U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

Boxed Warning and new recommendations to decrease risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab)

Safety Announcement

[9-25-2013] The U.S. Food and Drug Administration (FDA) has approved changes to the prescribing information of the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab) to add new *Boxed Warning* information about the risk of reactivation of hepatitis B virus (HBV) infection. The revised labels also will include additional recommendations for screening, monitoring, and managing patients on these drugs to decrease this risk. Both Arzerra and Rituxan are used to treat certain cancers of the blood and lymph system. Rituxan is also approved to treat other medical conditions, including rheumatoid arthritis. Both drugs suppress the body's immune system.

In patients with prior HBV infection, HBV reactivation may occur when the body's immune system is impaired. This infection can cause serious liver problems, including liver failure and death. Reactivation can occur in patients who previously had HBV infection that was clinically resolved, but who later require therapy for a condition such as cancer. When a treatment is given that can impair the body's immune system, the previous HBV infection can again become an active infection. The initial HBV infection may occur without obvious signs of liver disease, and it may remain dormant in liver tissue. Therefore, screening for evidence of prior exposure is necessary to reliably assess the risk of HBV reactivation.

The risk of HBV reactivation is already described in the *Warnings and Precautions* section of the labels for both drugs; however, cases continue to occur, including deaths, prompting FDA to examine this risk further for current evidence that may aid in recognition and reduction in the risk (see Data Summary). HBV reactivation is being added to the existing *Boxed Warning* of the Rituxan label, and a new *Boxed Warning* is being created for the Arzerra label to describe the risk. The *Warnings and Precautions* section also is being revised for each drug to express new recommendations.

To decrease the risk of HBV reactivation, we recommend that health care professionals:

- Screen <u>all patients</u> for HBV infection before starting treatment with Arzerra or Rituxan by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).

- Consult with hepatitis experts regarding monitoring and use of HBV antiviral therapy when screening identifies patients at risk of HBV reactivation due to evidence of prior HBV infection.
- Monitor patients with evidence of prior HBV infection for clinical and laboratory signs of hepatitis B or HBV reactivation during Arzerra or Rituxan therapy and for several months thereafter, since reactivations have occurred several months following completion of therapy with these drugs.
- In patients who develop reactivation of HBV while on Arzerra or Rituxan, immediately discontinue the drug and start appropriate treatment for HBV. Also discontinue any chemotherapy the patient is receiving until the HBV infection is controlled or resolved. Because of insufficient data, no recommendation can be made regarding the resumption of Arzerra or Rituxan in patients who develop HBV reactivation hepatitis.

Health care professionals and patients should discuss the risks of serious infections, including HBV, before starting treatment with Arzerra or Rituxan. Patients should talk to their health care professional if they have any questions or concerns about these drugs.

Facts about Arzerra (ofatumumab) and Rituxan (rituximab)

- Arzerra and Rituxan are in a class of drugs called anti-CD20-directed monoclonal antibodies.
- Arzerra is used to treat chronic lymphocytic leukemia (CLL) in patients who have further disease after treatment with the anti-cancer drugs fludarabine and alemtuzumab.
- Rituxan is used to treat non-Hodgkin's lymphoma and CLL. It is also used to treat other medical conditions, including rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis.

Additional Information for Patients

- If you have had hepatitis B or are a carrier of hepatitis B virus (HBV), receiving Arzerra (ofatumumab) or Rituxan (rituximab) could cause the virus to become an active infection again. HBV reactivation may cause serious liver problems, including liver failure and death.
- Before receiving Arzerra or Rituxan, tell your health care professional if you have or have had any severe infections, including HBV.
- If you have had HBV infection, your health care professional should monitor you for HBV infection during treatment and for several months after you stop treatment with Arzerra or Rituxan.
- Talk to your health care professional if you have any questions or concerns about Arzerra or Rituxan.
- Report side effects from Arzerra or Rituxan to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Hepatitis B virus (HBV) reactivation has occurred in patients with prior HBV exposure who are later treated with drugs classified as CD20-directed cytolytic antibodies, including Arzerra (ofatumumab) and Rituxan (rituximab). Some cases have resulted in fulminant hepatitis, hepatic failure, and death.
- 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 and, in severe cases, increase in bilirubin levels, liver failure, and death).
- Cases of HBV reactivation have been reported in patients who are hepatitis B surface antigen (HBsAg) positive.
- Cases have also been reported in patients who are HBsAg negative, but test positive for hepatitis B core antibody (anti-HBc). 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).
- Screen all patients for HBV infection before initiating treatment with Arzerra or Rituxan by measuring HBsAg and anti-HBc.
- Note that patients who have protective antibodies due to immunization will test positive only for anti-HBs.
- For patients who show evidence of prior HBV exposure by testing positive for HBsAg or anti-HBc, consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy.
- Monitor patients with evidence of prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following Arzerra or Rituxan therapy. HBV reactivation has been reported up to 12 months following completion of therapy.
- In patients who develop reactivation of HBV while on Arzerra or Rituxan, immediately discontinue the drug and institute appropriate HBV treatment. Also discontinue any concomitant chemotherapy the patient is receiving until the HBV infection is controlled or resolved. Because of insufficient data, no recommendation can be made regarding the resumption of Arzerra or Rituxan in patients who develop HBV reactivation hepatitis.
- Report adverse events involving Arzerra or Rituxan to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

FDA searched its Adverse Event Reporting System (AERS) database for reports submitted between the time of market approval of the drugs (November 1997 for Rituxan; October 2009 for Arzerra) and August 2012 of patients treated with Arzerra (ofatumumab) or Rituxan (rituximab) who had fatal hepatitis B-related acute liver injury.

The search identified 109 cases (Rituxan=106; Arzerra=3). Acute liver injury was attributed to hepatitis B virus (HBV) reactivation when the case data indicated an associated seroconversion of hepatitis B surface antigen (HBsAg) from negative to positive for those with either hepatitis B core antibody (anti-HBc) or a history of HBV, or the case reported an increase in HBV DNA level among those who were HBsAg positive before Arzerra or Rituxan treatment.

Of the 109 cases, 32 (Rituxan=31; Arzerra=1) contained sufficient data in the reports to meet the HBV reactivation criteria. HBsAg seroconversion was the basis of diagnosis for 69% (22/32) of cases. Nineteen of 22 cases that were HBsAg negative prior to initiation of Arzerra or Rituxan therapy were positive for anti-HBc (5 of the 22 cases were also hepatitis B surface antibody [anti-HBs] positive). No case had anti-HBs antibody alone. The remaining cases were HBsAg positive and diagnosed by an increase in HBV DNA level. Of the 32 cases, 10% (3/32) were on HBV antiviral prophylaxis and 28% (9/32) reported receiving antiviral treatment for HBV reactivation. The mean age of the patients was 62 years (range 27-84 years), and most were male (n=21); one case did not provide the age or sex. Duration of Arzerra or Rituxan therapy prior to HBV reactivation diagnosis was highly variable with a range of 63 days from the first dose to 12 months from the last dose. All cases had recent or concomitant exposure to other chemotherapy agents also.

Among the 77 patients who did not include the required data for the HBV reactivation criteria, 47% (36/77) had no documented screening and 32% (25/77) reported partial screening. The remaining 21% had insufficient information to distinguish reactivation from primary hepatitis B (8/77) or were from literature reports without validation (8/77).