Important Safety Information on
CELLCEPT® (mycophenolate mofetil)

June 2nd 2009

Direct Healthcare Professional Communication on the association of CellCept® (mycophenolate mofetil) with pure red cell aplasia

Dear Healthcare Professional,

Roche Products (Ireland) Limited wishes to inform you about important new safety information for CellCept® (mycophenolate mofetil).

- **Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with medicines including other immunosuppressants. In some cases dose reduction or discontinuation of CellCept led to resolution of the condition.**
- **Dose reduction or discontinuation of CellCept should be considered in patients who develop PRCA. Changes should be undertaken under specialist supervision.**

The information provided in this letter has been reviewed and endorsed by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) and the Irish Medicines Board.

Further information on the safety concern

CellCept and PRCA
CellCept is an immunosuppressant indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in adults receiving allogeneic renal, cardiac or hepatic transplants, and in children and adolescents (2-18 years) receiving renal transplants. It is estimated that approximately 500,000 patients have been exposed to CellCept worldwide since it was introduced.

Forty-one cases of PRCA have been reported worldwide to date in association with CellCept. Some patients were also receiving other medicines that could have contributed to the development of PRCA (alemtuzumab, tacrolimus, azathioprine and co-trimoxazole). In 16 of the reported cases, dose reduction (in 4 cases) or discontinuation (in 12 cases) of CellCept led to resolution of the condition. The mechanism by which CellCept may cause PRCA is not known. A causal association between CellCept and PRCA could not be excluded.

Further information on pure red cell aplasia (PRCA)
PRCA is a type of anaemia in which there is a selective reduction of red blood cell precursors on bone marrow examination. 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/mm^3 are criteria commonly used to establish the diagnosis. Other blood components such as platelets and white blood cells are not affected in PRCA.

Roche Products (Ireland) Limited
3004 Lake Drive
Citywest
Naas Road
Dublin 24
Ireland
(Registered Office)
Tel: 353-1-469 0700
Fax: 353-1-469 0790
Registered in Ireland
No. 214337

PRCA is associated with the following diseases: congenital PRCA (Diamond-Blackfan syndrome); thymoma; lymphoproliferative and myeloproliferative disorders, particularly chronic lymphocytic leukaemia; viral infections such as parvovirus B19, Epstein-Barr virus (EBV), viral hepatitis, Human T-lymphotrophic virus-1 (HTLV-1), mumps; systemic lupus erythematosus (SLE); autoimmune disorders; bone marrow or stem-cell transplantation. The following drugs have been associated with PRCA: antiepileptic medicines (e.g. phenytoin, carbamazepine, sodium valproate); azathioprine; chloramphenicol; sulfonamides; isoniazid; procainamide; and recombinant human erythropoietin.

Call for reporting
Roche monitors the safety of its products through established reporting mechanisms and notifies regulatory authorities of any serious adverse events. You can assist us in monitoring the safety of CellCept by reporting adverse reactions to us. Please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates. Any occurrence of serious and/or unexpected adverse reactions in patients receiving CellCept should be reported to:

Drug Surveillance Centre
Roche Products (Ireland) Limited
3004 Lake Drive, Citywest
Naas Road
Dublin 24, Tel: 01-4690700; Fax: 01-4690793
E-mail: Ireland.drug_surveillance_centre@roche.com

Any suspected adverse reaction can also be reported to the pharmacovigilance section of the IMB in the usual manner using the on-line reporting function on the IMB website (www.imb.ie) or alternatively by contacting the IMB at 01 6764971.

Should you have any questions or require additional information regarding the use of CellCept, please contact medical information at Roche Products (Ireland) Limited, 3004 Lake Drive, Citywest, Naas Road, Dublin 24, Tel: 01-4690700; Fax: 01-4690791; Email: Ireland.druginfo@roche.com.

Yours faithfully,

Edwin Carr, PhD
Director of Medical Affairs

Attachment:
Text of the revised Product Information (with changes made visible) as adopted at the April 2009 CHMP plenary meeting

Text of the revised summary of product characteristics

4.4 Special warnings and precautions for use

...

Patients taking CellCept should have complete blood counts weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year. If neutropenia develops (absolute neutrophil count < 1.3 x 103/µl), it may be appropriate to interrupt or discontinue CellCept.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept in combination with other immunosuppressants. The mechanism for mycophenolate mofetil induced PRCA is unknown. PRCA may resolve with dose reduction or cessation of CellCept therapy. Changes to CellCept therapy should only be undertaken under appropriate supervision in transplant recipients in order to minimise the risk of graft rejection (see section 4.8).

...

4.8 Undesirable effects

...

Blood and lymphatic system disorders:

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with CellCept (see section 4.4).