



NDA 50722/S033
NDA 50723/S032
NDA 50758/S030
NDA 50759/S038

SUPPLEMENT APPROVAL

Roche Palo Alto LLC
c/o Genentech, Inc.
Attention: Barbara S. Taylor, PhD
Regulatory Agent
1 DNA Way
San Francisco, CA 94080-4990

Dear Dr. Taylor:
Please refer to your Supplemental New Drug Applications (sNDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) as follows:

NDA Number	Supplement #	Drug Name	Submitted and received on
50722	033	CellCept (mycophenolate mofetil) Capsules, 250 mg	January 12, 2015
50723	032	CellCept (mycophenolate mofetil) Tablets, 500 mg	January 12, 2015
50758	030	CellCept (mycophenolate mofetil hydrochloride) Intravenous, 500mg/20 mL	January 12, 2015
50759	038	CellCept (mycophenolate mofetil) Oral Suspension, 200 mg/mL	January 12, 2015

We acknowledge receipt of your amendments dated June 30 and July 6, 2015.

These “Prior Approval” supplemental new drug applications provide for the following revisions to the Package Insert (additions are underlined and deletions are ~~struck through~~).

1. In the **WARNINGS/Embryofetal Toxicity** section, the terms “and nervous system” are added at the end of the subsection as follows:

Embryofetal Toxicity

Mycophenolate mofetil (MMF) can cause fetal harm when administered to a pregnant female. 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 and nervous system (see **PRECAUTIONS: Pregnancy**).

2. In the **WARNINGS/Pure Red Cell Aplasia (PRC)** section, last sentence, the words “SHOULD NEVER” are replaced with the words “MUST NOT.”
3. In the **PRECAUTIONS/Drug Interactions/Cyclosporine** subsection, the second paragraph is revised as follows:

Cyclosporine A interferes with MPA enterohepatic recirculation. In renal transplant patients, mean MPA exposure (AUC_{0-12h}) 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; changes in MPA exposure should be expected when switching patients from cyclosporine A to one of the immunosuppressants which do not interfere with MPA’s enterohepatic cycle (e.g. tacrolimus;belatacept).

4. In the **PRECAUTIONS/Drug Interactions** section, a new subsection titled “Telmisartan” is added as follows:

Telmisartan

Concomitant administration of telmisartan and CellCept resulted in an approximately 30% decrease in mycophenolic acid (MPA) concentrations. Telmisartan changes MPA’s elimination by enhancing PPAR gamma (peroxisome proliferator-activated receptor gamma) expression, which in turn results in an enhanced UGT1A9 expression and activity.

5. In the **PRECAUTIONS /Pregnancy** section, first paragraph, the terms “and nervous system” are added at the end of the first sentence as follows:

Pregnancy

Pregnancy Category D. See **WARNINGS** section.

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,~~ and nervous system. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. 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.

6. In the **ADVERSE REACTIONS/Postmarketing Experience** section, the *Congenital Disorders* and *Hematologic and Lymphatic* subsections are revised as follows:

Postmarketing Experience

Congenital Disorders: Embryofetal Toxicity: Congenital malformations, including ear, facial, cardiac and nervous system malformations and an increased incidence of first trimester pregnancy loss have been reported following exposure to mycophenolate mofetil during pregnancy (see **PRECAUTIONS: Pregnancy**).

Digestive: Colitis (sometimes caused by cytomegalovirus), pancreatitis, isolated cases of intestinal villous atrophy.

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

7. In the **DOSAGE AND ADMINISTRATION/ Preparation for Oral Suspension** section, in the first sentence of the third paragraph, the words “rats and rabbits” are replaced with the word “humans” as follows

Preparation of Oral Suspension

Mycophenolate mofetil has demonstrated teratogenic effects in ~~rats and rabbits~~ humans.

8. In the **DOSAGE AND ADMINISTRATION/CellCept Intravenous/Adults** subsection, last sentence the words “SHOULD NEVER” are replaced with the words “MUST NOT” as follows:

CAUTION: CELLCEPT INTRAVENOUS SOLUTION ~~SHOULD NOT~~ MUST NOT BE ADMINISTERED BY RAPID OR BOLUS INTRAVENOUS INJECTION (see **WARNINGS).**

9. In the **HANDLING AND DISPOSAL** section, first sentence the words “in rats and rabbits” are replaced with the words “in humans” as follows:

HANDLING AND DISPOSAL

Mycophenolate mofetil has demonstrated teratogenic effects ~~in rats and rabbits~~ in humans (see **Pregnancy and WARNINGS: Embryofetal Toxicity**).

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, which is identical to the labeling text submitted on June 30 and July 2, 2015.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling text for the package insert, with the addition of any labeling changes in pending “Changes Being Effectuated” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDAs, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in these supplemental applications, as well as annual reportable changes and annotate each change. To facilitate review of your submissions, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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REPORTING REQUIREMENTS

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

If you have any questions, call Judit Milstein, Chief, Project Management Staff, at (301) 796-0763.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Director for Safety
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

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

/s/

OZLEM A BELEN
07/09/2015