09th November 2009

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

Dear Healthcare Professional,

Summary

MabThera in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying anti-rheumatic drugs (DMARD) including one or more tumour necrosis factor (TNF) inhibitor therapies.

MabThera (rituximab) is a monoclonal antibody targeting the antigen CD20, which is present on the surface of normal and malignant B-lymphocytes and is indicated for the treatment of various malignancies, in addition to RA (see summary of product characteristics [SmPC]).

In September 2009 a case of Progressive Multifocal Leukoencephalopathy (PML) with a fatal outcome was reported in a patient with rheumatoid arthritis (RA) who had not previously received treatment with methotrexate or a TNF antagonist. This case represents the third case of PML reported in an RA patient receiving MabThera. Cases of PML have also been reported in patients with other autoimmune diseases treated with MabThera.

- Prescribers should be aware that PML (which is usually fatal) has now been reported in a patient with no other risk factors, other than treatment with MabThera
- Prescribers are therefore reminded that MabThera is not indicated for first line treatment of RA

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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. JC virus resides in the latent form in 40-80% of healthy adults. The factors leading to activation of the latent infection are not fully understood. PML has been reported in HIV-positive patients, immunosuppressed cancer patients, transplantation patients and patients with autoimmune diseases in the absence of MabThera treatment. There are no known interventions that can reliably prevent or adequately treat PML.

A third case of PML has been reported in a patient with RA treated with MabThera. This occurred in a 73-year old woman with a diagnosis of seronegative RA of 3 years. Concomitant and/or prior treatments for RA included leflunomide, hydroxychloroquine, and prednisone. Other medical history included hypertension, hypothyroidism, osteoporosis, recurrent bronchitis and a cerebrovascular accident. In February 2009, she received one course of MabThera (1000 mg given two weeks apart). She developed dysesthesias and ataxia 4 to 6 months following treatment with MabThera. PML was diagnosed based on clinical symptoms, MRI findings, and detection of JC viral DNA in the CSF by PCR.

This is the first case of PML in a patient with RA treated with MabThera who has not previously received treatment with methotrexate or a TNF antagonist.

Previously, two fatal cases of confirmed PML have been reported in patients with RA treated with MabThera. These cases involved a 51 year-old woman and a 73 year-old woman with possible risk factors for the development of PML, including oropharyngeal malignancy treated with chemotherapy and radiation therapy and/or long standing lymphopenia prior to and during MabThera treatment.

Approximately 100,000 RA patients have been exposed to MabThera.

The potential mechanism of MabThera in the development of PML is unclear.

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 and consultation with a neurologist should be considered.

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 (see section 4.4 of the SmPC).

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Physicians are requested to provide a copy of the patient alert card to the patient prior to MabThera administration.

Call for reporting

Healthcare professionals are reminded to continue to report adverse events to the Drug Surveillance Centre at 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 or to the pharmacovigilance section of the Irish Medicines Board 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.

Communication information

Should you have any questions or require additional information regarding the use of MabThera, 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 sincerely,

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Medical Advisor

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