



NDA 50-722/S-016  
NDA 50-723/S-013  
NDA 50-758/S-014  
NDA 50-759/S-019

Roche Palo Alto LLC  
c/o Hoffmann-La Roche, Inc.  
Attention: Wendy L. Corbett, Ph.D., MBA  
Senior Program Manager, Pharma Development Regulatory  
340 Kingsland Street  
Nutley, NJ 07110-1199

Dear Dr. Corbett:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Drug Product	Supplement Number	Date of Supplement	Date of Receipt
50-722	CellCept® (mycophenolate mofetil) Capsules, 250 mg	S-016	March 20, 2007	March 21, 2007
50-723	CellCept® (mycophenolate mofetil) Tablets, 500 mg	S-013	March 20, 2007	March 21, 2007
50-758	CellCept® (mycophenolate mofetil hydrochloride for injection), Intravenous, 500 mg/ 20 mL	S-014	March 20, 2007	March 21, 2007
50-759	CellCept® (mycophenolate mofetil for oral suspension), Oral Suspension, 200 mg/ mL	S-019	March 20, 2007	March 21, 2007

We acknowledge receipt of your submissions dated June 28, August 21, September 14 and September 21, 2007.

These supplemental new drug applications provide for revision to the package insert for CellCept® to include information on congenital malformations in offspring of patients exposed to mycophenolate mofetil during pregnancy.

The supplemental application provides for revisions as follows (deletions are ~~struck through~~ and additions are underlined):

1. The **BOXED WARNING** was modified as follows:

**Rx only**

**WARNING**

**Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should use CellCept. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.**

**Female users of childbearing potential must use contraception. Use of CellCept during pregnancy is associated with increased risk of pregnancy loss and congenital malformations.**

2. The **WARNINGS** section was modified as follows:

**WARNINGS**

(see boxed **WARNING**)

Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin (see **ADVERSE REACTIONS**). The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis. In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see **ADVERSE REACTIONS**).

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

CellCept has been administered in combination with the following agents in clinical trials: antithymocyte globulin (ATGAM®), OKT3 (Orthoclone OKT® 3), cyclosporine (Sandimmune®, Neoral®) and corticosteroids. The efficacy and safety of the use of CellCept in combination with other immunosuppressive agents have not been determined.

Lymphoproliferative disease or lymphoma developed in 0.4% to 1% of patients receiving CellCept (2 g or 3 g) with other immunosuppressive agents in controlled clinical trials of renal, cardiac, and hepatic transplant patients (see **ADVERSE REACTIONS**).

In pediatric patients, no other malignancies besides lymphoproliferative disorder (2/148 patients) have been observed (see **ADVERSE REACTIONS**).

**Pregnancy: Teratogenic Effects: Pregnancy Category D**

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Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant woman. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In the National Transplantation Pregnancy Registry (NTPR), there were data on 33 MMF-exposed pregnancies in 24 transplant patients; there were 15 spontaneous abortions (45%) and 18 live-born infants. Four of these 18 infants had structural malformations (22%). In postmarketing data (collected from 1995 to 2007) on 77 women exposed to system MMF during pregnancy, 25 had spontaneous abortions and 14 had a malformed infant or fetus. Six of 14 malformed offspring had ear abnormalities. Because these postmarketing data are reported voluntarily, it is not always possible to reliably estimate the frequency of particular adverse outcomes. These malformations seen in offspring were similar to findings in animal reproductive toxicology studies. For comparison, the background rate for congenital anomalies in the United States is about 3%, and NTPR data show a rate of 4-5% among babies born to organ transplant patients using other immunosuppressive drugs.

In animal reproductive toxicology studies, there were increased rates of fetal resorptions and malformations in the absence of maternal toxicity. Female rats and rabbits received mycophenolate mofetil (MMF) doses equivalent to 0.02 to 0.9 times the recommended human dose for renal and cardiac transplant patients, based on body surface area conversions. In rat offspring, malformations included anophthalmia, agnathia, and hydrocephaly. In rabbit offspring, malformations included ectopia cordis, ectopic kidneys, diaphragmatic hernia, and umbilical hernia.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. In certain situations, the patient and her healthcare practitioner may decide that the maternal benefits outweigh the risks to the fetus. Women using CellCept at any time during pregnancy should be encouraged to enroll in the National Transplantation Pregnancy Registry.

### **Pregnancy Exposure Prevention**

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 1 week prior to beginning therapy. CellCept therapy should not be initiated until a negative pregnancy test report is obtained.

Women of child-bearing potential (including pubertal girls and peri-menopausal women) taking CellCept must receive contraceptive counseling and use effective contraception. The patient should begin using her two chosen methods of contraception 4 weeks prior to starting CellCept therapy, unless abstinence is the chosen method. She should continue contraceptive use during therapy and for 6 weeks after stopping CellCept. Patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness. (See **PRECAUTIONS/Information for Patients** and **PRECAUTIONS/ Drug Interactions/Oral Contraceptives**)

~~Adverse effects on fetal development (including malformations) occurred when pregnant rats and rabbits were dosed during organogenesis. These responses occurred at doses lower than those~~

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~~associated with maternal toxicity, and at doses below the recommended clinical dose for renal, cardiac or hepatic transplantation. There are no adequate and well-controlled studies in pregnant women. However, as CellCept has been shown to have teratogenic effects in animals, it may cause fetal harm when administered to a pregnant woman. Therefore, CellCept should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus.~~

~~Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 1 week prior to beginning therapy. It is recommended that CellCept therapy should not be initiated by the physician until a report of a negative pregnancy test has been obtained.~~

~~Effective contraception must be used before beginning CellCept therapy, during therapy, and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method (see **PRECAUTIONS/Drug Interactions**). If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy (see **PRECAUTIONS/Pregnancy** and **Information for Patients**).~~

~~In patients receiving CellCept (2 g or 3 g) in controlled studies for prevention of renal, cardiac or hepatic rejection, fatal infection/sepsis occurred in approximately 2% of renal and cardiac patients and in 5% of hepatic patients (see **ADVERSE REACTIONS**).~~

### Neutropenia

Severe neutropenia [absolute neutrophil count (ANC)  $<0.5 \times 10^3/\mu\text{L}$ ] developed in up to 2.0% of renal, up to 2.8% of cardiac, and up to 3.6% of hepatic transplant patients receiving CellCept 3 g daily (see **ADVERSE REACTIONS**)....

3. The **PRECAUTIONS/Information for Patients** subsection was modified as follows:
- Give patients complete dosage instructions and inform them about the increased risk of lymphoproliferative disease and certain other malignancies.
  - Inform patients that they need repeated appropriate laboratory tests while they are taking CellCept.
  - Inform women of childbearing potential that use of CellCept in pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of birth defects, and that they must use effective contraception.
  - Discuss pregnancy plans with female patients of childbearing potential.
    - ◆ Any female of childbearing potential must use highly effective (two methods) contraception 4 weeks prior to starting CellCept therapy and continue contraception until 6 weeks after stopping CellCept treatment, unless abstinence is the chosen method (See **WARNINGS/Pregnancy**).
    - ◆ A patient who is planning a pregnancy should not use CellCept unless she cannot be successfully treated with other immunosuppressant drugs.

~~Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving CellCept. Patients should be given complete dosage instructions and informed of the~~

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~~increased risk of lymphoproliferative disease and certain other malignancies. Women of childbearing potential should be instructed of the potential risks during pregnancy, and that they should use effective contraception before beginning CellCept therapy, during therapy, and for 6 weeks after CellCept has been stopped (see **WARNINGS** and **PRECAUTIONS: Pregnancy**).~~

4. The **PRECAUTIONS/Drug Interactions/Oral Contraceptives** subsection was modified as follows:

However, it is recommended that oral contraceptives are coadministered with CellCept with caution and additional birth control methods be considered (see **PRECAUTIONS-WARNINGS/Pregnancy**).

5. The **PRECAUTIONS/Pregnancy** subsection was modified as follows:

### **Pregnancy**

~~**Category C** Teratogenic Effects: Pregnancy Category D. See **WARNINGS** section~~

~~In teratology studies in rats and rabbits, fetal resorptions and malformations occurred in rats at 6 mg/kg/day and in rabbits at 90 mg/kg/day, in the absence of maternal toxicity. These levels are equivalent to 0.03 to 0.92 times the recommended clinical dose in renal transplant patients and 0.02 to 0.61 times the recommended clinical dose in cardiac transplant patients on a BSA basis. In a female fertility and reproduction study conducted in rats, oral doses of 4.5 mg/kg/day caused malformations (principally of the head and eyes) in the first generation offspring in the absence of maternal toxicity. This dose was 0.02 times the recommended clinical dose in renal transplant patients and 0.01 times the recommended clinical dose in cardiac transplant patients when corrected for BSA.~~

~~There are no adequate and well-controlled studies in pregnant women. CellCept should not be used in pregnant women unless the potential benefit justifies the potential risk to the fetus. Effective contraception must be used before beginning CellCept therapy, during therapy and for 6 weeks after CellCept has been stopped (see **WARNINGS** and **PRECAUTIONS: Information for Patients**).~~

6. The **ADVERSE REACTIONS/Postmarketing Experience** subsection was modified as follows:

*Congenital Disorders:* Congenital malformations including ear malformations have been reported in offspring of patients exposed to mycophenolate mofetil during pregnancy (see **WARNINGS/Pregnancy**).

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html> that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions “**SPL for approved supplements NDA 50-722/S-016, NDA 50-723/S-013, NDA 50-758/S-014, and NDA 50-759/S-019.**”

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In addition, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed the revised product labeling and has determined that it contains significant new risk information relating to your drug product. We are hereby requesting that all promotional materials for your drug products that include representations about your drug product be revised to include the new risk information immediately. These revisions should include prominent disclosure of the important new information described in the **BOXED WARNINGS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS** sections of the revised package labeling. Please submit a written response to this request on or before September 28, 2007, stating whether you intend to comply with this request, by facsimile at (301)796-9878 or by mail to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you issue a letter communicating important information about these drug products (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH  
Food and Drug Administration  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Kristen Miller, Pharm.D., Safety Regulatory Project Manager, at (301) 796-1600.

Sincerely,

*{See appended electronic signature page}*

Renata Albrecht, M.D.  
Director  
Division of Special Pathogen and Transplant  
Products  
Office of Antimicrobial Products  
Center for Drug Evaluation and Research

Enclosure

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**This is a representation of an electronic record that was signed electronically and  
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/s/

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Renata Albrecht  
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