CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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

MEDICAL REVIEW

MEMORANDUM

SEP 2 1 2000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

DATE: 4/28/00

FROM: Joyce A Korvick, MD, MPH /S/ 4/24/2000
Medical Officer, DSPIDP

SUBJECT: **MEDICAL OFFICER REVIEW**
NDA : 50-722/S004
NDA File #50-723/ S-003
NDA File #50-758/ S-003
NDA File #50-759/ S-004
Date: August 16, 1999

SPONSOR: Roche Pharmaceuticals

SUBSTANCE: CellCept ®(mycophenolate mofetil, MMF)

DATE SUBMITTED/DATE RECEIVED: 8/16/99 - 8/18/99

I. Contents: This Supplement was submitted from Roche Pharmaceuticals in order to revise the package insert. The majority of the submission refers to changes related to the pharmacokinetics of CellCept®. This review of the label will consider the medical/clinical changes that are being requested.

II. LIST OF PROPOSED CHANGES RELATIVE TO MEDICAL CLINICAL ISSUES:
The following proposed changes in wording are quoted from the annotated label provided by the applicant, and refer to page numbers from that annotated label.

Page 9: para 2: "Geriatric Use: Pharmacokinetics in the elderly have not been studied".

Medial Officer Comment and Recommendation:
This statement appears within the pharmacokinetic section and is a factual statement. This statement is acceptable to the FDA.

Page 13: para 4: "WARNINGS (see boxed WARNING): Patients receiving immunosuppressive regimens.....Over-suppression of the immune system can also increase susceptibility to infection, *'including opportunistic infections, fatal infections and sepsis'*".

Medial Officer Comment and Recommendation:

This is a factual statement. It is acceptable to the FDA.

Page 15: para 5: "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:."

Medial Officer Comment and Recommendation:

This statement appears in the PRECAUTIONS section of the label. This statement is repeated verbatim from the Opportunistic Infection section of the original label. Therefore it is acceptable to place it in the PRECAUTIONS section of this proposed label.

Page 16: para 1: "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)."

Medial Officer Comment and Recommendation:

This statement was confirmed by the reviewer upon inspection of the Opportunistic Infection tables in the previously approved label. Accordingly, they are factual statements and are acceptable to the FDA.

Page 16: para 2: "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".

Medial Officer Comment and Recommendation:

This is a true statement, although the combination has not been studied, this statement may add to the safe management of patients treated with CellCept. It is appropriate to place in the PRECAUTIONS section of the label.

Page 16: para 4: "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)."

Medial Officer Comment and Recommendation:

This statement is based upon CDC recommendations:

1.) Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Use of vaccines and immune globulin in persons with altered immunocompetence. MMWR 1993;42(No. RR-04):1-16.

immunization recommendations of the Advisory Committee on ... Practices (ACIP). MMWR 1994;43(No. RR-01):1-38.

3.) Centers for Disease Control and Prevention. Update: Vaccine side effects, adverse reactions, contraindications, and precautions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996;45 (No. RR-12):1-35.

The following wording has been taken from the Neoral and Sandimmune labels regarding this issue for comparison:
Vaccination: During treatment with cyclosporine, vaccination may be less effective; and the use of live attenuated vaccines should be avoided.

The wording is the same, except the emphasis in the CellCept label is on live attenuated viruses. This wording is acceptable to the FDA given the safety concerns for these products in immunocompromised individuals.

Page 16: para10: "Drug Interactions: Drug Interactions studies with mycophenolate mofetil have been conducted with .....and

Medial Officer Comment and Recommendation:

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Page 18: para 2: " Oral Contraceptives:

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REPLACES THE FOLLOWING PARAGRAPH

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Medial Officer Comment and Recommendation:

While this study provides additional information regarding the potential interaction of CellCept with contraceptives, it does not definitively exclude the possibility of the potential failure of contraceptive agents. In this regard it is recommended that additional wording be placed in the label. Please see Biopharmaceutics review for recommended wording.

[redacted]

Medial Officer Comment and Recommendation:

Please delete this paragraph from the proposed label.

[redacted]

Page 19: para 3: " 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)."

Medial Officer Comment and Recommendation:

This wording is acceptable (see comment above).

Page 20: para 5: " Geriatric Use: Elderly patients may be at an increased risk of adverse reactions compared with younger individuals (see ADVERSE REACTIONS)."

Medial Officer Comment and Recommendation:

With regard to geriatric statements in the proposed label, the applicant is referred to the Geriatric Rule in the Code of Federal Regulations (21 CFR 201.55

[10]). This section of the CFR is very specific regarding wording of geriatric statements within the label. It appears that the statement from 21 CFR 201.57(f)(10)(A) is appropriate given the level of information known about the use of CellCept in patients over the age of 65 years. The applicant should place these statements below just before the statement that has been proposed.

"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 disease or other drug therapy."

Page 20: para 8: " 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)."

Medial Officer Comment and Recommendation:
This statement refers to findings in the original NDA review and so we find this wording acceptable.

Medial Officer Comment and Recommendation:

[redacted]

Page 33: para 9: " 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)."

Medial Officer Comment and Recommendation:
This statement is acceptable.

For additional comments regarding the proposed changes in the pharmacokinetics section of the label, see the biopharmacology review.

The labeling changes agreed upon by the applicant as a result of this review have been approved in the final draft label dated July 25, 2000. These changes are reflected in all of the formulations approved: capsules, tablets, infusion and suspensions.

Concurrence:
HFD-590 Team Leader: Cavaillé-Coll, M /S/ 7/26/00
HFD-590 Acting Division Director: Albrecht, R /S/ 7/21/00

CC:
HFD-590 Division Files
NDA File #50-722/S004
NDA File #50-723/ S-003
NDA File #50-758/ S-003
NDA File #50-759/ S-004
HFD-590 chemistry: Seggel
HFD-590 pharmtox: Hastings
HFD-590 micro: Bula
HFD-590 stat: Higgins
HFD-590 biopharm: Kumi

APPEARS THIS WAY
ON ORIGINAL