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


Yours sincerely,

Genentech, a Member of the Roche Group

Bruce Cooper, M.D.
Head, US Medical Affairs
2.4 Recommended Dose as a Component of Zevalin ®

1.3 Rheumatoid Arthritis (RA)

- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to-severely active RA who have received radiation therapy within the last 12 months or are scheduled to receive it within 12 months, or who have a history of diffuse large B-cell lymphoma.

- Rituxan should be administered as a single-agent every 8 weeks for 12 doses to patients with RA who have not achieved or at the end of the 6 month remission induction period.

- Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct hypogammaglobulinemia and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias.

- Live virus vaccines are not recommended.

- The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m² in combination with cyclophosphamide is not significantly different from that observed in NHL patients treated with rituximab alone.

- In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent. 147 patients who received FC.

- In placebo-controlled studies, patients received 2 × 500 mg or 2 × 1000 mg intravenous infusions of Rituxan daily over 5 days. In the active-controlled, double-blind study, 62% (61/99) of patients in the Rituxan group experienced an infection compared to 49% (48/99) of patients in the cyclophosphamide group. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and chills.

- In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the majority of depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months following completion of Rituxan therapy.

- The frequency and the profile of infusion-related reactions were similar to those observed in NHL patients treated with rituximab monotherapy.

- Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, dyspnea, flushing, hypotension, hypocalcemia, asthenia) were seen at a similar rate in RA and NHL patients receiving rituximab.

- The incidence of infections was similar in RA and NHL patients treated with rituximab.

- The pharmacokinetic profile of rituximab was similar in RA and NHL patients.

- Possible mechanisms of cell lysis

  - Fc domain recruits immune effector functions to mediate B-cell lysis
  - B-cell depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months following completion of Rituxan therapy.

- Hepatitis B reactivation with fulminant hepatitis occurs in patients treated with Rituxan. Screen all patients for HBV infection before treatment initiation, and monitor patients for hepatitis B reactivation.

- Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. These reactions include toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of infusion to over 6 months post treatment.

- Hypogammaglobulinemia

- Infusional reactions

- Hypotension

- Dyspnea

- Flushing

- Asthenia

- Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

- Cardiac: Myocardial infarction

- Gastrointestinal: Ulcerative enteritis

- Respiratory: Pneumonitis

- Hypogammaglobulinemia

- Lymphoma

- Hematologic: Neutropenia, thrombocytopenia

- Hypocalcemia

- Seizure

- Toxic epidermal necrolysis

- Hypogammaglobulinemia

- Hypogammaglobulinemia
Dosage and Administration (2.1) 05/2013

Do not administer as an intravenous push or bolus.

Geriatric Use: In CLL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of R.
2.4 Recommended Dose as a Component of Zevalin ®

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

1.1 Non‑Hodgkin's Lymphoma (NHL)

In patients with relapsed or refractory, low‑grade or follicular, CD20‑positive, B‑cell NHL treated in single‑arm studies of Rituxan administered as a single agent. [230 patients who received FC.]

In Study 11, the following Grade 3 and 4 adverse reactions occurred more frequently in R‑FC‑treated patients than in FC only patients: dyspepsia (17% vs. 2%), rash (8% vs. 2%), and peripheral edema (4% vs. 0%).

The incidence of serious infections was 11% in the Rituxan‑treated patients and 10% in the cyclophosphamide plus FC patients. The proportion of patients with neutropenia (Grade 3 or 4) was similar in the two groups (15% vs. 18% for cyclophosphamide plus FC and Rituxan, respectively).

For patients who did not achieve a complete or partial response to Rituxan in combination with chemotherapy, as single ‑agent maintenance chemotherapy regimens were used.

The recommended dose is 375 mg/m 2 as an intravenous infusion according to the following schedules:

- Initiate infusion at a rate of 100 mg/hr.
- In the absence of infusion toxicity, increase rate by 100 mg/hr.
- Continue until the scheduled infusion time or until clinical benefit is achieved.

PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months after therapy is discontinued. A 14 day course of trimethoprim/sulfamethoxazole is recommended.

None.

Infusions may be administered at a rate of 100 mg/hr, increasing by 100 mg/hr intervals every 30 minutes, to a maximum of 400 mg/hr.

The recommended dose is 100 mg/m 2 as an intravenous infusion according to the following schedules:

- Initiate infusion at a rate of 100 mg/hr.
- In the absence of infusion toxicity, increase rate by 100 mg/hr.
- Continue until the scheduled infusion time or until clinical benefit is achieved.

Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count ≥5000/mm 3 should not receive rituximab.

2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

The recommended dose is 375 mg/m 2 as an intravenous infusion according to the following schedules:

- Initiate infusion at a rate of 100 mg/hr.
- In the absence of infusion toxicity, increase rate by 100 mg/hr.
- Continue until the scheduled infusion time or until clinical benefit is achieved.

Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms (5.9).

Other important adverse reactions include infusion reactions, serious infections, and PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months after therapy is discontinued.

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the infusion of rituximab.

In exploratory analyses defined by age, there was no observed benefit from the addition of Rituxan to cyclophosphamide plus FC in younger patients. The overall incidence and rate of all serious adverse events was higher in patients 65 years old and older compared to younger patients.

The estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal half‑life was 20 days.

Possible mechanisms of cell lysis.


2. Recommended Dose as a Component of Zevalin®

1.4 Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)

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Warnings and Precautions (5.3) 04/2013

Rituxan® (rituximab)

Dosage and Administration (2.1) 05/2013

Injection for Intravenous Infusion

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Rituxan should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions. Administer Only as an Intravenous Infusion.

every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg intravenous or oral prednisone 60 mg daily was used to manage steroid-dependent side effects (4.2).

Infection and asthenia. Common adverse reactions (≥ 25%) in clinical trials of CLL were: infusion reactions and neutropenia (6.1).

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.3).

first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).

Polyangiitis (MPA)

14.3 Diffuse Large B-cell NHL (DLBCL)

11 DESCRIPTION

5.6 Infections

2.8 Preparation for Administration

50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.

Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent (2.2)

Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose over the next 90 minutes. Rituxan can then be given every 2 weeks for a total of 4 doses. Rituxan can also be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.

For patients with previously treated CLL, the frequency of prolonged neutropenia was 24.8% for patients who received Rituxan compared to 10.9% for patients who received placebo. Rituxan-treated patients also had a lower incidence of grade 3/4 infections than placebo-treated patients (6.3).

Any Adverse Reactions

Neutropenia

Asthenia

Hypogammaglobulinemia (IgA, IgG or IgM below the lower limit of normal) has been observed in patients with CLL. In some patients, the decrease in immunoglobulin was reversible and occurred more frequently in patients who received high-dose chemotherapy compared to patients who received fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 4 cycles of treatment. Thirty-three percent of patients who received Rituxan had a reduction in immunoglobulin levels greater than or equal to 50% from baseline. Twenty percent of patients had a reduction greater than or equal to 75% from baseline and 7% of patients had a reduction greater than or equal to 90% from baseline.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in the labeling are made on the basis of their importance to the patient and the potential for avoiding or managing them.

IgG, IgA, IgM, and total immunoglobulin concentrations were determined by nephelometry and turbidimetry. Decreases in immunoglobulin levels were based on the lower limit of normal (LLN) for each patient. The reference ranges for total immunoglobulin levels were 350 to 1600 mg/dL for IgG, 100 to 500 mg/dL for IgA, and 90 to 400 mg/dL for IgM.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once every 2 weeks for 6 cycles, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal half-life was 32 days (range, 14 to 62 days). Male patients and patients with body weight ≥ 125 kg had higher clearance and volume of distribution than female patients and patients with body weight < 125 kg. The unknown risks to the infant from oral ingestion of rituximab to the mother should be considered before administering rituximab to pregnant females (8.1).

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B lymphocytes. This interaction results in apoptosis of the lymphocytes. The mechanism of cell lysis includes complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC).
RITUXAN

Study 3

b Estimates of Cox regression stratified by center.

dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan 375 mg/m² on Day 1 of each cycle for refractory, low-grade NHL received Rituxan 375 mg/m² weekly for 4 doses. Results are summarized in Table 4.

The main outcome was progression-free survival (PFS), defined as the time from randomization in the maintenance/observation arm to the earliest of progression, relapse, or death. Results are presented in Table 4.

There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to Rituxan as compared to those who received no additional treatment.

Additional Rituxan exposure beyond induction was not associated with further improvements in outcome. Median PFS was 7.9 months in the Rituxan arm and 5.5 months in the no additional treatment arm. The median PFS was not reached in the CVP arm and patients who had no progression in the first year also had no progression in the second year.

Results are summarized in Table 4.

The main outcome measure in both studies was progression-free survival (PFS), defined as the time from randomization to the earliest of progressive disease, relapse, or death. Efficacy results are presented in Table 7.

Patients who tolerated the 90-minute rituximab infusion at Cycle 2 continued to receive Rituxan, 375 mg/m² intravenous infusion, once weekly for 4 doses every 6 months for up to 16 doses or no Rituxan for 16 doses. Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 1 week of each rituximab treatment cycle.

Retreatment with Rituxan

Inadequate Response to TNF Antagonists

86%

% Patients with 30% or More Improvement in Disease Activity

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Week 24</th>
<th>Week 52</th>
<th>Week 104</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Placebo (n=201)</td>
<td>27%</td>
<td>21%</td>
<td>NA</td>
<td></td>
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<tr>
<td>FC (n=101)</td>
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<td></td>
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<tr>
<td>Rituxan + MTX (n=103)</td>
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</table>

- Placebo: 27% at Week 24 (95% CI: 20, 34)
- FC: 21% at Week 24 (95% CI: 14, 28)
- Rituxan + MTX: 31% at Week 24 (95% CI: 24, 38)

Mean Radiographic Change From Baseline to 104 Weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>80% N/A</th>
<th>90% N/A</th>
<th>95% N/A</th>
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<tbody>
<tr>
<td>Placebo (n=201)</td>
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<td></td>
<td></td>
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<tr>
<td>FC (n=101)</td>
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<td></td>
<td></td>
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<tr>
<td>Rituxan + MTX (n=103)</td>
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</tbody>
</table>

- Placebo: 80% at Week 80 (95% CI: 70, 85)
- FC: 90% at Week 90 (95% CI: 80, 95)
- Rituxan + MTX: 95% at Week 95 (95% CI: 85, 99)

What is Rituxan?

Rituxan is a prescription medicine that is used to treat some types of cancer, rheumatoid arthritis, and a blood disease called primary or secondary lymphoma or chronic lymphocytic leukemia. Rituxan is also used to treat some diseases that are caused by immune system disorders.

Possible Side Effects of Rituxan

Rituxan can cause serious side effects that can lead to death, including:

- Nausea, vomiting, or diarrhea
- Progressive disease
- Relapse
- Death

Common side effects during Rituxan treatment include:

- Fatigue
- Headache
- Swelling of the hands and feet
- Changes in the color of the skin
- Changes in heart and lung function

What are the ingredients in Rituxan?

Rituxan contains the following inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and MPA.
A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight weekly dosings with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in animals received rituximab via the intravenous route during early gestation (organogenesis period; post-coitum). Hazard ratio 0.56 (0.43, 0.71) 0.76 (0.6, 0.96) 0.56 (0.43, 0.71) 0.76 (0.6, 0.96)

### Efficacy Results in Studies 11 and 12

**ACR Responses in Study 1 and Study 2 (Percent of Patients)**

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>15.0</td>
<td>16.0</td>
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<tr>
<td>ACR50</td>
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**ES**

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
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<tbody>
<tr>
<td>ES 0.44</td>
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<td>0.75</td>
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**Swollen Joint Count**

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<thead>
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<th></th>
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<td>Swollen Joint Count 20.0</td>
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**Disability Index (HAQ)**

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<th>Study 2</th>
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<tr>
<td>Disability Index (HAQ) 2.0</td>
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</table>

**Change during First Year**

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change during First Year 16</td>
<td>0.44</td>
<td>1.19</td>
</tr>
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</table>

**What is the most important information I need to know about RITUXAN?**

- **Severe skin and mouth reactions.**
  - Patients may develop severe rashes, peeling skin, swelling of your lips, tongue, throat, or face, which can be life-threatening.
  - If you get any of these symptoms, tell your doctor or get medical help right away.

- **Infection.**
  - You have a higher risk of developing infections when you’re taking RITUXAN. Tell your doctor if you get any symptoms of infection.

- **PML.**
  - PML is a rare, serious brain infection. It can be caused by a virus called JC virus. It can cause permanent disability or even death. Patients who received RITUXAN for GPA or MPA have a higher risk of PML. If you develop signs of PML, tell your doctor right away.

- **Hypothyroidism.**
  - Patients who received RITUXAN may develop hypothyroidism, which can affect your thyroid gland. Your doctor will monitor your thyroid function while you’re taking RITUXAN.

**What should I know about infections?**

- **Increased risk of infections.**
  - Patients taking RITUXAN have a higher risk of developing infections, especially infections of the lungs, blood, and skin. Your doctor will monitor you for infections.

**What should I know about the use of Rituxan with other medicines?**

- **Increased risk of infections.**
  - Patients taking RITUXAN have a higher risk of developing infections, especially infections of the lungs, blood, and skin. Your doctor will monitor you for infections.

**What should I know about the use of Rituxan with other medicines?**

- **Increased risk of infections.**
  - Patients taking RITUXAN have a higher risk of developing infections, especially infections of the lungs, blood, and skin. Your doctor will monitor you for infections.

**What should I know about the use of Rituxan with other medicines?**

- **Increased risk of infections.**
  - Patients taking RITUXAN have a higher risk of developing infections, especially infections of the lungs, blood, and skin. Your doctor will monitor you for infections.
of the pregnant animals. The B-cell counts returned to normal levels, and immunologic function was
restored. Rituximab was administered as loading doses on post-coitum (PC) days 20, 21 and 22, at
weekly intervals for a total of 8 doses. Results are summarized in Table 4.

Study 5
Bulky Disease
Of these 60 patients, 5 received more than one additional course of Rituxan. Results are summarized in Table 4.

Table 4
Weekly × 8

Study 2
Weekly × 4

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an
administration of Rituxan 3.8–35.6 months (median 14.5 months) prior to retreatment with Rituxan.

All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm received
administrations of cyclophosphamide, doxorubicin, vincristine, and prednisone. Patients in the Rituxan+CHOP
arm received this regimen plus Rituxan at 375 mg/m² weekly for 4 doses. Results are summarized in Table 4.

The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter open-label studies
for the treatment of B-cell chronic lymphocytic leukemia (CLL). Patients with Rai stage I–IV CLL were
randomized to Rituxan as single-agent maintenance therapy, 375 mg/m² every 8 weeks for up to 12 doses or to
placebo + MTX, the majority between Weeks 24–28. The proportions of patients achieving ACR 20, 50, and
70 responses were similar in both Rituxan dose groups and were higher than placebo. These improvements were
maintained at 48 weeks.

In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan + MTX and 72% of
patients initially randomized to placebo continued to receive their assigned treatment through Week 24. Patients
who continued to receive Rituxan had a greater improvement in health status with Rituxan compared to
placebo, as measured by the HAQ-DI. From baseline to Week 24, a greater proportion of Rituxan-treated patients had an improvement in HAQ-DI
of at least 0.44 compared to placebo (HAQ-DI: -0.44 ± 0.27 vs. -0.09 ± 0.31, p < 0.001). These improvements were maintained at 48 weeks.

In a randomized, double-blind, active-controlled multicenter, non-inferiority study, conducted in two phases – a 6 month
and a 24-month phase – patients with active rheumatoid arthritis with inadequate response or intolerance to prior
Tumor Necrosis Factor (TNF) antagonist therapy were randomized to receive either Rituxan 1000 mg intravenously (IV) followed by
250 mg IV every 2 weeks for 8 doses or placebo. The primary endpoint was the proportion of patients achieving an American College of
Rheumatology (ACR) 20 response at Week 24. Patients who continued to receive Rituxan had a greater improvement in health status with Rituxan compared to
placebo, as measured by the HAQ-DI. From baseline to Week 24, a greater proportion of Rituxan-treated patients had an improvement in HAQ-DI
of at least 0.44 compared to placebo (HAQ-DI: -0.44 ± 0.27 vs. -0.09 ± 0.31, p < 0.001). These improvements were maintained at 48 weeks.

In a phase II study, patients with active rheumatoid arthritis with inadequate response to prior TNF antagonist therapy were randomized to receive either Rituxan 1000 mg IV followed by 250 mg IV every 2 weeks for 8 doses or placebo. The primary endpoint was the proportion of patients achieving an ACR 20 response at Week 24. Patients who continued to receive Rituxan had a greater improvement in health status with Rituxan compared to
placebo, as measured by the HAQ-DI. From baseline to Week 24, a greater proportion of Rituxan-treated patients had an improvement in HAQ-DI
of at least 0.44 compared to placebo (HAQ-DI: -0.44 ± 0.27 vs. -0.09 ± 0.31, p < 0.001). These improvements were maintained at 48 weeks.

What is PML?
PML is a rare, often fatal, viral infection caused by a type of retrovirus called John Cunningham virus (JCV). Rituxan has been designed and approved to treat a number of different cancers and immune-related diseases. However, when used to treat these conditions, Rituxan can cause an increased risk of developing PML. PML can result in death or severe disability. There is no known treatment for PML.

What is the sign of PML?
PML may cause symptoms such as fatigue, fever, chills, and muscle weakness. Other symptoms may include a high blood pressure or white blood cell count, a decrease in the number of red blood cells, and a decrease in platelet levels. These symptoms may develop at any time during treatment with Rituxan. PML may cause symptoms such as fatigue, fever, chills, and muscle weakness. Other symptoms may include a high blood pressure or white blood cell count, a decrease in the number of red blood cells, and a decrease in platelet levels. These symptoms may develop at any time during treatment with Rituxan. PML may cause symptoms such as fatigue, fever, chills, and muscle weakness. Other symptoms may include a high blood pressure or white blood cell count, a decrease in the number of red blood cells, and a decrease in platelet levels. These symptoms may develop at any time during treatment with Rituxan.

What are the potential side effects of Rituxan?
• weakness
• tiredness
• infection
• diarrhea
• fever
• headache
• nausea
• vomiting

Tell your doctor or get medical help right away if you get any of these serious side effects or if your symptoms get worse:
• feeling light-headed or faint when getting up from sitting or lying down
• difficulty breathing
• chest pain
• shortness of breath
• loss of appetite
• sudden increase in weight
• swelling in the legs, ankles, or hands
• slow heartbeat
• numbness or tingling in your hands or feet
• tremors

Common side effects during Rituxan treatment include:
• weakness
• tiredness
• infection
• diarrhea
• fever
• headache
• nausea
• vomiting

Tell your doctor about any side effect that bothers you or that does not go away.

Precautions and Special Information
Rituxan was studied in clinical trials to evaluate its safety and effectiveness. Your doctor has decided that the benefits of Rituxan for your condition outweigh the risks. It is important that you understand the risks of Rituxan and the benefits it may provide. If you have any questions about these risks or benefits, please talk to your doctor or pharmacist.

Rituxan is approved for use by people 18 years and older. It is not known if Rituxan is safe and effective for use by people younger than 18 years.

Rituxan is given by infusion through a needle placed in a vein (intravenous infusion), in your arm. Talk to your doctor about how you will receive Rituxan.

Rituxan is a prescription medicine used to treat:
• chronic lymphocytic leukemia (CLL)
• non-Hodgkin’s lymphoma (NHL), including follicular and diffuse large B-cell lymphoma
• rheumatoid arthritis

Rituxan is not for use by people who are sensitive or allergic to rituximab or any of the ingredients in Rituxan. Rushing the signs and symptoms: Initial and re-treatment courses

Table 13
What is the most important information I should know about Rituxan?
A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight
13.2 Animal Toxicology and/or Pharmacology

Results are summarized in Table 4. The median time to onset of response was 50 days. Disease‑related signs and

The safety and effectiveness of Rituxan in previously untreated, low‑grade or follicular, CD20+ NHL were
demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.

Overall survival at 2 years: 74% 63% 69% 58% 95% 86%

In Study 10, a total of 363 patients with previously untreated follicular NHL (n=113) or DLBCL (n=250) were evaluated

Reducing the Signs and Symptoms: Initial and Re‑Treatment Courses

Response

Median PFS (months) 39.8 31.5 26.7 21.7

b Since all patients received a first course of Rituxan, no comparison between Placebo + MTX and Rituxan + MTX is made

Table 8

Study 12*

Hazard Ratio for PFS

18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients

inadequate response to TNF antagonists

You should not receive certain vaccines before or after you receive Rituxan.

Inadequate Response to TNF Antagonists

You should not receive certain vaccines before or after you receive Rituxan.
Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 50% had Bulky Disease had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by a blinded, independent observer. Rituxan was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of Study 3 is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX as a BVAS/GPA of 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 0.36 units compared to 1.08 units for the MTX monotherapy group. A statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the MTX monotherapy group. A statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the MTX monotherapy group.

In Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively. In Study 10, a total of 363 patients with previously untreated follicular NHL (n=113) or DLBCL (n=250) were evaluated.

In Study 12, 44% of patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response after two cycles of chemotherapy. Among all enrolled adult patients with moderately to severely active RA who had a prior inadequate response to at least one TNF inhibitor.

In Study 12, 44% of patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response after two cycles of chemotherapy. Among all enrolled adult patients with moderately to severely active RA who had a prior inadequate response to at least one TNF inhibitor.
IMPORTANT DRUG WARNING