



**IMPORTANT DRUG WARNING
UPDATED SAFETY INFORMATION**

**Subject: Reports of Progressive Multifocal Leukoencephalopathy (PML) in
Systemic Lupus Erythematosus and Vasculitis (unapproved indications)**

Dear Health Care Professional:

Following discussions with the European Medicines Agency and the Irish Medicines Board, Hoffman-La Roche wishes to inform you of safety information for MABTHERA® (Rituximab).

- **Two reports of progressive multifocal leukoencephalopathy (PML) leading to death, have been observed in patients with Systemic Lupus Erythematosus (SLE) receiving MABTHERA®. A further single report of PML has also been observed in a patient with Vasculitis receiving MABTHERA®**
- **Because these events have arisen during use in unapproved indications from a population of unknown size, the incidence of PML among patients with SLE or Vasculitis being treated with MABTHERA® is not known. PML has also been reported in SLE and Vasculitis patients not treated with MABTHERA®. A causal relationship between MABTHERA® and PML has not been established.**
- **Physicians treating patients with SLE or Vasculitis should consider PML in any patient presenting with new onset neurological manifestations. Consultation with a Neurologist, brain MRI and lumbar puncture may be considered as clinically indicated.**

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.

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PML has been reported in HIV positive patients, immunosuppressed cancer patients, transplantation patients and patients with autoimmune disease including SLE. Abnormalities in T cells have been described as important for reactivation of JC virus and PML. Very rare (<1/10,000) cases of PML have been described in NHL patients receiving chemotherapy alone or receiving MABTHERA®; in the majority of cases this occurred in combination with chemotherapy or as part of hematopoietic stem cell transplant. This information has been provided to the EMEA and has been assessed by the CHMP together with a revision of the SmPC. The CHMP has endorsed the proposed wording included in the SmPC.

JC virus infection with resultant PML and death has been reported in 2 patients with SLE treated with MABTHERA®. Both of these patients had longstanding SLE with multiple courses of immunosuppressant use prior to receiving MABTHERA®. These patients were diagnosed with PML within 12 months of their last infusion of MABTHERA®. JC virus infection with resultant PML has also been reported in 1 patient with ANCA-negative Vasculitis/Cyroglobulinaemia (Hepatitis C negative). This patient had a six year history of unremitting disease resulting in multiple amputations. The patient received immunosuppressive (including cytotoxic) therapy prior to receiving MABTHERA®, and continued to receive immunosuppressive therapy in combination with MABTHERA®. PML was diagnosed within 12 months of the first exposure to MABTHERA® and the patient is currently undergoing treatment.

PML has been reported in patients with SLE receiving prednisone, azathioprine, cyclophosphamide and other immunosuppressants without concomitant MABTHERA® and also in patients with Vasculitis receiving immunosuppressants without concomitant MABTHERA®. A causal relationship between MABTHERA® and PML has not been established. The overall incidence of PML in patients with SLE or Vasculitis is not known. Other than these three cases, there have been no other reports of PML in patients with autoimmune diseases receiving MABTHERA®. We continue to follow this closely and any new information will be promptly communicated.

Physicians treating patients with autoimmune diseases should consider the diagnosis of PML in any patient presenting with new onset neurological manifestations. Consultation with a Neurologist, brain MRI and lumbar puncture may be considered as clinically indicated. There is no currently accepted screening test for PML.

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

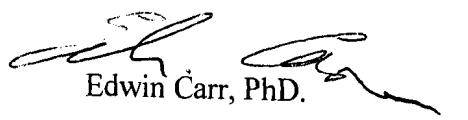
MABTHERA® (Rituximab) is a recombinant chimeric anti-CD20 monoclonal antibody indicated for treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy. In the European Union and many countries worldwide, MABTHERA is indicated for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy. MABTHERA maintenance therapy is indicated for patients with relapsed/refractory follicular lymphoma responding to induction therapy with chemotherapy with or without MABTHERA. MABTHERA is indicated for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's Lymphoma in combination with CHOP chemotherapy. 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 including one or more tumour necrosis factor (TNF) inhibitor therapies. MABTHERA® is not indicated for the treatment of SLE or Vasculitis.

MABTHERA® has been used for over 10 years to treat patients with NHL and other hematological malignancies and approximately one million patients have been exposed to MABTHERA® since its marketing authorisation.

Should you have any questions or require additional information regarding the use of MABTHERA®, please contact the Drug Information Department Roche Products (Ireland) Ltd. on (01) 469 0700.

Finally, you are requested to report any suspected adverse reactions associated with the use of MABTHERA (rituximab) to Roche Products (Ireland) Limited or to the Pharmacovigilance Section of the Irish Medicines Board in the usual way.

Sincerely,



Edwin Carr, PhD.
Director of Medical Affairs