Roche

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 treatment of:

- stage III-IV follicular lymphoma
- in patients who are chemoresistant or who are in their second or subsequent relapse after chemotherapy. In the European Union and many countries worldwide,
- in combination with chemotherapy for the treatment of previously untreated patients with stage III-IV follicular lymphoma.
- as maintenance therapy or patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without Mabthera
- in combination with CHOP chemotherapy, for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's Lymphoma
- for the treatment of adult patients with severe active rheumatoid arthritis, in combination with methotrexate, in patients 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 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 (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

Five cases of PML have been reported in patients treated for autoimmune diseases, systemic lupus erythematosus (2), single cases of 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 indentified in the company global safety database of confirmed or suspected PML in patients receiving MabThera in any approved or non-approved indication (69 in oncologic indications, one in a haematologic indication (autoimmune haemolytic anaemia), five in autoimmune disorders and one in unknown indication.

Further information on recommendations to healthcare professionals:
Physicians should be alert to first signs and symptoms suggestive of PML. These include visual disturbances, motor dysfunction, and cognition impairment usually association with clumsiness, blindness, strong weakness like hemiparesis and behaviour changes. The additional signs are sensory deficits, vertigo and convulsive seizures.

If a patient develops these symptoms, MabThera must be discontinued until the diagnosis of PML is excluded.

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, further evaluation, that may include MRI scan, lumbar puncture to test for JC viral DNA in CSF and repeat neurological assessment, should be conducted.

In patients who develop PML, MabThera should be discontinued and reductions or discontinuation in concomitant immunosuppressive therapy considered. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

Call for reporting
Healthcare professionals are reminded to continue to report adverse reactions to Roche Products (Ireland) Limited or to the Pharmacovigilance Section of the Irish Medicines Board in the usual way.

Communication information
If you have further questions on this issue please contact the Drug Information Department at Roche Products (Ireland) Limited on (01) 469 0700.

Yours sincerely,

Edwin Carr PhD
Director of Medical Affairs