



NDA 50-722/S-015  
NDA 50-723/S-012  
NDA 50-758/S-013  
NDA 50-759/S-018

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 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA Number	Drug Product	Supplement Number	Date of Supplement	Date of Receipt
50-722	CellCept <sup>®</sup> (mycophenolate mofetil) Capsules, 250 mg	S-015	February 28, 2007	March 1, 2007
50-723	CellCept <sup>®</sup> (mycophenolate mofetil) Tablets, 500 mg	S-012	February 28, 2007	March 1, 2007
50-758	CellCept <sup>®</sup> (mycophenolate mofetil hydrochloride for injection) Intravenous, 500 mg/ 20 mL	S-013	February 28, 2007	March 1, 2007
50-759	CellCept <sup>®</sup> (mycophenolate mofetil for oral suspension) Oral Suspension, 200 mg/mL	S-018	February 28, 2007	March 1, 2007

We acknowledge receipt of your submission dated October 24, 2007. These submissions constitute a complete response to our approvable letter dated October 16, 2007.

These supplemental application provides for revisions as follows (~~struckthrough text~~ = deletions, underlined text = additions):

1. In the **PRECAUTIONS/Drug Interactions** subsection, the first paragraph has been revised as follows:

Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, sevelamer, trimethoprim/sulfamethoxazole, norfloxacin, and metronidazole. Drug interaction studies have not been conducted with other drugs that may be commonly administered to renal, cardiac or hepatic transplant patients. CellCept has not been administered concomitantly with azathioprine.

2. The **PRECAUTIONS/Drug Interactions/Cyclosporine** subsection has been revised as follows:

Cyclosporine (Sandimmune<sup>®</sup>) 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 stable renal transplant patients. The mean ( $\pm$ SD) AUC(0-12h) and C<sub>max</sub> of cyclosporine after 14 days of multiple doses of mycophenolate mofetil were 3290 ( $\pm$ 822) ng•h/mL and 753 ( $\pm$ 161) ng/mL, respectively, compared to 3245 ( $\pm$ 1088) ng•h/mL and 700 ( $\pm$ 246) ng/mL, respectively, 1 week before administration of mycophenolate mofetil. ~~The effect of cyclosporine on mycophenolate mofetil pharmacokinetics could not be evaluated in this study; however, plasma concentrations of MPA were similar to that for healthy volunteers.~~

In renal transplant patients, mean MPA exposure (AUC<sub>0-12h</sub>) was approximately 30-50% greater when mycophenolate mofetil is administered without cyclosporine compared with when mycophenolate mofetil is coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP-2) transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine.

3. In the **PRECAUTIONS/Drug Interactions** subsection, a new subsection titled Sevelamer has been added as follows:

#### Sevelamer

Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA C<sub>max</sub> and AUC<sub>0-12h</sub> by 36% and 26% respectively. This data suggest that sevelamer and other calcium free phosphate binders should not be administered simultaneously with CellCept. Alternatively, it is recommended that sevelamer and other calcium free phosphate binders preferentially could be given 2 hours after CellCept intake to minimize the impact on the absorption of MPA.

4. In the **PRECAUTIONS/Drug Interactions** subsection, a new subsection titled Norfloxacin and Metronidazole has been added as follows:

Norfloxacin and Metronidazole

Following single-dose administration of mycophenolate mofetil (1 g) to 11 healthy volunteers on day 4 of a 5 day course of a combination of norfloxacin and metronidazole, the mean MPA AUC<sub>0-48h</sub> was significantly reduced by 33% compared to the administration of mycophenolate mofetil alone (p<0.05). Therefore, CellCept is not recommended to be given with the combination of norfloxacin and metronidazole. There was no significant effect on mean MPA AUC<sub>0-48h</sub> when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately. The mean (±SD) MPA AUC<sub>0-48h</sub> after coadministration of mycophenolate mofetil with norfloxacin or metronidazole separately was 48.3 (±24) µg·h/mL and 42.7 (±23) µg·h/mL, respectively, compared with 56.2 (±24) µg·h/mL after administration of mycophenolate mofetil alone.

5. In the **PRECAUTIONS/Drug Interactions** subsection, a new subsection titled Rifampin has been added as follows:

Rifampin

In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure (AUC<sub>0-12h</sub>) has been observed with concomitant administration of mycophenolate mofetil and rifampin. Therefore, CellCept is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.

We have completed our review of these application and they are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Submit labeling [21 CFR 314.50(1)] 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 and verification, 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-015, NDA 50-723/S-012, NDA 50-758/S013, and NDA 50-759/S-018.**”

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  
5515 Security Lane  
HFD-001, Suite 5100  
Rockville, MD 20852

NDA 50-722/S-015  
NDA 50-723/S-012  
NDA 50-758/S-013  
NDA 50-759/S-018  
Page 4

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 Hyun Son, Pharm.D., 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: 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/

-----  
Renata Albrecht  
12/20/2007 11:12:42 AM