

October 2009

**IMPORTANT DRUG WARNING**  
**Regarding RITUXAN® (Rituximab)**

Dear Healthcare Professional:

Genentech, Inc. and Biogen Idec, Inc. would like to inform you of important new safety information regarding Rituxan (rituximab) and progressive multifocal leukoencephalopathy.

- A third case of progressive multifocal leukoencephalopathy (PML) has been reported in a patient with rheumatoid arthritis treated with Rituxan. This occurred in a 73-year old woman with a diagnosis of seronegative rheumatoid arthritis of 3 years. Concomitant and/or prior treatments for rheumatoid arthritis 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 Rituxan (1000 mg given two weeks apart). She developed dysesthesias and ataxia 4 to 6 months following treatment with Rituxan. 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 rheumatoid arthritis treated with Rituxan who has not previously received treatment with a TNF antagonist. PML has been reported in patients with rheumatoid arthritis, including those treated with other immunosuppressive medications in the absence of Rituxan.

Previously, 2 fatal cases of confirmed PML have been reported in patients with rheumatoid arthritis treated with Rituxan. 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 Rituxan treatment.

The overall reporting incidence of PML in patients with rheumatoid arthritis receiving Rituxan is rare (3 reports in approximately 100,000 rheumatoid arthritis patients that have been exposed). However, the information to date suggests that patients with RA who receive Rituxan have an increased risk of PML.

Physicians should consider PML in any patient being treated with Rituxan who presents with new onset neurologic manifestations. Consultation with a neurologist, brain MRI, and lumbar puncture should be considered as clinically indicated (see USPI section 5.4). In patients who develop PML, Rituxan should be discontinued.

A copy of the current Rituxan Prescribing Information is enclosed. We encourage you to review the full prescribing information and discuss this important safety information with your patients.

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 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. There are no known interventions that can reliably prevent or adequately treat PML.

Rituxan in combination with methotrexate is indicated to reduce signs and symptoms and slow the progression of structural damage in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. Rituxan is also indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin's lymphoma (NHL) as a single agent, and for the treatment of previously untreated follicular, CD20-positive, B-cell NHL in combination with CVP chemotherapy. Rituxan is indicated for the treatment of non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL, as a single agent, after first-line treatment with CVP chemotherapy. Rituxan is also indicated for previously untreated diffuse large B-cell, CD20-positive, NHL in combination with CHOP or other anthracycline-based chemotherapy regimens.

Rituxan has been associated with fatal infusion reactions, tumor lysis syndrome (TLS), severe mucocutaneous reactions and progressive multifocal leukoencephalopathy (PML). Hepatitis B reactivation and cardiac arrhythmias and angina have also been observed. Patients should be closely observed for signs of infection if biologic agents and/or DMARDs other than methotrexate are used concomitantly. Common adverse reactions include hypertension, nausea, upper respiratory tract infection, arthralgia, pruritus, and pyrexia.

Should you have any questions regarding the use of Rituxan, please refer to the Rituxan Product Information at [www.gene.com](http://www.gene.com), or call our Medical Information/Communications Department at 1-800-821-8590.

Healthcare professionals should report any serious adverse events suspected to be associated with the use of Rituxan to Genentech at 1-888-835-2555. Alternatively, this information may be reported to FDA's MedWatch reporting system online (<https://www.accessdata.fda.gov/scripts/medwatch/>), by phone (1 800-FDA-1088), by facsimile (1-800-FDA-0178), or mail using the MedWatch Form FDA 3500 (FDA Medical Products Reporting Program, 5600 Fishers Lane, Rockville, MD 20852-9787).

Sincerely,

A handwritten signature in black ink, appearing to read 'H Barron', with a stylized, cursive script.

Hal Barron, M.D.

Executive Vice President, Head of Global Development: Oncology, Inflammation, Virology and Ophthalmology, Chief Medical Officer, USA, Genentech Inc.

A handwritten signature in black ink, appearing to read 'David T. Hagerty', with a cursive script.

David Hagerty, M.D.

VP, CMO Rheumatology, Biogen Idec, Inc.