Roche

Pharmaceuticals

**Health Canada Endorsed Important Safety Information on CellCept® (mycophenolate mofetil)**

October 13, 2006

Dear Health Care Professional:

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

Hoffmann-La Roche Limited, following discussion with Health Canada, would like to inform you of important safety and efficacy information regarding the termination of the Heart STN clinical trial due to an observed increased incidence of grade IIIA acute rejection in heart transplant patients switched from a calcineurin inhibitor (CNI) to sirolimus in combination with CellCept at 12 weeks post heart transplantation.

- **CellCept is indicated for the prevention of organ rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.**
- **CellCept should be used in combination with cyclosporine and corticosteroids.**
- **The safety and efficacy of sirolimus in combination with CellCept following withdrawal of initial calcineurin inhibitor therapy has not been established.**

The Heart STN clinical trial 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 transplant. Following heart transplantation, all patients received the standard immunosuppressive therapy for their centre, including CellCept, in combination with either cyclosporine or tacrolimus, and corticosteroids. Fifteen patients were randomized to one of two arms in the trial. In the treatment group, seven heart transplant recipients were switched from CNI to sirolimus at 12 weeks post heart transplantation while maintaining standard CellCept and corticosteroid therapy. In the control/standard treatment arm, eight patients continued to receive CNI, CellCept and corticosteroid therapy.

**Hoffmann-La Roche Limited/Limitée**

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Of seven patients randomized to the sirolimus, CellCept and corticosteroid arm, four experienced a grade IIIA rejection within 4 weeks of discontinuing the CNI. Three of these patients responded well to treatment with corticosteroids and the fourth patient experienced hemodynamic compromise, but recovered. No cases of graft loss were reported.

No specific safety concerns were noted regarding the use of CellCept in patients receiving the standard care regimen.

As a conservative measure, Hoffmann-La Roche Limited terminated this clinical trial. 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.

On review of the recommended doses and levels used in other similarly designed studies (Bestetti et al 2006, Hunt et al 2005, Meiser et al 2005, Groetzner et al, 2004), it is possible that the sirolimus and mycophenolic acid (MPA) concentrations achieved in the investigational treatment group were not sufficient to maintain adequate immunosuppression. 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 standard care.

In Canada, no patients were enrolled in this clinical trial. Three of the 4 rejection episodes occurred at one centre in the United States. The results of this study will be submitted to the International Society of Heart and Lung Transplant (ISHLT) meeting in April 2007.

Canadian transplant physicians are therefore requested to notify their respective hospital Research Ethics Boards with respect to this information.

Adverse drug reactions (ADRs) that occur within the context of a clinical trial that are **both** serious and unexpected are subject to expedited reporting to Health Canada. A completed *ADR Expedited Reporting Form* should be attached to the front of the report and reports should be submitted, by fax to the:

- Therapeutic Products Directorate for Pharmaceuticals: 613-941-2121
- Biologics and Genetic Therapies Directorate for Biologics and Radiopharmaceuticals: 613-957-0364

For more information on clinical trials and ADR reporting within the context of a clinical trial please refer to the following guidance document:
http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec_e.html.

Managing marketed health product-related adverse reactions depends on health care professionals and consumers reporting them. Reporting rates determined on the basis of spontaneously reported post-marketing adverse reactions are generally presumed to underestimate the risks associated with health product treatments. Any case of serious or other serious or unexpected adverse reactions in patients receiving CellCept should be reported to Hoffmann-La Roche Limited or Health Canada at the following addresses:

Hoffmann-La Roche Limited
Drug Safety Department
2455 Meadowpine Boulevard
Mississauga, Ontario, L5N 6L7
or call toll free at: 1-888-762-4388
or Fax at: 905-542-5864
or email to: mississauga.drug_safety@roche.com

**Any suspected adverse reaction can also be reported to:**
Canadian Adverse Drug Reaction Monitoring Program (CADRMP)
Marketed Health Products Directorate
HEALTH CANADA
Address Locator: 0701C
OTTAWA, Ontario, K1A 1B9
Tel: (613) 957-0337 or Fax: (613) 957-0335
To report an Adverse Reaction, consumers and health professionals may call toll free:
Tel: (866) 234-2345
Fax: (866) 678-6789
cadrmp@hc-sc.gc.ca

The AR Reporting Form and the AR Guidelines can be found on the Health Canada web site or in *The Canadian Compendium of Pharmaceuticals and Specialties*.

**For other inquiries related to this communication, please contact Health Canada at:**
Marketed Health Products Directorate (MHPD)
E-mail: mhpd_dpsc@hc-sc.gc.ca
Tel: (613) 954-6522
Fax: (613) 952-7738

Should you have any questions or require additional information regarding the use of CellCept, please contact the Drug Information Department at Hoffmann-La Roche Limited at 1-888-762-4388 from 8:30 a.m. to 4:30 p.m. Monday to Friday Eastern Standard Time.

Sincerely,

***Original signed by***

Lorenzo Biondi,
Vice President, Medical and Regulatory Affairs
Hoffmann-La Roche Limited

References

Bestetti R, Theodoropoulos TAD, Burdmann EA et al. Switch from calcineurin inhibitors to sirolimus-induced renal recovery in heart transplant recipients in the midterm follow-up. Transplantation Mar 15 2006;81(5):692-696.

Hunt J, Lerman M, Magee MJ et al. Improvement of renal dysfunction by conversion from calcineurin inhibitors to sirolimus after heart transplantation. J Heart Lung Transplant 2005;24:1863-1867.

Meiser B, Reichart B, Adamidis I et al. First experience with de novo calcineurin-inhibitor-free immunosuppression following cardiac transplantation. Am J Transplant 2005;5:827-831.

Groetzner J, Meiser B, Landwehr P et al. Mycophenolate mofetil and sirolimus as calcineurin inhibitor-free immunosuppression for late cardiac-transplant recipients with chronic renal failure. Transplantation February 27 2004;77(4):568-574.