

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-722/S-004

50-723/S-003

50-758/S-003

50-759/S-004

APPROVAL LETTER

~~NDA 50-722/S-004~~

NDA 50-723/S-003

NDA 50-758/S-003

NDA 50-759/S-004

Syntex (U.S.A.) LLC
Attention: Sabine Geisel, Ph.D.
Senior Regulatory Program Manager
3401 Hillview Avenue
Palo Alto, California 94304

Dear Dr. Geisel:

Please refer to your supplemental new drug applications dated August 16, 1999 (NDA 50-722/S-004), and May 11, 2000 (NDAs 50-723/S-003, 50-758/S-003, 50-759/S-004), received on August 18, 1999, and May 12, 2000, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act 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 note that these applications are subject to the exemption provisions contained in section 125(d)(2) of Title I of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated June 6, July 12, July 18, and July 25, 2000.

These supplemental new drug applications provide for the following changes to the package insert (as well as other minor editorial changes):

- 1) **DESCRIPTION:** The phrase "... an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor" was added to the first sentence of this section to read:

"CellCept (mycophenolate mofetil) is the 2-morpholinoethyl ester of mycophenolic acid (MPA); an immunosuppressive agent; inosine monophosphate dehydrogenase (IMPDH) inhibitor."

- 2) **CLINICAL PHARMACOLOGY**

- **Pharmacokinetics Metabolism:** The following sentence was added to the first paragraph of this section:

"In vivo, MPAG is converted to MPA via enterohepatic recirculation."

- **Pharmacokinetics Excretion:** The phrase "At clinically encountered," was added to the fourth sentence of the first paragraph in this section:

"At clinically encountered concentrations, MPA and MPAG are usually not removed by hemodialysis."

The following sentence was also added:

“Bile acid sequestrants, such as cholestyramine, reduce MPA AUC by interfering with enterohepatic circulation of the drug (see **OVERDOSAGE**).”

- **Pharmacokinetics Renal Insufficiency:** The following sentences were added to the third paragraph in this section:

“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.”

The following was added as a fourth paragraph:

“In 8 patients with primary non-function of the organ following renal transplantation, plasma concentrations of MPAG accumulated about 6- to 8-fold after multiple dosing for 28 days. Accumulation of MPA was about 1- to 2-fold.”

- **Pharmacokinetics Hepatic Insufficiency:** The fourth sentence of this section was modified to include “such as primary biliary cirrhosis.” The phrases “severe hepatic impairment (aminopyrine breath test less than 0.2% of dose) due to” and “MMF was rapidly converted to MPA” were added so that the section reads:

“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. MPA AUC was 44.1 $\mu\text{g}\cdot\text{h/mL}$ (± 15.5).”

- **Pharmacokinetics Geriatric Use:** This new sentence was added to the **CLINICAL PHARMACOLOGY** section:

“Pharmacokinetics in the elderly have not been studied.”

- 3) **WARNINGS (see boxed WARNING):** The third sentence of the first paragraph was modified to add “including opportunistic infections, fatal infections and sepsis” to read:

“Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections and sepsis.”

The eighth paragraph was changed to read:

“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**).”

4) **PRECAUTIONS General:** The following sentences were added to this section:

“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**).”

The phrase “both have the potential to cause bone marrow suppression and” was added to read:

“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.”

The following sentences were also added to this section:

“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**).”

- **Phenylketonurics:** The second and third sentences were added to this section to read:

“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.”

- **Drug Interactions Ganciclovir:** This sentence was added to the end of the section:

“In patients with renal impairment in which MMF and ganciclovir are coadministered, patients should be monitored carefully.”

- **Drug Interactions Oral Contraceptives:** This section was modified substantially and the following replaced the old language to read:

“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**).”

- **Drug Interactions Live Vaccines:** This new section was added to the package insert to read:

“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**).”

- **Geriatric Use:** This new section was added to the package insert:

“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**).”

- 5) **ADVERSE REACTIONS CellCept (oral):** This new sentence was added to the **ADVERSE REACTIONS** section:

“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**).”

- 6) **DOSAGE AND ADMINISTRATION CARDIAC TRANSPLANTATION**

- **CellCept Capsules, Tablets and Oral Suspension:** The following sentence was added to the section:

“However, in stable renal transplant patients, CellCept may be administered with food if necessary.”

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental NDAs 50-722/S-004; 50-723/S-003; 50-758/S-003; 50-759/S-004." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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
ON ORIGINAL**