

**IMPORTANT
DRUG
WARNING**

October 25, 2013

Subject: Rituxan® (rituximab) Label Update in the Screening for Hepatitis B Infection and Management of Hepatitis B Reactivation

Dear Healthcare Provider:

Genentech Inc. and Biogen Idec, Inc. would like to inform you that the U.S. Food and Drug Administration (FDA) has approved changes to the prescribing information of drugs classified as CD20-directed cytolytic antibodies, including Rituxan® (rituximab), to add new *Boxed Warning* information about the risk of reactivation of hepatitis B virus (HBV) infection.

Summary

The risk of HBV reactivation was already described in the *Warnings and Precautions* section of the label for Rituxan. The revised label includes updated information on screening, monitoring, and managing patients on Rituxan to decrease this risk.

Further information on the Rituxan label update in the screening for hepatitis B infection and management of hepatitis B virus (HBV) reactivation (in Warnings and Precautions section 5.3)

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including Rituxan. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with Rituxan. For patients who show evidence of prior hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during Rituxan treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following Rituxan therapy. HBV reactivation has been reported up to 24 months following completion of Rituxan therapy.

In patients who develop reactivation of HBV while on Rituxan, immediately discontinue Rituxan and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming Rituxan in patients who develop HBV reactivation. Resumption of Rituxan in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B.

Additional information

A recent analysis of the events of hepatitis B reactivation (Roche data on file from worldwide drug safety surveillance) revealed that the use of rituximab has been associated with hepatitis B reactivation in patients with positive Hep B surface antigen (HBsAg+ve) as well as negative Hep B surface antigen and positive anti-HB core antibody (HBsAg-ve/HBcAb+ve), particularly when administered in combination with steroids or chemotherapy. As of August 2012, in all patients treated with rituximab, Hepatitis B reactivation has been estimated to be rare (<1/1000 and >1/10,000) in hemato-oncology and very rare (<1/10,000) in autoimmune diseases⁽¹⁾.

For further information on the updated management of Hepatitis B Virus (HBV) reactivation, please refer to the Drug Safety Communication issued by the FDA on September 25, 2013.

This letter is not a comprehensive description of the risks associated with the use of Rituxan. Please read the accompanying Prescribing Information that includes the Medication Guide for a complete description of these risks. The Medication Guide contains information that can be used to facilitate discussions with patients about the known and potential risks of therapy.

In collaboration with the FDA to provide clarity to healthcare providers, additional updates have been included in *Warnings and Precautions*, as well as in *Dosage and Administration* of the Prescribing Information, and the Medication Guide.

Call for Reporting

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

Company Contact Point

Should you have any questions regarding the use of Rituxan, please feel free to contact Genentech Medical Information/Communications Department at 1-800-821-8590.

Reference

⁽¹⁾: Council for International Organizations of Medical Sciences (CIOMS) Working Group IV. Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. Geneva: World Health Organization; 1998.

Yours sincerely,

Genentech, a Member of the Roche Group



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