DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-722/S-021
NDA 50-723/S-019
NDA 50-758/S-019
NDA 50-759/S-024

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

Dear Dr. Corbett:

Please refer to your supplemental new drug applications dated December 18, 2008, received December 19, 2008, 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-021	December 18, 2008	December 19, 2008
50-723	CellCept® (mycophenolate mofetil) Tablets, 500 mg	S-019	December 18, 2008	December 19, 2008
50-758	CellCept® (mycophenolate mofetil hydrochloride for injection) Intravenous, 500 mg	S-019	December 18, 2008	December 19, 2008
50-759	CellCept® (mycophenolate mofetil) Oral Suspension, 200 mg/mL	S-024	December 18, 2008	December 19, 2008

We acknowledge receipt of your submissions dated June 4, 2009.

These supplemental new drug applications provide for the following changes to the package insert and medication guide:

PACKAGE INSERT

1. In the **WARNINGS** section of the package insert, a new paragraph is added as follows:

   Pure Red Cell Aplasia (PRCA)
   Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents. The mechanism for mycophenolate mofetil induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of CellCept therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

2. In the **PRECAUTIONS/Drug Interactions** subsection of the package insert, a new subsection is added as follows:

   Ciprofloxacin and Amoxicillin plus Clavulanic Acid

   A total of 64 CellCept-treated renal transplant recipients received either oral ciprofloxacin 500 mg bid or amoxicillin plus clavulanic acid 375 mg for 7 or at least 14 days. Approximately 50% reductions in median trough MPA concentrations (pre-dose) from baseline (CellCept alone) were observed in 3 days following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA concentrations tended to diminish within 14 days of antibiotic therapy and ceased within 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction is an antibiotic-induced reduction in glucuronidase-possessing enteric organisms leading to a decrease in enterohepatic recirculation of MPA. The change in trough level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

3. In the **ADVERSE REACTIONS** section, Tables 8 and 10, the word “hemic” is replaced by the word “hematologic”

4. In the **ADVERSE REACTIONS**/**Postmarketing Experience** subsection of the package insert, a new sentence is added as follows:

   Hematologic and Lymphatic: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents.

MEDICATION GUIDE:

5. In the **What should I tell my healthcare provider before taking CellCept** section, the second bullet is revised as follows:

   - **have Phenylketonuria (PKU).** CellCept oral suspension contains aspartame (a source of phenylalanine)

6. In the "**Tell your healthcare provider about all of the medicines you are taking including prescription and nonprescription medicines, vitamins and herbal supplements**" section, the 3rd bullet is modified as follows:

   - Acyclovir (Zovirax®), valacyclovir (Valtrex®), ganciclovir (Cytovene®-IV, Vitrasert®), valganciclovir (Valcyte®)

7. In the "**Tell your healthcare provider about all of the medicines you are taking including prescription and nonprescription medicines, vitamins and herbal supplements**", a new bullet is added as follows:

   - ciprofloxacin (Cipro®, Cipro® XR, Ciloxan®, Proquin® XR) and amoxicillin plus clavulanic acid (Augmentin®, Augmentin XR™)

8. In the **How should I take CellCept?** section, the 5th bullet is revised as follows:

   - Most people take CellCept by mouth either as blue and ~~orange~~ brown capsules or lavender tablets. Some people may get CellCept soon after their transplant surgery as an infusion into a vein

9. The "**What are the possible side effects of CellCept?**" section, the 4th and 5th bullets are modified as follows:

   - **red blood cells.** Red blood cells carry oxygen to your body tissues. You have a higher chance of getting severe anemia when your red blood cell count is low

   - **platelets**. Platelets help with blood clotting

   Your healthcare provider will do blood tests before you start taking CellCept and during treatment with CellCept to check your blood cell counts.

   Tell your healthcare provider right away if you have any signs of infection (see **"What is the most important information I should know about CellCept?"**), ~~Also, tell your healthcare provider about~~ or any unexpected bruising or bleeding. Also, tell your healthcare provider if you have unusual tiredness, lack of energy, dizziness or fainting.

10. The "**Common side effects include**" section, is modified as follows:

    Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or to Roche Professional Drug Safety at 1-800-526-6367.

11. In the **"General Information about CellCept"** section, the second paragraph is modified as follows:

    - For more information, ~~go to www.rocheusa.com/products/CellCept or~~ call 1-800-526-6367 or visit www.rocheusa.com/products/cellcept.

12. After the Copyright information the sentence is modified as follows:

    - For additional copies of this Medication Guide, please call ~~1-800-526-6367~~ 1-800-617-8191 or visit www.rocheusa.com/products/cellcept.

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 for the package insert and medication guide submitted on June 4, 2009.

The final printed labeling (FPL) must be identical to the enclosed package insert

As soon as possible, please submit the 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 to the enclosed labeling for the package insert. Upon receipt, we will transmit this version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as, "**SPL for approved NDA 50-722/S-021, NDA 50-723/S-019, NDA 50-758/S-019, NDA 50-759/S-024."**

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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, call Judit Milstein, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, M.D., MPH
Deputy Director of Safety
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Package Insert

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ozlem Belen

6/18/2009 12:39:15 PM