IMPORTANT DRUG WARNING

June 2008

Subject: Important Changes in the CellCept® (mycophenolate mofetil) Prescribing Information – Reports of Progressive Multifocal Leukoencephalopathy (PML) 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 Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients treated with CellCept. The new PML 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 PML:

WARNINGS

Infections

Progressive Multifocal Leukoencephalopathy (PML)

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.

Roche Laboratories Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

ADVERSE REACTIONS

Postmarketing Experience

Cases of progressive multifocal leukoencephalopathy (PML), sometimes fatal, have been reported in patients treated with CellCept. The reported cases generally had risk factors for PML, including treatment with immunosuppressant therapies and impairment of immune function.

SUMMARY OF INFORMATION ON PML AND CASES REPORTED WITH CELLCEPT:

PML is a rare, progressive, demyelinating disease of the central nervous system (CNS) that usually leads to death or severe disability. PML is caused by the reactivation of the JC virus, a polyomavirus that resides in latent form in 70%-90% of the adult population worldwide. JC virus usually remains latent, typically only causing PML in immunocompromised patients. The factors leading to activation of the latent infection are not fully understood although abnormalities in T-cells have been described as important for reactivation of JC virus and PML. Patients usually present with focal CNS abnormalities and radiographic evidence of white matter disease without mass effect.

PML has been described in transplant patients involving different immunosuppressant medicines. Seventy-five percent of all the PML cases reported in transplant recipients presented subacutely: hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia were the most frequently presented features. PML should be considered in any transplant recipient who develops neurological symptoms prompting consultation with a neurologist as clinically indicated. Other than reducing the amount of immunosuppression in patients who develop PML, there are no interventions that may prevent, treat or stop the progression of PML if disease develops. In transplant patients, reduced immunosuppression may place the graft at risk.

On July 8, 2007, Roche searched its global safety database for CellCept cases potentially associated with PML. Ten confirmed and seven possible cases were reported. Diagnoses were confirmed by detection of JC virus in the cerebrospinal fluid and/or brain biopsy. The indication for CellCept use for the ten confirmed cases was as follows: six solid organ transplant patients (three renal, two lung, and one heart transplant patient) and four systemic lupus erythematosus (SLE) patients. The indication for CellCept use for the possible cases was as follows: four solid organ transplant patients (three renal, one heart) and two SLE patients. The seventh possible case was an HIV-positive patient who received CellCept after being diagnosed with PML and who subsequently died of PML infection. Transplant patients were taking concomitant immunosuppressants including steroids, cyclosporine, tacrolimus and azathioprine; SLE patients were taking concomitant medications including steroids, cyclophosphamide, and cyclosporine.

Of the 17 cases, seven had a fatal outcome, five improved, and five had an unknown outcome or the event was ongoing at the time of reporting. One of the fatal cases initially improved with no signs of PML at two years after diagnosis and later died of unrelated causes.

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, 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.

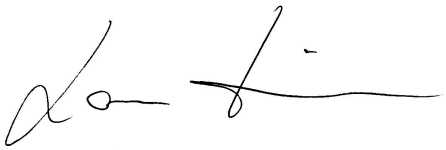
- Patients receiving immunosuppressive regimens involving combinations of drugs, including CellCept, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.
- Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections, and sepsis.
- 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) $<0.5 \times 10^3/\mu L$] 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 $<1.3 \times 10^3/\mu L$), dosing with CellCept should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately (see **DOSAGE AND ADMINISTRATION**).
- 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 ≥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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16-004-104-193-0608

MDM R4409-08