

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-722/S-004

50-723/S-003

50-758/S-003

50-759/S-004

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

NDA 50-722/S-004
NDA 50-723/S-003
NDA 50-758/S-003
NDA 50-759/S-004

**APPEARS THIS WAY
ON ORIGINAL**

Labeling Review of Supplemental Labeling Revisions (SLR):

Materials Reviewed:

NDA 50-722 (Capsules):

<u>SLR</u>	<u>Date submitted</u>	<u>Date received</u>	<u>Date completed</u>
004	August 16, 1999	August 18, 1998	July 27, 2000

Amendments

004	June 6, 2000	June 16, 2000	July 27, 2000
004	July 7, 2000	July 7, 2000	July 27, 2000
004	July 12, 2000	July 13, 2000	July 27, 2000
004	July 18, 2000	July 19, 2000	July 27, 2000
004	July 25, 2000	July 26, 2000	July 27, 2000

NDA 50-723 (Tablets):

<u>SLR</u>	<u>Date submitted</u>	<u>Date received</u>	<u>Date completed</u>
003	May 11, 2000	May 12, 2000	July 27, 2000

Amendments

003	June 6, 2000	June 16, 2000	July 27, 2000
003	July 7, 2000	July 7, 2000	July 27, 2000
003	July 12, 2000	July 13, 2000	July 27, 2000
003	July 18, 2000	July 19, 2000	July 27, 2000
003	July 25, 2000	July 26, 2000	July 27, 2000

NDA 50-758 (Intravenous):

<u>SLR</u>	<u>Date submitted</u>	<u>Date received</u>	<u>Date completed</u>
003	May 11, 2000	May 12, 2000	July 27, 2000

Amendments

003	June 6, 2000	June 16, 2000	July 27, 2000
003	July 12, 2000	July 13, 2000	July 27, 2000
003	July 18, 2000	July 19, 2000	July 27, 2000
003	July 25, 2000	July 26, 2000	July 27, 2000

NDA 50-759 (Oral Solution):

<u>SLR</u>	<u>Date submitted</u>	<u>Date received</u>	<u>Date completed</u>
004	May 11, 2000	May 12, 2000	July 27, 2000

Amendments

004	June 6, 2000	June 16, 2000	July 27, 2000
004	July 7, 2000	July 7, 2000	July 27, 2000
004	July 12, 2000	July 13, 2000	July 27, 2000
004	July 18, 2000	July 19, 2000	July 27, 2000
004	July 25, 2000	July 26, 2000	July 27, 2000

- Last approved package insert for CellCept® dated March 20, 2000
- FDA memorandum concerning the Division's proposed labeling revisions dated June 2, 2000
- FDA memorandum concerning oral contraceptives dated July 7, 2000

Sponsor: Hoffmann-La Roche, Incorporated

NDA 50-722/S-004
NDA 50-723/S-003
NDA 50-758/S-003
NDA 50-759/S-004

3

Products:

CellCept® (mycophenolate mofetil) Capsules, 250 mg
CellCept® (mycophenolate mofetil) Tablets, 500 mg
CellCept® (mycophenolate mofetil) Intravenous
CellCept® (mycophenolate mofetil) Oral Solution, 200 mg/mL

Background:

The new drug applications for CellCept® (mycophenolate mofetil), 250-mg capsules, 500-mg tablets, intravenous, and 200 mg/mL oral solution, were originally approved on May 3, 1995, June 19, 1997, August 12, 1998, and October 1, 1998, respectively.

On August 16, 1999, Hoffmann-La Roche, Inc. submitted a labeling supplement – “Changes Being Effected” (CBE) that provided for the following changes to the CellCept® label:

INTERACTIONS:

The use of live attenuated vaccines should be avoided during treatment with CellCept® has been added. In patients with renal impairment administered both mycophenolate mofetil and ganciclovir, there should be careful monitoring has been added.

PHARMACOKINETICS:

Information on the pharmacokinetic metabolites of mycophenolate mofetil and the conversion of MPAG to free MPA via enterohepatic recirculation has been provided. The fact that bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug has been added. Accumulation of MPAG and MPA in patients with primary non-function of the organ following renal transplantation is reported.

PRECAUTIONS:

The statement that in cardiac transplant patients the overall incidence of opportunistic infections was approximately 10% higher in CellCept®-treated patients than those receiving azathioprine therapy, but not associated with excess mortality due to infection/sepsis in CellCept®-treated patients has been added here.

GERIATRIC USE:

In compliance with the FDA final rule regarding addition of information to the labeling on the safe and effective use of drugs in the elderly we have added statements to the following sections: Precautions, Adverse Reactions, Dosage and Administration, and Pharmacokinetics.

DOSAGE AND ADMINISTRATION: CellCept® Capsules, Tablets, and Oral Suspension

the revised labeling provided within. Although the MPA C_{max} is decreased when drug is taken with food, the MPA AUC is not affected. As the AUC is highly predictive of the likelihood of allograft rejection after renal transplantation, while other pharmacokinetic parameters such as MPA max have poorer predictive power for this outcome, the efficacy of MMF should not be substantially affected if the drug is administered with food.

Upon review of the submissions noted above, the interaction studies between CellCept® and tacrolimus, the information on pharmacokinetic metabolites, and the proposed change to the Dosage and Administration section, it was determined that approval from the Division would be required before Hoffmann-La Roche could alter the package insert.

A memorandum was faxed to Hoffman-La Roche on June 2, 2000, which proposed changes to the package insert and requested further information concerning Protocol BP15543 entitled, "A pharmacokinetic/ pharmacodynamic interaction study of mycophenolate mofetil and oral contraceptives in patients with severe plaque type psoriasis," (see attachment 1). A satisfactory response was submitted by Hoffman-La Roche dated June 6, 2000 and received on June 16, 2000.

After consulting with Dr. Ameeta Parekh, Clinical Pharmacology Team Leader co-located with the Division of Reproductive and Urologic Drug Products (HFD-580). The FDA faxed another memorandum to Hoffmann-La Roche on July 7, 2000 concerning the PRECAUTIONS, *Drug Interactions*, *Oral Contraceptives* subsection (see attachment 2).

Hoffmann-La Roche responded with a submission on July 12, 2000, which was acceptable to Drs. Kumi and Korvick, effectively completing negotiations concerning these labeling supplements. In her review dated July ??, 2000, Dr. Joyce Korvick, Medical Officer, proposed that the ~~_____~~ from the CellCept® label, revised the Geriatric Use statement, and deleted the annual review statement from the Postmarketing Experience section. In his review dated July 19, 2000, Dr. Kofi Kumi, Clinical Pharmacologist, proposed several changes to the CLINICAL PHARMACOLOGY and PRECAUTIONS sections with the most prominent being the Oral Contraceptives paragraph (see attachment 2). The sponsor complied with Dr. Korvick and Dr. Kumi's recommendations and submitted revised proposed draft labeling on July 25, 2000.

Electronic Review of Submissions:

The proposed package insert for CellCept® dated July 25, 2000, was electronically compared to the last approved label dated March 20, 2000. The changes are indicated by strikeout and underline. If there was any negotiation involved with a particular change, the bracketed reference that follows it will indicate the review that should be consulted.

1) **DESCRIPTION:**

(Page 1, lines 16-8): "CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor."

2) **CLINICAL PHARMACOLOGY Pharmacokinetics Distribution:**

(Page 4, line 104-6): "The mean (\pm SD) apparent volume of distribution of MPA in ~~_____~~ 12 healthy volunteers is approximately 3.6 (\pm 1.5) and 4.0 (\pm 1.2) L/kg following IV and oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin."

3) **CLINICAL PHARMACOLOGY Pharmacokinetics Metabolism:**

(Page 4, lines 124-5): The following sentence was added to this section: "In vivo, MPAG is converted to MPA via enterohepatic recirculation." [Dr. Kofi Kumi, page 2]

(Page 4, lines 134-6): "Increased plasma concentrations of mycophenolate mofetil metabolites (MPA 50% increase and MPAG about ~~_____~~ 3-fold to 6-fold increase) are observed in patients with renal insufficiency (see CLINICAL PHARMACOLOGY: *Special Populations*)."

4) **CLINICAL PHARMACOLOGY Pharmacokinetics Excretion:**

(Pages 4, lines 140-4): "At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 μ g/mL), small amounts of MPAG are removed. Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug (see OVERDOSAGE)."

5) **CLINICAL PHARMACOLOGY Pharmacokinetics Pharmacokinetics in Healthy Volunteers:**

(Page 7, lines 162-3): "Five mL of the 200 mg/mL constituted oral suspension have been shown to be bioequivalent to four 250 mg capsules."

6) **CLINICAL PHARMACOLOGY Pharmacokinetics Renal Insufficiency:**

(Pages 7-8, lines 173-6): "In addition, the single-dose plasma MPAG AUC was ~~_____~~ 3-fold to 6-fold higher in volunteers with severe renal impairment than in volunteers with mild renal impairment or healthy volunteers, consistent with the known renal elimination of MPAG."

(Page 8, lines 184-89): "There is a potential for a transient increase in the free fraction and concentration of plasma MPA in patients with delayed graft function. However, dose adjustment does not appear to be necessary in patients with delayed graft function. Mean plasma MPAG AUC₀₋₁₂ was ~~_____~~ 2-fold to 3-fold higher than in posttransplant patients without delayed graft function (see PRECAUTIONS: General and DOSAGE AND ADMINISTRATION)." [Kumi, page 3]

(Page 8, lines 190-2): "In 8 patients with primary non-function of the organ following renal transplantation, plasma concentrations of MPAG accumulated about 6-fold to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1-fold to 2-fold." [Kumi, page 3]

7) **CLINICAL PHARMACOLOGY *Pharmacokinetics Hepatic Insufficiency:***

(Page 8, lines 203-7): "Hepatic disease with other etiologies, such as primary biliary cirrhosis, may show a different effect. In a single-dose (1 g) intravenous study of 6 volunteers with severe hepatic impairment (aminopyrine breath test less than 0.2% of dose) due to alcoholic cirrhosis, MMF was rapidly converted to MPA." [Kumi, page 3]

8) **CLINICAL PHARMACOLOGY *Pharmacokinetics Geriatric Use:***

(Page 9, line 219): "Geriatric Use: Pharmacokinetics in the elderly have not been studied." [Kumi, page 4]

9) **CLINICAL STUDIES *Renal Transplant:***

(Page 10, lines 240-2): "CellCept, in combination with corticosteroids and cyclosporine reduced (statistically significant at $p < 0.05$ level) the incidence of treatment failure within the first 6 months following transplantation."

(Page 11, lines 257): "_____ The cumulative incidence of 12-month graft loss or patient death is presented below."

(Page 12, lines 263-4, table title): "Renal Transplant Studies/Cumulative Incidence of Combined Graft Loss and or Patient Death at 12 Months"

10) **CLINICAL STUDIES *Cardiac Transplant:***

(Page 12, lines 271-4): "The two primary efficacy endpoints were: (1) the proportion of patients who, after transplantation, had at least one endomyocardial biopsy-proven rejection with hemodynamic compromise, or were retransplanted or died, within the first 6 months, and (2) the proportion of patients who died or were retransplanted during the first 12 months following transplantation."

11) **WARNINGS:**

(Page 13, lines 302-3): "Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis."

(Page 14, lines 311-3): "Lymphoproliferative disease or lymphoma developed in approximately 1.0% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal and cardiac transplant patients (see ADVERSE REACTIONS)."

(Page 14, lines 331-4): "In the four (three renal and one cardiac) controlled studies for prevention of renal or cardiac transplant rejection, similar rates of fatal infection/sepsis (<2%) occurred in patients receiving CellCept (2 g or 3 g) or control therapy in combination with other immunosuppressive agents (see ADVERSE REACTIONS)."

12) **PRECAUTIONS *General:***

(Page 15, lines 366-8): "In patients with delayed renal graft function posttransplant, mean MPA AUC₀₋₁₂ was comparable, but MPAG AUC₀₋₁₂ was _____ 2-fold to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function."

(Page 15, lines 375-81): "In cardiac transplant patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with CellCept than in those receiving azathioprine therapy, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with CellCept (see ADVERSE REACTIONS). There were more herpes virus (H. simplex, H. zoster, and cytomegalovirus) infections in cardiac transplant patients treated with CellCept compared to those treated with azathioprine (see ADVERSE REACTIONS)."

(Page 16, lines 382-4): "It is recommended that CellCept not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically."

(Page 16, lines 389-95): "On theoretical grounds, because CellCept is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome. During treatment with CellCept, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see PRECAUTIONS: Drug Interactions: Live Vaccines)."

13) **PRECAUTIONS *Phenylketonurics:***

(Page 16, lines 397-400): "Therefore, care should be taken if CellCept Oral Suspension is administered to patients with phenylketonuria. CAUTION: CELLCEPT INTRAVENOUS SOLUTION SHOULD NEVER BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION."

14) **PRECAUTIONS *Drug Interactions Acyclovir:***

(Page 17, lines 416-7): "Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to ~~10~~ 12 healthy volunteers resulted in no significant change in MPA AUC and C_{max} ."

15) **PRECAUTIONS *Drug Interactions Cholestyramine:***

(Page 17, lines 434-6): "Following single-dose administration of 1.5 g mycophenolate mofetil to ~~10~~ 12 healthy volunteers pretreated with 4 g tid of cholestyramine for 4 days, MPA AUC decreased approximately 40%."

16) **PRECAUTIONS *Drug Interactions Cyclosporine:***

(Page 17, lines 436-8): "Cyclosporine (Sandimmune[®]) pharmacokinetics (at doses of 275 to 415 mg/day) were unaffected by single and multiple doses of 1.5 g bid of mycophenolate mofetil in ~~10~~ 10 stable renal transplant patients."

17) **PRECAUTIONS *Drug Interactions Ganciclovir:***

(Page 17, lines 444-6): "Following single-dose administration to ~~10~~ 12 stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and IV ganciclovir (5 mg/kg)."

(Pages 17-8, lines 452-5): "Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the ~~two drugs~~ two drugs ~~will~~ will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which MMF and ganciclovir are coadministered, patients should be monitored carefully."

18) **PRECAUTIONS *Drug Interactions Oral contraceptives:***

(Page 18, lines 456-66): "

A study of coadministration of CellCept (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 to 0.04 mg) and levonorgestrel (0.05 to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 to 0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC₍₀₋₂₄₎ was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC₍₀₋₂₄₎ significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60-70%) in the data, especially for ethinylestradiol. Mean serum levels of LH, FSH and progesterone were not significantly affected. CellCept may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. However, it is recommended that oral contraceptives are coadministered with CellCept with caution and additional birth control methods be considered (see PRECAUTIONS: Pregnancy)." [Kumi, pages 4-5]

- 19) **PRECAUTIONS Drug Interactions Trimethoprim/sulfamethoxazole:**
(Page 18, lines 467-70): "Following single-dose administration of mycophenolate mofetil (1.5 g) to ~~12~~ 12 healthy male volunteers on day 8 of a 10 day course of Bactrim™ DS (trimethoprim 160 mg/sulfamethoxazole 800 mg) administered bid, no effect on the bioavailability of MPA was observed."
- 20) **PRECAUTIONS Drug Interactions Live Vaccines:**
(Page 18, lines 482-4): "Live Vaccines: During treatment with CellCept, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective (see PRECAUTIONS: General)."
- 21) **PRECAUTIONS Geriatric Use:**
(Page 20, lines 531-7): "Geriatric Use: Clinical studies of CellCept 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 or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals (see ADVERSE REACTIONS)." [Dr. Korvick, pages 4-5]
- 22) **ADVERSE REACTIONS**
(Page 20, lines 538-40): "The principal adverse reactions associated with the administration of CellCept include diarrhea, leukopenia, ~~sepsis~~ sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections."
- 23) **ADVERSE REACTIONS CellCept (oral):**
(Page 20, lines 546-9): "Elderly patients, particularly those who are receiving CellCept as part of a combination immunosuppressive regimen, may be at increased risk of certain infections (including CMV tissue invasive disease) and possibly gastrointestinal hemorrhage and pulmonary edema, compared to younger individuals (see PRECAUTIONS)."
- 24) **ADVERSE REACTIONS Postmarketing Experience:**
(Page 32):

In a telephone conversation with Dr. Sabine Geisel (July 25, 2000), Hoffman-La Roche agreed to take out this statement because the reviewers and the Division of Drug Marketing, Advertising, and Communication believed it was too broad in scope, only specific instances of noteworthy adverse reactions should be in this section. Eventually, it was believed that differences in the adverse reactions reported through postmarketing experience with those seen in the controlled studies would force the sponsor to delete this statement anyway.
- 25) **OVERDOSAGE:**
(Page 32, lines 684-7): "However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine (see CLINICAL PHARMACOLOGY: Pharmacokinetics)."
- 26) **DOSAGE AND ADMINISTRATION CARDIAC TRANSPLANTATION CellCept Capsules, Tablets, and Oral Suspension:**
(Page 33, lines 701-2): "However, in stable renal transplant patients, CellCept may be administered with food if necessary."
- 27) **DOSAGE AND ADMINISTRATION CARDIAC TRANSPLANTATION CellCept Capsules, Tablets, and Oral Suspension Patients With Hepatic Impairment:**
(Page 33, lines 706-9): "Patients With Hepatic Impairment: No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies (see CLINICAL PHARMACOLOGY: Pharmacokinetics)."

No data are available for cardiac transplant patients with severe hepatic parenchymal disease. [Kumi, page 6]

- 28) **DOSAGE AND ADMINISTRATION CARDIAC TRANSPLANTATION *CellCept Capsules, Tablets, and Oral Suspension Geriatric Use:***
(Page 33, lines 711-3): "*Geriatric Use:* The recommended dose of 1 g bid for renal transplant patients and 1.5 g bid for cardiac transplant patients is appropriate for elderly patients (see PRECAUTIONS: *Geriatric Use*)."
- 29) **DOSAGE AND ADMINISTRATION Preparation of Oral Suspension**
(Page 33, line 715-7): "Preparation of Oral Suspension It is recommended that CellCept Oral Suspension be constituted by the pharmacist prior to dispensing to the patient. CellCept Oral Suspension should not be mixed with any other medication."
- 30) **DOSAGE AND ADMINISTRATION *CellCept Intravenous Preparation of Infusion Solution (6 mg/mL):***
(Page 34-5, lines 752-3): "Avoid direct contact of the prepared solution of CellCept Intravenous with skin or mucous membranes."
- 31) **HANDLING AND DISPOSAL:**
(Page 36, lines 801-2): "Avoid direct contact of the prepared solution of CellCept Intravenous with skin or mucous membranes."

Conclusions/Recommendations:

These labeling changes are acceptable. An approval letter should be sent advising the applicant that these NDA supplements be approved. Final printed labeling for CellCept® should be requested, and should be identical to the revised draft labeling submitted July 25, 2000, received July ??, 2000.

Matthew A. Bacho
Regulatory Project Manager, HFD-590

Renata Albrecht, M.D.
Acting Director, HFD-590

Attachments:

1. FDA memorandum concerning the Division's proposed labeling revisions dated June 2, 2000
2. FDA memorandum concerning oral contraceptives dated July 7, 2000

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Matthew Bacho

11/16/00 02:53:22 PM

CSO

Renata Albrecht signed the hard copy of this SLR review on November 15
, 2000.

Renata Albrecht

12/6/00 01:45:38 PM

MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

**MEMORANDUM OF TELEFACSIMILE CORRESPONDENCE**

DATE: July 7, 2000

TO: Sabine Geisel, Ph.D.
Senior Regulatory Program Manager
Hoffman-La Roche Inc.
(650) 354-2370
(650) 852-1861 (fax)

FROM: Matthew A. Bacho, Regulatory Project Manager

THROUGH: Marc Cavaillé-Coll, M.D., Ph.D., Medical Officer Team Leader
Funmilayo O. Ajayi, Ph.D., FCP, Clin. Pharm. & Biopharm. Team Leader
Kofi A. Kumi, Ph.D., Clinical Pharm. & Biopharmaceutics Reviewer
Ameeta Parekh, Ph.D., Clin. Pharm. & Biopharm. Team Leader, DRUDP

NDAs: 50-722/S-004 (CellCept® Capsules)
50-723/S-003 (CellCept® Tablets)
50-758/S-003 (CellCept® Intravenous)
50-759/S-004 (CellCept® Oral Solution)

SUBJECT: Labeling Changes

With reference to the NDAs for CellCept® and your labeling supplement of August 16, 1999, our clinical pharmacologists would like to make the following comment and changes regarding your proposed label for CellCept®:

Although no clinically relevant changes were observed in the LH, FSH, and progesterone upon coadministration of the studied oral contraceptives (OC) with mycophenolate mofetil, this data is derived from a limited number of subjects on each OC and the label should specify the OCs studied.

PRECAUTIONS: *Drug Interactions Oral Contraceptives*

A study of coadministration of CellCept (1 g bid) and combined oral contraceptives containing ethinylestradiol (0.02 to 0.04 mg) and levonorgestrel (0.05 to 0.20 mg), desogestrel (0.15 mg) or gestodene (0.05 to 0.10 mg) was conducted in 18 women with psoriasis over 3 consecutive menstrual cycles. Mean AUC₍₀₋₂₄₎ was similar for ethinylestradiol and 3-keto desogestrel; however, mean levonorgestrel AUC₍₀₋₂₄₎ significantly decreased by about 15%. There was large inter-patient variability (%CV in the range of 60 -70%) in the data, especially for ethinylestradiol. Mean serum levels of LH, FSH and progesterone were not significantly affected. CellCept may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. However, it is recommended that oral contraceptives are coadministered with CellCept with caution and additional birth control methods be considered (See PRECAUTIONS: Pregnancy).



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.

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

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Matthew Bacho

7/7/00 03:36:32 PM

CSO

This memorandum was faxed to the sponsor on July 7, 2000.

Kofi Kumi

8/15/00 01:20:44 PM

PHARMACOLOGIST

Ameeta Parekh

11/7/00 08:38:45 AM

BIOPHARMACEUTICS

Funmilayo Ajayif

11/30/00 04:10:29 PM

BIOPHARMACEUTICS

Marc Cavaille Coll

12/6/00 03:15:51 PM

MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

NDA 50-722/S-004 and S-005
NDA 50-723/S-003 and S-005
NDA 50-758/S-003 and S-004
NDA 50-759/S-004 and S-006

Hoffmann-La Roche Incorporated
Attention: Melanie Bishop
Program Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110

Dear Ms. Bishop:

We acknowledge receipt of your September 7, 2000 submissions containing final printed labeling in response to our July 27 and July 28, 2000 letters approving your supplemental new drug applications for CellCept® (mycophenolate mofetil) Capsules, 250 mg, CellCept® (mycophenolate mofetil) Tablets, 500 mg, CellCept® (mycophenolate mofetil) Intravenous, and CellCept® (mycophenolate mofetil) Oral Solution, 200 mg/mL.

We have reviewed the labeling that you submitted in accordance with our July 27 and 28, 2000 letters, and we find it acceptable.

If you have any questions, please contact Matthew A. Bacho, Regulatory Project Manager, at (301) 827-2127.

Sincerely,

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Evaluation IV
Center for Drug Evaluation and Research

**APPEARS THIS WAY
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