Information for Healthcare Professionals

Rituximab
(marketed as Rituxan)

FDA ALERT [12/2006]: This Alert highlights important emerging safety information about Rituxan. Two patients have died after being treated with Rituxan for systemic lupus erythematosus (SLE). The cause of death was a viral infection of the brain called progressive multifocal leukoencephalopathy (PML) that is caused by reactivated JC virus. Latent JC virus is present in about 80 percent of adults.

Rituxan is a powerful immunosuppressant that eliminates mature circulating B-cells for up to nine months. Rituxan is approved for CD20-positive, B-cell, non-Hodgkins lymphoma and for moderately-to severely-active rheumatoid arthritis when there has been inadequate response to other treatments. Rituxan is being studied for other indications, and is prescribed off-label for other serious diseases and conditions such as SLE. The sponsor estimates that approximately 10,000 patients with SLE have been treated with Rituxan. Reactivation or exacerbation of viral infections including JC virus leading to PML may occur when patients receive Rituxan for any reason. FDA is working with the sponsor to gather additional information about the occurrence of PML in patients treated with Rituxan and to strengthen the Warnings about the risk of PML in the product labeling for Rituxan. Patients who have been treated with Rituxan and present or develop new neurological signs or symptoms should be evaluated for PML.

This information reflects FDA's preliminary analysis of data concerning this drug. FDA is considering, but has not reached a final conclusion about, this information. FDA intends to update this sheet when additional information or analyses become available.

To report any serious adverse events associated with the use of this drug, please contact the FDA MedWatch program using the contact information at the bottom of this sheet.

Recommendations and Considerations for physicians:

- Rituxan may cause exacerbations of viral infections or viral reactivation, including reactivation of the JC virus, which can lead to PML.
- Physicians should maintain a high index of suspicion for the development of PML in patients under treatment with Rituxan. When these patients develop new neurological signs or symptoms they should be evaluated for PML.
- Physicians should report suspected PML or other serious adverse events following Rituxan therapy to MedWatch.

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Information for the patient:

When a decision to treat a patient with Rituxan has been made, physicians and other healthcare professionals should discuss the following with the patient:

- Treatment with Rituxan can be beneficial and result in the improvement of the patient's disease or condition, but it also has serious risks.

- The serious risks from treatment with Rituxan include severe and fatal reactions within 24 hours of the infusion (such as severe bronchospasm, hypotension, hypoxia and pulmonary infiltrates) and reactivation or exacerbation of viral infections during and up to several months after treatment.

- PML is one of the viral infections that may develop several months after treatment with Rituxan. PML is a rare and usually fatal disease that is characterized by brain damage that worsens over time. There are no known effective treatments for PML.

- Patients should call their health care provider if they experience any new neurological symptoms or signs, because these could be warning signs of PML. Neurological warning signs include:
  - major changes in vision, unusual eye movements,
  - loss of balance or coordination,
  - disorientation or confusion.

Background and Data Summary:

- Rituxan (Rituximab) is a monoclonal antibody that depletes mature B cells. Following treatment with Rituxan, circulating B cells are almost completely depleted for up to nine months. The current labeling for Rituxan carries a ***Warning*** about reactivation of viral diseases with potentially serious or life threatening consequences. One of the noted serious viral infections, either new, reactivated or exacerbated is PML.

- PML is a rare, progressive, demyelinating disease of the central nervous system that usually leads to death or severe disability. PML is caused by the reactivation of the JC virus, a polyomavirus that remains latent in up to 80% of healthy adults, typically only causing PML in immunocompromised patients. There is no known effective treatment for PML.

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- In February 2006, the labeling for Rituxan was updated to include information about patients with non-Hodgkins lymphoma who developed PML. As of December 2006, there were approximately 23 reports of patients who were treated with Rituxan for hematologic malignancies and subsequently developed PML. Many of the patients were receiving Rituxan in combination with chemotherapy, or as part of a hematopoietic stem cell transplantation.

- Recently FDA received two reports to its Adverse Event Reporting System about patients who were treated with Rituxan for SLE, developed PML and later died. Treatment of SLE is not a labeled indication for Rituxan. The sponsor estimates that approximately 10,000 patients with SLE have been treated with Rituxan. Below is a summary of these two patient reports.

    - One patient was a female aged 70 years with a history of lupus nephritis and hemolytic anemia. Her prior medical history included previous treatment with cyclophosphamide and azathioprine and long-term treatment with varying doses of corticosteroids. After receiving four infusions of Rituxan in 2004 and two more in 2005, she developed vertigo, tongue biting, and difficulty walking. Her MRI had multiple brain lesions and histologic sections on brain biopsy showed characteristic findings of PML. She died in March of 2006.

    - A second female patient was 45 years old with a history of SLE since 1982. Her prior medical history included previous treatment with cyclophosphamide and IV methylprednisolone. She was treated with Rituxan for three courses from 2002 to 2005. She was also taking prednisolone from 2002 to 2003. In April of 2006 she developed new neurological signs and symptoms. Her MRI showed multiple brain lesions and her CSF examination was positive for JC virus infection by polymerase chain reaction testing, confirming the diagnosis of PML. She died in July of 2006.

- FDA is working with the sponsor to ensure that healthcare professionals who prescribe, and patients who take, Rituxan are fully informed of the risk of PML with Rituxan therapy.