers:

We acknowledge the receipt of your fax of March 13, 2000 with the request for information, i.e. individual patient data for selected key baseline characteristics.

Please find enclosed a diskette with the requested dataset as SAS transport file.
The following data are provided:
Individual patient data for
- primary cause of hepatic failure
- CMV serologic status for donor and recipient
- Hepatitis B serologic status for donor and recipient.

For your convenience, we have also provided individual patient data for Hepatitis C serologic status for donor and recipient. These data were already included as part of the efficacy dataset in the modified datasets provided on CD ROM and submitted to NDA 50-722 / S-005 on February 4, 2000. The enclosed diskette also contains a Word file with the data definition table.

Chronic Hepatitis B or positive HBsAg was an exclusion criteria for study MYCS2646. The enclosed dataset contains data from 4 recipients with positive Hepatitis B serologic status, consistent with data entered into the clinical database. When preparing these datasets for submission to the Division, we noted some discrepancies. We inquired at the clinical site and found that 3 of the 4 patients had in fact negative HBsAg levels and therefore were not noted as protocol violations. The 3 patients were patient # 56707, #56713 and #56716. All 3 patients were from the same investigational site of Dr. Lewis Teperman, New York University Medical Center. In each case there was a discrepancy between the Case Report Form IEC (Inclusion/Exclusion Criteria) and the Case Report Form PI (Patient Information), both filled out at the time of the baseline visit. For all 3 patients, Form IEC showed correctly that the

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patients had no chronic Hepatitis B or positive HBsAg, however, on Form PI the patient's pre-transplant Hepatitis B serologic status was incorrectly marked as positive. We sincerely apologize for this discrepancy on the data. As this discrepancy was only detected after database closure and is not expected to affect the results of the efficacy and safety analyses, the CRFs and the clinical data base will be corrected and the discrepancy will be presented as an erratum in the final study report.

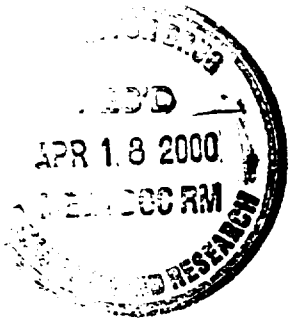
We appreciate your continued support of the CellCept program. Please do not hesitate to contact either Ms. Carmen Rodriguez or me by phone at (650) 354-2370 or (650) 855-5923, respectively, or by fax at (650) 852-1861 should you have any further questions,

Sincerely,

Mae f Lai for Sabine Geisel

Sabine Geisel, Ph.D.
Sr. Regulatory Program Manager
Roche Global Development

1 Desk copy (without diskette) to Mr. Matthew Bacho
via: FedEx



Roche

NEW CORRESP

April 17, 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-005 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Supplement for Hepatic Indication
Dataset for Selected Key Baseline Characteristics
Submission of Additional Copies

Dear Reviewers:

On April 14, 2000, we received a voicemail from Matthew Bacho informing us that a diskette with the dataset for selected key baseline characteristics submitted on March 20, 2000 was damaged.

We apologize for this inconvenience. Please find enclosed two additional copies of the diskette with the requested dataset.

Please do not hesitate to contact either Ms. Carmen Rodriguez or me by phone at (650) 354-2370 or (650) 855-5923, respectively, or by fax at (650) 852-1861 should you have any further questions.

Sincerely,

Sabine Geisel, Ph.D.
Sr. Regulatory Program Manager
Roche Global Development

via: FedEx

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

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Palo Alto
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Phone (650) 855-5050

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Roche

April 26, 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]ENT
Bm
SE1-005

SUBJECT: **NDA 50-722 / S-005 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Supplement for Hepatic Indication
Findings at one of the Investigational Sites of the Pivotal Liver Study (MYCS2646)

Dear Reviewers:

Following FDA's request of March 13, 2000 for datasets for selected key baseline characteristics of study MYCS2646, discrepancies were found on the Hepatitis B serologic status of three patients from the investigational site of Dr. Lewis Teperman, New York University Medical Center, Center Number 224571. Roche informed FDA of these discrepancies in a letter on March 20, 2000. This led Roche to re-monitor the source documents and CRFs pertaining to baseline data and efficacy parameters of 19 of the 20 enrolled patients (11 AZA, 8 MMF) from this site (the charts for patient MMF-56702 were being microfilmed; hence re-monitoring of this patient's data will be completed at a follow-up visit). The data review was done by Roche monitors between April 3 and 13, 2000. Dr. Teperman and the site personnel have been cooperative in this re-monitoring effort.

The primary findings of this re-monitoring effort and their impact on the study analyses are described below. Important discrepancies between the source documents and the CRFs were found, and Roche has implemented actions to assure data integrity and correct these discrepancies. However, the discrepancies found do not affect the primary efficacy endpoints (which assessed allograft rejection during the first 6 months posttransplant and death/retransplantation during the first 12 months posttransplant) and do not affect the conclusions of study MYCS2646.

- <u>Biopsies not reported on CRFs</u>
  Biopsies of four patients (3 AZA, 1 MMF) were not reported on the CRFs. Three of these biopsies were negative for rejection and hence do not affect the rejection endpoints. One of these biopsies (day 8, AZA-56708) was positive, in a patient who also had a rejection at day 93 post-transplant that was reported in the original analysis. Therefore, the results of the analysis of the primary rejection endpoint (proportion of patients with biopsy-proven and treated rejection during the first six months posttransplant, analyzed using the CMH generalized association test) were unchanged by the addition of this previously unreported rejection episode.

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The results of secondary analyses were affected, as follows: The time-to-event analysis changed slightly in that one new rejection occurred on day 8 and one less rejection occurred on day 93. However, there was no change to the statistical findings nor their clinical interpretation. The log rank p-value of this time-to-event analysis did not change (expressed to four decimal places), remaining p=0.0593. The rejection occurring on day 8 was mild whereas the rejection on day 93 was severe and hence this increased the number of patients with mild rejection in the AZA group from 57 to 58 and decreased the number of severe rejections from 9 to 8 (1 patient represents approximately 0.03% of the AZA group).

- Grade or date of biopsy
  Three discrepancies involving the grade or date of biopsy were found. (1) The grade of one rejection episode was recorded as mild on the CRF and "mild to moderate" in the source documents (the central reading of this biopsy was mild). (2) Two [redacted] reports existed for the same biopsy (one noting mild rejection and one noting moderate rejection); the grade recorded on the CRF was mild. This rejection occurred after six months posttransplant (on day 330) and thus does not affect the categorization of rejection grade for the primary endpoint. There was no central reading to consider in this case because these were done only for the first six months posttransplant. (3) The date of one biopsy on the CRF differed from that in the source documents by one day.

- Inclusion/exclusion
  A patient (AZA-56706) with a history of adenocarcinoma of the colon (Dukes B) was entered into the trial. According to the investigator (telephone conversation) this was an incidental finding restricted to a polyp in a colon segment resected for inflammatory bowel disease. The patient was considered cured at the time of surgery. Roche is in the process of verifying this information in source documents. Nevertheless, the entry of this patient was in violation of the protocol requirements.

- Informed consent
  Two patients (MMF-56703, AZA-56712) who, according to patients' records, have very limited knowledge of English signed an English informed consent. Roche is in the process of further investigating this finding.

In addition to the above-described actions Roche has implemented the following action plan:

1. Re-monitoring actions at Dr. Teperman's site

Although the safety of MMF in renal, cardiac and hepatic transplantation is well documented and it is unlikely that the overall safety profile will change based on potential discrepancies in data from nine patients, Roche will re-monitor source documents and CRFs at Dr. Teperman's site for safety data. This effort will begin approximately May 15 based upon the availability of site staff and should be completed by the end of May. The scope of re-monitoring will be as follows:

- Key safety parameters including adverse events, serious adverse events, opportunistic infections and concomitant medications will be re-monitored for all MMF patients at this site (9 patients total, 5 have prematurely withdrawn from the study, 4 patients are currently participating in the study). Since the primary concern is potential inaccuracies in the reporting of the test drug, MMF, it was felt justified to restrict re-monitoring to the MMF arm.
- Source documents and CRFs of the five MMF patients, who withdrew from the trial due to adverse events will be re-monitored for the last 30 days prior to study withdrawal.
- Source documents and CRFs of the four MMF patients who are still active will be re-monitored for the last 30 days prior to their last visit before the database cut date for the NDA supplement (i.e. March 29, 1999).

2. Revisions to database and to regulatory documents included in the liver supplement

After conclusion of the re-monitoring,

- a detailed list with all findings will be provided to FDA.
- All CRFs affected will be corrected and CRFs previously submitted to the liver supplement will be re-submitted in the corrected form to the NDA.
- The Roche database and all affected analyses will be corrected.
- Tables in the study report will be corrected as appropriate and an addendum to the report will be submitted to the FDA together with the corrected datasets.

We anticipate that the corrected documents and datasets will be available by mid July.

We would like to receive the Division's input on the acceptability of the planned submission of these corrected documents to the liver supplement during the review period.

For your information, the Office of Compliance, Division of Scientific Investigations is currently conducting inspections at the investigational sites of the three major enrollers for study MYCS2646:

[redacted]

We appreciate your continued support of the CellCept program. Please do not hesitate to contact either Ms. Carmen Rodriguez or me by phone at (650) 354-2370 or (650) 855-5923, respectively, or by fax at (650) 852-1861 should you have any further questions,

Sincerely,

S. Geisel

Sabine Geisel, Ph.D.
Sr. Regulatory Program Manager
Roche Global Development

via: FedEx

Roche

May 19, 2000

Division of Special Pathogens and Immunologic Drug Products, HFD-590
Food and Drug Administration
Center for Drug Evaluation and Research
5201 Corporate Blvd., 4th Floor
Rockville, MD 20850

NDA SUPPL AMENDMENT

SEI-005 BM

SUBJECT: **NDA 50-722 / S-005 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Supplement for Hepatic Indication
Errata to Study Report for the Pivotal Liver Study MYCS2646

Dear Reviewers:

In a letter of April 26, 2000, Roche informed the FDA about findings at one of the investigational sites of study MYCS2646 and the action plan that was consequently implemented. On May 5, 2000, we followed-up on the letter in a telephone conference with Mr. Bacho. In this telephone conference, Roche proposed to submit errata to the study report correcting all important discrepancies within the next two weeks. Minor revisions would be incorporated at the time the study report containing 3-year data is finalized. Today, Mr. Bacho informed us that the Division finalized the review of Roche's letter of April 26 and agreed with the company's assessment that the findings do not affect the primary efficacy endpoints and the conclusions of study MYCS2646. The reviewers further agreed to the submission of the errata to the stucy report. Thus, please find attached the errata for study MYCS2646. In addition, a summary document providing background information on the most significant findings at Dr. Teperman's site is included for ease of review.

We appreciate your continued support of the CellCept program. Should you have any further questions, please do not hesitate to contact either Ms. Carmen Rodriguez or me by phone at (650) 354-2370 or (650) 855-5923, respectively, or by fax at (650) 852-1861

Sincerely,

S. Geisel

Sabine Geisel, Ph.D.
Sr. Regulatory Program Manager

ORIGINAL

via: FedEx

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

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California 94304-1397

Phone: (650) 855-5050

Roche

NDA NO. 50-759 REF. NO. 006

NDA SUPPL. SE1

JUN 23 2000
MEGA DOC RM
EVALUATION AND RESEARCH

June 22, 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 50-759 - CellCept® Oral Suspension (mycophenolate mofetil for oral suspension)**
Abbreviated Supplement for Hepatic Indication

Dear Reviewers:

We are hereby submitting an abbreviated supplement for hepatic indication to NDA 50-759. The supporting clinical data for use of oral CellCept in hepatic transplantation was submitted to NDA 50-722 / S-005 CellCept 250 mg capsules on October 1, 1999. As outlined in the cover letter for that supplement, Roche proposed extending the current indication of CellCept to the prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants. For ease of review, a copy of the cover letter for the supplement for hepatic indication is attached to this submission.

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,

Carmen R. Rodriguez

Carmen R. Rodriguez, M.Sc.
Regulatory Program Director
Roche Global Development

Archival copy: NDA 50-759
Cover letter by fax to Mr. Matthew Bacho

ORIGINAL

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

3401 Hillview Avenue
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California 94304-1397

Phone: (650) 855-5050

Roche

NDA NO. 50-723 REF. NO. 005
SE1

Pharmaceuticals

June 22, 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 50-723 - CellCept® 500 mg Tablets (mycophenolate mofetil)**
Abbreviated Supplement for Hepatic Indication

Dear Reviewers:

We are hereby submitting an abbreviated supplement for hepatic indication to NDA 50-723. The supporting clinical data for use of oral CellCept in hepatic transplantation was submitted to NDA 50-722 / S-005 CellCept 250 mg capsules on October 1, 1999. As outlined in the cover letter for that supplement, Roche proposed extending the current indication of CellCept to the prophylaxis of organ rejection in patients receiving allogeneic hepatic transplants. For ease of review, a copy of the cover letter for the supplement for hepatic indication is attached to this submission.

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,

Carmen R. Rodriguez

Carmen R. Rodriguez. M.Sc.
Regulatory Program Director
Roche Global Development

Archival copy: NDA 50-723
Cover letter by fax to Mr. Matthew Bacho

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

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Palo Alto
California 94304-1397

Phone: (650) 855-5050

Roche

June 29, 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

SUBJECT: **NDA 50-722 / S-005 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Supplement for Hepatic Indication
Response to FDA Request for Information Dated June 20, 2000

SE5-005 BM

Dear Reviewers:

We acknowledge the receipt of your fax of June 20, 2000 with the request for information regarding the supplement for hepatic indication. Please find attached our responses to the questions. For ease of review, we also included photocopies of journal articles referenced in the responses.

We appreciate your continued support of the CellCept program. Please do not hesitate to contact either Ms. Carmen Rodriguez or me by phone at (650) 354-2370 or (650) 855-5923, respectively, or by fax at (650) 852-1861 should you have any further questions.

Sincerely,

Sabine Geisel, Ph.D.
Sr. Regulatory Program Manager
Roche Global Development

Desk copies (3) Attn. Mr. Matthew Bacho
via: FedEx

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

3401 Hillview Avenue
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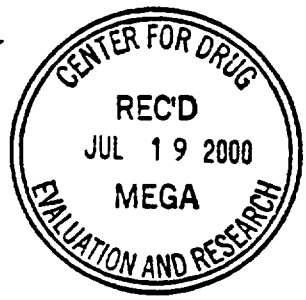
California 94304-1397

Phone: (650) 855-5050

Roche

July 7, 2000

NDA [illegible] AMENDMENT



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-005 - CellCept® 250 mg Capsules (mycophenolate mofetil)**
Supplement for Hepatic Indication
Information Pertaining to Pulmonary Fibrosis in Connection with CellCept

SE [illegible]EM

Dear Reviewers:

We acknowledge the receipt of your fax of today, July 18, 2000.

As agreed during yesterday's teleconference, we discussed your proposal for adding pulmonary fibrosis to the post-marketing section of the CellCept label with Roche's Drug Safety Risk Management group. Please find attached all available information pertaining to pulmonary fibrosis in connection with CellCept.

As stated in the attached document, monitoring of pulmonary fibrosis in connection with CellCept started in November of 1997 and is currently ongoing. The document includes an overview of all cases of pulmonary fibrosis (12) contained in the Roche drug safety database. It further contains the results of a literature search on this topic and an overview of the epidemiology of the disease. The appendices to this review provide copies of MedWatch forms of these twelve cases for your reference. In addition, a copy of the publication referenced in the Drug Safety report where a patient with advanced retroperitoneal fibrosis was successfully treated with CellCept is also included for ease of your review.

Based on the review of these cases, there is at present no evidence to suggest a causal relationship between mycophenolate mofetil and the development of pulmonary fibrosis. Keeping the epidemiology and the individual risk factors in mind, Roche will continue to closely monitoring this issue. In light of this information, we look forward to further discussing with you the need for immediate inclusion of pulmonary fibrosis into the post-marketing section of the US label.

Please contact either Ms. Carmen Rodriguez or me by phone at (650) 354-2370 or (650) 855-5923, respectively, or by fax at (650) 852-1861 should you require any further information.

Sincerely,

Sabine Geisel, Ph.D.
Sr. Regulatory Program Manager

ORIGINAL

Copies via FedEx: 1 archival, 3 desk copies to Mr. Matthew Bacho
Cover letter by FAX to Mr. Matthew Bacho

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