



**IMPORTANT
DRUG
WARNING**

August 2009

Subject: Important Changes in the CellCept® (mycophenolate mofetil) Prescribing Information – Reports of Pure Red Cell Aplasia (PRCA) in Patients Treated with CellCept

Dear Health Care Professional:

Roche Laboratories Inc. would like to inform you that based on postmarketing data from the Roche worldwide adverse event reporting system, cases of Pure Red Cell Aplasia (PRCA) have been reported in patients treated with CellCept. The new PRCA safety information has been added to the WARNINGS and ADVERSE REACTIONS sections of the CellCept Prescribing Information. This new important safety information in the CellCept Prescribing Information includes:

REVISIONS TO PRODUCT LABELING REGARDING PRCA:

WARNINGS

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.

ADVERSE REACTIONS

Postmarketing Experience

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

SUMMARY OF INFORMATION ON PRCA AND CASES REPORTED WITH CELLCEPT:

PRCA is a type of anemia in which there is a selective reduction of red blood cell precursors on bone marrow examination. PRCA describes a condition in which red blood cell precursors in bone marrow are nearly absent. A threshold of less than 5% erythroblasts in the bone marrow with adequate cellularity and a peripheral blood reticulocyte count of less than 10,000/mm³ are criteria commonly used to establish the diagnosis of PRCA. Other blood components such as platelets and white blood cells are not affected in PRCA.

PRCA may be idiopathic or occur as a manifestation of an underlying condition. Approximately 5% of all cases of PRCA are drug induced. Patients with PRCA may present with fatigue, lethargy, and/or abnormal paleness of the skin (pallor). Anemia is the primary clinical concern in PRCA. The degree of anemia can range from subclinical to severe. Anemia in acute self-limited PRCA is barely noticeable; however, profound anemia can occur in chronic acquired PRCA and in congenital PRCA. Patients with severe anemia have symptoms and signs of uncompensated anemia and present with weakness, tachycardia, and dyspnea.

On February 24, 2008, Roche searched its global safety database for CellCept cases potentially associated with PRCA. Forty-one cases of PRCA were reported in patients receiving CellCept. Some patients were also receiving other medicines that could have contributed to the development of PRCA (alemtuzumab, tacrolimus, and azathioprine). In 16 of the reported cases, dose reduction (4 cases) or discontinuation (12 cases) of CellCept led to resolution of the condition. The mechanism by which CellCept is associated with PRCA is not known but may be related to immunosuppression. When PRCA occurs in a patient on multiple immunosuppressants, the relative contribution of the drugs to PRCA and the prophylaxis of rejection must be considered before a decision is made to discontinue a drug.

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, or by mail to MedWatch, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787.

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.

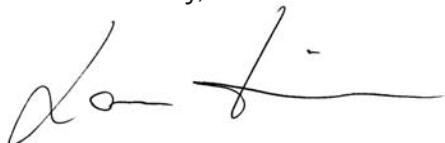
- Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.
- Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, and sepsis.
- Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. Hemiparesis, apathy, confusion, cognitive deficiencies and ataxia were the most frequent clinical features observed. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.
- 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 patient 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 **DOSAGE AND ADMINISTRATION**).
- Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressive agents. 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.
- 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 complete 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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Vice President
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