DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-722/S-013
NDA 50-723/S-010
NDA 50-758/S-012
NDA 50-759/S-015

Roche Palo Alto LLC
c/o Hoffmann-La Roche, Inc.
Attention: Mr. Anthony J. Corrado
Director, Drug Regulatory Affairs
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Mr. Corrado:

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

NDA	Drug Product	Supplement Number	Letter Date	Receipt Date
50-722	CellCept® (mycophenolate mofetil) Capsules, 250 mg	S-013	April 15, 2005	April 18, 2005
50-723	CellCept® (mycophenolate mofetil) Tablets, 500 mg	S-010	April 15, 2005	April 18, 2005
50-758	CellCept® (mycophenolate mofetil hydrochloride for injection), Intravenous, 500 mg/ 20 mL	S-012	April 15, 2005	April 18, 2005
50-759	CellCept® (mycophenolate mofetil hydrochloride for oral suspension), Oral Suspension, 200 mg/mL	S-015	April 15, 2005	April 18, 2005

We acknowledge receipt of your submissions to the above supplemental NDAs dated May 3, 2005.

These prior approval supplements provide for the following changes to the package insert (additions are indicated by a double underline and deletions are struck out):

1. The following changes were made to the **PRECAUTIONS/ Drug Interactions** subsection:

Drug Interactions~~:~~
Drug interaction studies with mycophenolate mofetil have been conducted with acyclovir, antacids, cholestyramine, cyclosporine, ganciclovir, oral contraceptives, and trimethoprim/sulfamethoxazole. 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.

Acyclovir~~:~~
Coadministration of mycophenolate mofetil (1 g) and acyclovir (800 mg) to 12 healthy volunteers resulted in no significant change in MPA AUC and Cmax. However, MPAG and acyclovir plasma AUCs were increased 10.6% and 21.9%, respectively. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for ~~the two drugs~~ mycophenolate and acyclovir or its prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the concentrations of both drugs.

Ganciclovir:
Following single-dose administration to 12 stable renal transplant patients, no pharmacokinetic interaction was observed between mycophenolate mofetil (1.5 g) and intravenous ganciclovir (5 mg/kg). Mean (±SD) ganciclovir AUC and Cmax (n=10) were 54.3 (±19.0) μg•h/mL and 11.5 (±1.8) μg/mL, respectively, after coadministration of the two drugs, compared to 51.0 (±17.0) μg•h/mL and 10.6 (±2.0) μg/mL, respectively, after administration of intravenous ganciclovir alone. The mean (±SD) AUC and Cmax of MPA (n=12) after coadministration were 80.9 (±21.6) μg•h/mL and 27.8 (±13.9) μg/mL, respectively, compared to values of 80.3 (±16.4) μg•h/mL and 30.9 (±11.2) μg/mL, respectively, after administration of mycophenolate mofetil alone. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the two drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are coadministered, patients should be monitored carefully.

2. "Leukopenia" was added to the **ADVERSE REACTIONS/ Pediatrics** subsection:

Pediatrics~~:~~
The type and frequency of adverse events in a clinical study in 100 pediatric patients 3 months to 18 years of age dosed with CellCept oral suspension 600 mg/m2 bid (up to 1 g bid) were generally similar to those observed in adult patients dosed with CellCept capsules at a dose of 1 g bid with the exception of abdominal pain, fever, infection, pain, sepsis, diarrhea, vomiting, pharyngitis, respiratory tract infection, hypertension, leukopenia, and anemia, which were observed in a higher proportion in pediatric patients.

3. The first paragraph of the **OVERDOSAGE** section was revised as follows:

OVERDOSAGE: ~~There has been no reported experience of overdosage of mycophenolate mofetil in humans.~~
The experience with overdose of CellCept in humans is very limited. The events received from reports of overdose fall within the known safety profile of the drug. The highest dose administered to renal transplant patients in clinical trials has been 4 g/day. In limited experience with cardiac and hepatic transplant patients in clinical trials, the highest doses used were 4 g/day or 5 g/day. At doses of 4 g/day or 5 g/day, there appears to be a higher rate, compared to the use of 3 g/day or less, of gastrointestinal intolerance (nausea,

vomiting, and/or diarrhea), and occasional hematologic abnormalities, principally neutropenia, leading to a need to reduce or discontinue dosing.

4. Editorial changes were made throughout the package insert which include the addition of table numbers, reformatting the subsection titles from italics to Arial font, and deleting the colons after the subsection titles. These changes were made to be in compliance with the electronic submissions.

We have completed the review of these supplemental new drug applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the agreed upon labeling text (enclosed). Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (text for the package insert submitted May 3, 2005).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submission in Electronic Format – NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions as "**FPL for approved supplements NDA 50-722/S-013, NDA 50-723/S-010, NDA 50-758/S-012, and NDA 50-759/S-015."** Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about these drug products (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 these NDAs and a copy to the following address:

MedWatch: The FDA Safety Information and Adverse Event Reporting Program
Office Of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Mail Stop 4447
Silver Spring, MD 20993-0002

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 call Brenda Marques, 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

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

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