



7 November 2008

Direct Healthcare Professional Communication on rituximab (MabThera) and  
Progressive Multifocal Leukoencephalopathy (PML) in patients treated for Autoimmune  
Diseases including Rheumatoid Arthritis

Dear Health Care Professional

MabThera (rituximab) is a monoclonal antibody representing a glycosylated immunoglobulin indicated for the treatment of:

- Non-Hodgkin's Lymphoma
  - o in combination with chemotherapy for the treatment of previously untreated patients with stage III-IV follicular lymphoma.
  - o as maintenance therapy for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without Mabthera
  - o in patients who are chemoresistant or who are in their second or subsequent relapse after chemotherapy.
  - o in patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy
- Rheumatoid Arthritis
  - o in combination with methotrexate in adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs including one or more tumour necrosis factor (TNF) inhibitor therapies.

Mabthera is not indicated for the treatment of other autoimmune diseases.

### Summary

- In June 2008, a case of Progressive Multifocal Leukoencephalopathy (PML) was reported in a patient with rheumatoid arthritis reported in a long-term safety extension clinical study.
- The case occurred 18 months after the last dose of MabThera and is confounded by chemotherapy for the patient's development of oropharyngeal cancer.
- The case underlines the importance of:
  - o continued clinical vigilance
  - o prompt discontinuation of MabThera when PML is suspected with subsequent appropriate evaluation including magnetic resonance imaging (MRI) scan and lumbar puncture
- The content of this letter has been agreed with the European Authorities.

### Further information on the safety concern

Progressive Multifocal Leukoencephalopathy (PML) is a rare, progressive, demyelinating disease of the central nervous system that usually leads to death or severe disability. PML is caused by activation of the JC virus, a polyomavirus that resides in latent form in up to 80% of healthy adults. 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.

**Roche Products Limited**

Registered Office:  
6 Falcon Way, Shire Park,  
Welwyn Garden City, AL7 1TW,  
Registered Number 100674

Tel. 0800 3281629  
Medinfo.uk@roche.com

Five cases of PML have been reported in patients treated for autoimmune diseases: systemic lupus erythematosus (2 cases); and single cases in patients with vasculitis, Wegener's granulomatosis and rheumatoid arthritis.

MabThera has been used for over 10 years to treat patients with non-Hodgkin's lymphoma and other haematological malignancies and approximately 1.5 million patients have been exposed to MabThera since its marketing authorisation. As of 29 July 2008, there were 76 reports identified in the company global safety database of confirmed or suspected PML in patients receiving MabThera in any approved or non-approved indication: 69 in oncological indications, one in a haematological indication (autoimmune haemolytic anaemia), five in autoimmune disorders and one in an unknown indication.

**Further information on recommendations to healthcare professionals:**

- o Physicians should be alert to first signs and symptoms suggestive of PML. These include visual disturbances, motor dysfunction, and cognition impairment usually associated with clumsiness, blindness, marked weakness including hemiparesis and behavioural changes. Additional signs include sensory deficits, vertigo and convulsions.
- o If a patient develops these signs and symptoms, MabThera must be discontinued until the diagnosis of PML is excluded.
- o The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. If any doubt exists, there should be further evaluation, that may include MRI scan, lumbar puncture to test for JC viral DNA in CSF and repeat neurological assessment.
- o In patients who develop PML, MabThera should be discontinued and concomitant immunosuppressive therapy should be reduced or discontinued. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

**Call for reporting**

Healthcare professionals should report any adverse event suspected to be associated with the use of MabThera to the Medicines and Healthcare Products Regulatory Agency (MHRA), using a Yellow Card available directly from the MHRA, CHM Freepost, London SW8 5BR, or electronically via the MHRA website at: <http://www.yellowcard.gov.uk>. Adverse events should also be reported to Roche by phone on 01707 367554, by fax on 01707 367582 or e-mail at [Welwyn.uk\\_dsc@roche.com](mailto:Welwyn.uk_dsc@roche.com).

**Communication information**

If you have further questions on this issue please contact Roche Medical Information on 0800 3281629 or 01707 361010.

Yours sincerely,



Dr M Rashford  
Medical Director  
Roche Products Limited