Roche

Pharmaceuticals

IMPORTANT SAFETY INFORMATION

February 1, 2007

Subject: **Higher than expected incidence of acute rejection in cardiac transplant patients switched from calcineurin inhibitors in combination with CellCept® (mycophenolate mofetil) to Rapamune® (sirolimus) in combination with CellCept® at 12 weeks post heart transplantation**

Dear Health Care Professional:

Roche Laboratories Inc., following discussion with the U.S. Food and Drug Administration, would like to inform you of important safety information regarding the termination of the Heart Spare The Nephron (STN) clinical trial due to an observed increased incidence of grade IIIA acute rejection in heart transplant patients switched from a calcineurin inhibitor (CNI) in combination with CellCept® (mycophenolate mofetil) to Rapamune® (sirolimus) in combination with CellCept® at 12 weeks post heart transplantation.

The safety and efficacy of CellCept® in combination with sirolimus following withdrawal of initial calcineurin inhibitor therapy has not been established.

The Heart STN clinical trial[1] was designed to investigate whether renal function benefit could be achieved with the withdrawal of calcineurin inhibitor therapy followed by the introduction of sirolimus at 12 weeks post heart transplantation. Following heart transplantation, all patients received the immunosuppressive therapy for their center, including CellCept® in combination with either cyclosporine or tacrolimus, and corticosteroids.[2] Fifteen patients had been randomized to one of two arms in the trial

[1] Roche Study MT18328, Heart Spare the Nephron (STN) Study: A prospective, open label, randomized, multicenter, multinational study evaluating the overall efficacy and safety including the effect on renal function of sirolimus (Rapamune®) replacing CNI in a regimen of CNI, mycophenolate mofetil (MMF) and steroids in heart transplant patients.

[2] In the terminated Heart STN clinical trial, at the time of switch, a target MPA trough level of 2.0 µg/mL and a sirolimus trough level of 5-10 ng/mL (HPLC) or 6-12 ng/mL (EMIT) were to be achieved. CNI trough levels were monitored to the standard of care.

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

when this study was stopped prematurely. In the treatment group, seven heart transplant recipients were switched from CNI to sirolimus at 12 weeks post heart transplantation while maintaining CellCept® (CellCept® dosing to achieve a protocol suggested minimum MPA trough of 2.0 µg/mL) and corticosteroid therapy. In the control treatment arm, eight patients continued to receive CNI, CellCept® and corticosteroid therapy.

Of the seven patients randomized to the sirolimus, CellCept® and corticosteroid arm, four experienced a grade IIIA rejection within 5 weeks of discontinuing the CNI.[3] Three of the four rejection episodes occurred at one center in the United States. Three of these patients responded well to treatment with corticosteroids and the fourth patient recovered after experiencing hemodynamic compromise. No cases of graft loss occurred. There were no similar episodes of rejection in patients receiving the calcineurin based regimen (CNI, CellCept® and corticosteroids).

F. Hoffmann-La Roche Ltd. terminated this clinical trial when these results were reported. There is limited data available from this study to draw a firm conclusion regarding the difference in the rejection rate between the two treatment arms.

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 Roche in monitoring the safety of CellCept® by reporting any serious adverse events that occur with the use of CellCept® by phone to 1-800-526-6367 or by FAX at 1-800-532-3931.

Alternatively, any serious adverse events may be reported to the FDA's MedWatch Adverse Event Reporting program online [at www.fda.gov/MedWatch/report.htm], by phone [1-800-FDA-1088], or by returning the postage-paid FDA form 3500 [which may be downloaded from www.fda.gov/MedWatch/getforms.htm] by mail [to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787] or fax [1-800-FDA-0178].

CellCept® Product Information:
Indications and Usage: 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.

Dosage and Administration: A dose of 1.5 g bid administered intravenously (over NO LESS THAN 2 HOURS) or 1.5g bid oral (daily dose of 3 g) is recommended for use in adult cardiac transplant patients.

---

[3] Of the four patients randomized to the sirolimus, CellCept® and corticosteroid arm who experienced a grade IIIA rejection, there were two patients who had low concentrations of sirolimus and one patient who had an MPA level that was below the protocol suggested minimum trough level prior to rejection.

WARNING: Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. 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.

Contraindications: Allergic reactions to CellCept® have been observed; therefore, CellCept® is contraindicated in patients with 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).

Warnings: There are no adequate and well-controlled studies in pregnant women. However, as CellCept® has been shown to have teratogenic effects in animals, it may cause fetal harm when administered to a pregnant woman. Therefore, CellCept® should not be used in pregnant women unless the potential benefit justfies the potential risk to the fetus.

Women of childbearing potential should have a negative serum or urine pregnancy test with a sensitivity of at least 50 mlU/mL within 1 week prior to beginning therapy.

Effective contraception must be used before beginning CellCept® therapy, during therapy and for 6 weeks following discontinuation of therapy, even where there has been a history of infertility, unless due to hysterectomy. Two reliable forms of contraception must be used simultaneously unless abstinence is the chosen method. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

If neutropenia develops (ANC <0.3 x 10(3)/mcL), dosing with CellCept® should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately.

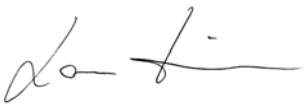
Precautions: In cardiac patients, the overall incidence of opportunistic infections was approximately 10% higher in patients treated with CellCept® than in those receiving azathioprine therapy, but this difference was not associated with excess mortality due to infection/sepsis among patients treated with CellCept®.

Adverse Events: Roche has previously included adverse events for CellCept® that show a greater than 30% incidence in the study population.

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

Should 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 a.m. to 6:00 p.m. Eastern Standard Time Monday through Thursday, and 8:30 a.m. to 5:00 p.m. on Friday.

Yours Sincerely,



Lars E. Birgerson, M.D., Ph.D.
Vice President, US Medical Affairs

Enclosure: CellCept® Prescribing Information

Rapamune is a registered trademark of Wyeth Pharmaceuticals Inc.

16-004-104-180-0307