



**IMPORTANT  
DRUG  
WARNING**

October 2007

**Subject: Important Changes in the CellCept® (mycophenolate mofetil) Prescribing Information – Use of CellCept is Associated with Increased Pregnancy Loss and Congenital Malformations/Change from Pregnancy Category C to Pregnancy Category D**

Dear Health Care Professional:

Roche Laboratories Inc. would like to inform you that use of CellCept during pregnancy is associated with increased pregnancy loss and congenital malformations. This new important safety information in the CellCept Prescribing Information includes:

**Boxed WARNING and WARNINGS:**

- Increased risk of first trimester pregnancy loss and increased risk of congenital malformations, especially external ear and facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney.

**PRECAUTIONS/Pregnancy:**

- Changed to Pregnancy Category D based on positive evidence of fetal risk observed in postmarketing data and from the United States National Transplantation Pregnancy Registry, similar to malformations seen in animal reproductive toxicology studies.

**PRECAUTIONS/Information for Patients:**

- Informing females of childbearing potential about risks (pregnancy loss/malformations) associated with CellCept use during pregnancy.
- Requiring that female patients of childbearing potential must receive contraceptive counseling and must use effective contraception.
- Advising that a patient who is planning a pregnancy should not use CellCept unless she cannot be successfully treated with other immunosuppressant drugs.

**The pregnancy category for CellCept has been changed from Category C (Risk of Fetal Harm Cannot be Ruled Out) to Category D (Positive Evidence of Fetal Risk).**

This change is a result of postmarketing data from the United States National Transplantation Pregnancy Registry (NTPR), and additional postmarketing data collected in women exposed to systemic MMF during pregnancy.

Based on postmarketing data from the NTPR and Roche worldwide adverse event reporting system, use of CellCept 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 December 2006, the NTPR published data from prospective cases where 24 female transplant patients reported 33 pregnancies exposed to mycophenolate mofetil-containing regimens. 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 systemic 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. Similar structural malformations have been observed in preclinical animal reproductive toxicology studies.

During the development of CellCept, animal reproductive toxicology studies were performed to assess the potential for birth defects, and there were increased rates of fetal resorptions and malformations in the absence of maternal toxicity. Female rats and rabbits received mycophenolate mofetil 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.

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 is obtained. Women of childbearing 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. A patient who is planning pregnancy should not use CellCept unless she cannot be successfully treated with other immunosuppressant drugs.

**National Transplantation Pregnancy Registry:** To monitor fetal outcomes of pregnant women exposed to CellCept, a National Transplantation Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-877-955-6877.

Roche Laboratories will continue to monitor the safety of CellCept through established reporting mechanisms and notify regulatory authorities of any serious adverse events for evaluation. You can assist us in monitoring the safety of CellCept by reporting adverse reactions to us at 1-800-526-6367, by FAX at 1-800-532-3931, or to FDA at [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or by mail to MedWatch, HF-2, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20851.

## **Important Information about CellCept® (mycophenolate mofetil)**

### **Indications:**

CellCept is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. CellCept should be used concomitantly with cyclosporine and corticosteroids.

### **Contraindications:**

Allergic reactions to CellCept have been observed; therefore, CellCept is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product. CellCept Intravenous is contraindicated in patients who are allergic to Polysorbate 80 (TWEEN).

### **Important Safety Information:**

#### **WARNING:**

**Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. 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. Physicians should inform female patients that CellCept use during pregnancy is associated with increased rates of pregnancy loss and congenital malformations.**

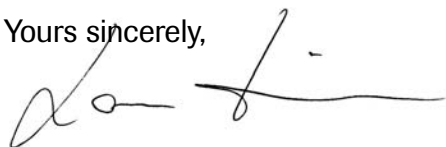
- Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.
- Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, and sepsis.
- CellCept can cause fetal harm when administered to a pregnant woman. A patient who is planning a pregnancy should not use CellCept unless she cannot be successfully treated with other immunosuppressant drugs. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patients should be apprised of the potential hazard to the fetus.
- Women of childbearing potential (including pubertal girls and peri-menopausal women) taking CellCept must receive contraceptive counseling and use effective contraception. The patient should begin using her chosen contraceptive method 4 weeks prior to starting CellCept therapy. She should continue contraceptive use during therapy and for 6 weeks after stopping CellCept. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. Patients should be aware that CellCept reduces blood levels of the hormones in the oral contraceptive pill and could theoretically reduce its effectiveness.

- 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. Patients receiving CellCept should be monitored for neutropenia. If neutropenia develops (ANC  $<1.3 \times 10^3/\mu\text{L}$ ), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see the **DOSAGE AND ADMINISTRATION** section of the CellCept Prescribing Information).
- Gastrointestinal bleeding (requiring hospitalization) has been observed in approximately 3% of renal, in 1.7% of cardiac, and in 5.4% of hepatic transplant patients treated with CellCept 3 g daily.
- Common adverse events that were reported in  $\geq 20\%$  of patients in CellCept group in controlled studies in prevention of renal, cardiac or hepatic allograft rejection are listed in Table 8 of the **ADVERSE REACTIONS** section of the CellCept Prescribing Information.

Please see the enclosed CellCept complete Prescribing Information, which includes additional information for Warnings, Precautions, and Dosage and Administration.

If you have any questions or require additional information regarding the use of CellCept, please contact the Roche Pharmaceuticals Service Center at 1-800-526-6367 from 8:30 AM to 6:00 PM Eastern Standard Time, Monday through Thursday, and 8:30 AM to 5:00 PM on Friday.

Yours sincerely,



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