HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRUXIMA safely and effectively. See full prescribing information for TRUXIMA.
TRUXIMA® (rituximab-abbs) injection, for intravenous use
Initial U.S. Approval: 2015
TRUXIMA (rituximab-abbs) is biosimilar* to RITUXAN® (rituximab) injection, for intravenous use.

WARNING: FATAL INFUSION-RELATED REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY
See full prescribing information for complete boxed warning.

• Fatal infusion-related reactions within 24 hours of rituximab infusion; approximately 60% of fatal reactions occurred with first infusion. Monitor patients and discontinue TRUXIMA infusion for severe reactions (5.1).
• Severe mucocutaneous reactions, some with fatal outcomes (5.2).
• Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death (5.3).
• Progressive multifocal leukoencephalopathy (PML) resulting in death (5.4).

Recent Major Changes
Indications and Usage (1.1, 1.2, 1.3, 1.4) 12/2019
Dosage and Administration (2.3, 2.4, 2.5, 2.6) 12/2019
Warnings and Precautions (5.10, 5.12, 5.13) 12/2019

Indications and Usage
TRUXIMA (rituximab-abbs) is a CD20-directed cytolytic antibody indicated for the treatment of adult patients with:
• Non-Hodgkin’s Lymphoma (NHL) (1.1).
  ◦ Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.
  ◦ Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
  ◦ Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
  ◦ Previously untreated diffuse large B-cell, CD20-positive NHL in combination with first-line chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.
  ◦ Chronic Lymphocytic Leukemia (CLL) (1.2).
  ◦ Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).
  ◦ Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.3).
  ◦ Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids (1.4).

Dosage and Administration
Administer only as an intravenous infusion.
Do not administer as an intravenous push or bolus.
TRUXIMA should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur.
The dose for NHL is 375 mg/m² (2.2).
The dose for CLL is 375 mg/m² in the first cycle and 500 mg/m² in cycles 2-6, in combination with FC, administered every 28 days (2.3).
The dose as a component of Zevalin® (ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m² (2.4).

Dosage Forms and Strengths
Injection: 100 mg/10 mL (10 mg/mL) and 500 mg/50 mL (10 mg/mL) solution in single-dose vials (3).

Contraindications
None (4)

Warnings and Precautions
• Tumor lysis syndrome: Administer aggressive intravenous hydration, anti-hyperuricemic agents, monitor renal function (5.5).
• Infections: Withhold TRUXIMA and institute appropriate anti-infective therapy (5.6).
• Cardiac adverse reactions: Discontinue infusions in cases of serious or life-threatening events (5.7).
• Renal toxicity: Discontinue in patients with rising serum creatinine or oliguria (5.8).
• Bowel obstruction and perforation: Consider and evaluate for abdominal pain, vomiting, or related symptoms (5.9).
• Immunizations: Live virus vaccinations prior to or during TRUXIMA treatment not recommended (5.10).
• Embryo-Fetal toxicity: Can cause neonatal harm. Advise of potential risk to neonates and use of effective contraception (5.11).

Adverse Reactions
Most common adverse reactions in clinical trials were:
• NHL (≥25%): infusion-related reactions, fever, lymphopenia, chills, infection and asthma (6.1).
• CLL (≥25%): infusion-related reactions and neutropenia (6.1).
• RA (≥10%): upper respiratory tract infection, nasopharyngitis, urticaria, rash, and bronchitis (other important adverse reactions include infusion-related reactions, serious infections, and cardiovascular events) (6.2).
• GPA and MPA (≥15%): infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema, infusion-related reactions (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact TEVA Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Drug Interactions
Renal toxicity when used in combination with cisplatin (5.8).

Use in Specific Populations
• Lactation: Advise not to breastfeed (8.2).
• Geriatric Use: In CLL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of rituximab to FC (8.5).

Seer 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
• Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of Truxima has been demonstrated no benefit with the addition of rituximab to FC (8.5).

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WARNING: FATAL INFUSION-RELATED REACTIONS, SEVERE MUCOCUTANEOUS REACTIONS, HEPATITIS B VIRUS REACTIVATION and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Infusion-Related Reactions
Administration of rituximab products, including TRUXIMA, can result in serious, including fatal, infusion-related reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion-related reactions occurred in association with the first infusion. Monitor patients closely. Discontinue TRUXIMA infusion for severe reactions and provide medical treatment for Grade 3 or 4 infusion-related reactions (see Warnings and Precautions (5.1), Adverse Reactions (6.1)).

Severe Mucocutaneous Reactions
Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab products (see Warnings and Precautions (5.2)).

Hepatitis B Virus (HBV) Reactivation
HBV reactivation can occur in patients treated with rituximab products, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with TRUXIMA. Discontinue TRUXIMA and concomitant medications in the event of HBV reactivation (see Warnings and Precautions (5.3)).

Progressive Multifocal Leukoencephalopathy (PML)
In patients with RA, GPA or MPA, obtain CBC with differential and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias (see Adverse Reactions (6.1)). In patients with RA, GPA or MPA, obtain CBC with differential and platelet counts at two to four month intervals during TRUXIMA therapy. Continue to monitor for cytopenias after final dose and until resolution.

1 INDICATIONS AND USAGE
1.1 Non–Hodgkin’s Lymphoma (NHL)
TRUXIMA (rituximab-abbs) is indicated for the treatment of adult patients with:
- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent.
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first-line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

1.2 Chronic Lymphocytic Leukemia (CLL)
TRUXIMA is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.

1.3 Rheumatoid Arthritis (RA)
TRUXIMA in combination with methotrexate is indicated for the treatment of adult patients with moderately-to-severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies.

1.4 Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)
TRUXIMA, in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA).

2 DOSAGE AND ADMINISTRATION
2.1 Important Dosing Information
Administer only as an Intravenous Injection (see Dosage and Administration (2.8)). Do not administer as an intravenous push or bolus. TRUXIMA should only be administered by a healthcare professional with appropriate medical support to manage severe infusion-related reactions that can be fatal if they occur (see Warnings and Precautions (5.1)). Premedicate before each infusion (see Dosage and Administration (2.7)).

Prior to First Infusion: Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with TRUXIMA (see Warnings and Precautions (5.3)). Obtain complete blood counts including platelets (CBC) prior to the first dose.

During TRUXIMA Therapy:
In patients with lymphoid malignancies, during treatment with TRUXIMA monotherapy, obtain complete blood counts (CBC) with differential and platelet counts prior to each TRUXIMA dose. During treatment with TRUXIMA and chemotherapy, obtain CBC with differential and platelet counts at weekly intervals and more frequently in patients who develop cytopenias (see Adverse Reactions (6.1)). In patients with RA, GPA or MPA, obtain CBC with differential and platelet counts at two to four month intervals during TRUXIMA therapy. Continue to monitor for cytopenias after final dose and until resolution.

- First Infusion: Initiate at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- Subsequent Infusions:
  - Standard Infusion: Initiate at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
  - For previously untreated follicular NHL and DLBCL patients:
    - If patients did not experience a Grade 3 or 4 infusion related adverse event during Cycle 1, a 90-minute infusion can be administered in Cycle 2 with a glucocorticoid-containing chemotherapy regimen.
    - Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in Cycle 2, the same rate can be used when administering the remainder of infusion related reactions.

- Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count ≥5000/mm³ before Cycle 2 should not be administered the 90-minute infusion (see Clinical Studies (14.4)).
- Interrupt the infusion or slow the infusion rate for infusion-related reactions (see Boxed Warning, Warnings and Precautions (5.1)). Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2 Recommended Dose for Non–Hodgkin’s Lymphoma (NHL)
The recommended dose is 375 mg/m² as an intravenous infusion according to the following schedules:
- Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
  - Administer once weekly for 4 or 8 doses.
- Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
  - Administer once weekly for 4 doses.
- Previously Untreated, Follicular, CD20-Positive, B-Cell NHL
  - Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate TRUXIMA maintenance eight weeks following completion of a rituximab product in combination with chemotherapy. Administer TRUXIMA as a single-agent every 8 weeks for 12 doses.
- Non-progressing, Low-Grade, CD20-Positive, B-Cell NHL, after first-line CVP chemotherapy
  - Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- Diffuse Large B-Cell NHL
  - Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)
The recommended dose is:
- 375 mg/m² the day prior to the initiation of FC chemotherapy, then 500 mg/m² on Day 1 of cycles 2–6 (every 28 days).

2.4 Recommended Dose as a Component of Zevalin® for treatment of NHL
- When used as part of the Zevalin therapeutic regimen, infuse 250 mg/m² in accordance with the Zevalin package insert. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

2.5 Recommended Dose for Rheumatoid Arthritis (RA)
- Administer TRUXIMA as two-1000 mg intravenous infusions separated by 2 weeks.
- Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion-related reactions.
- Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.
- TRUXIMA is given in combination with methotrexate.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

2.6 Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Induction Treatment of Adult Patients with Active GPA/MPA

- Administer TRUXIMA as a 375 mg/m² intravenous infusion once weekly for 4 weeks for patients with active GPA or MPA.
- Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone as per clinical practice. This regimen should begin within 14 days prior to or with the initiation of TRUXIMA and may continue during and after the 4 week induction course of TRUXIMA treatment.

Follow up Treatment of Adult Patients with GPA/MPA who have achieved disease control with induction treatment

- Administer TRUXIMA as two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion every 6 months thereafter based on clinical evaluation.
- If induction treatment of active disease was with a rituximab product, initiate follow up treatment with TRUXIMA within 24 weeks after the last induction infusion with a rituximab product or based on clinical evaluation, but no sooner than 16 weeks after the last induction infusion with a rituximab product.
- If induction treatment of active disease was with other standard of care immunosuppressants, initiate TRUXIMA follow up treatment within the 4 week period that follows achievement of disease control.

2.7 Recommended Dose for Premedication and Prophylactic Medications

Premedicate with acetaminophen and an antihistamine before each infusion of TRUXIMA. For patients administered TRUXIMA according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion [see Clinical Studies (14.4)]. For RA, GPA and MPA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

Provide prophylaxis treatment for Pneumocystis jirovecii pneumonia (PCP) and P. jirovecii pneumonia manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

4.1 Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has been reported in patients who are carriers of HBV. The risk of clinical hepatitis or HBV reactivation appears to be increased in patients who develop clinical hepatitis during and after several months following TRUXIMA therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy.

In patients who develop reactivation of HBV while on TRUXIMA, immediately discontinue TRUXIMA and any concomitant chemotherapy, and institute appropriate management. Patients with clinical manifestations of HBV reactivation and elevated alanine aminotransferase or other laboratory signs of hepatitis or HBV reactivation during and for several months following TRUXIMA therapy. HBV reactivation is defined as an abrupt increase in HBV DNA levels or detection of HBsAg in a patient who was previously HBsAg negative and anti-HBc positive. Reactivation also has occurred in patients who appear to have resolved HBV 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 levels or detection of HBsAg in a patient who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication following 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 TRUXIMA. For patients who show evidence of prior hepatitis treatment, discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

5.3 Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has been reported in patients who are carriers of HBV. The risk of clinical hepatitis or HBV reactivation appears to be increased in patients who develop clinical hepatitis during and after several months following TRUXIMA therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy.

In patients who develop reactivation of HBV while on TRUXIMA, immediately discontinue TRUXIMA and any concomitant chemotherapy, and institute appropriate management. Patients with clinical manifestations of HBV reactivation and elevated alanine aminotransferase or other laboratory signs of hepatitis or HBV reactivation during and for several months following TRUXIMA therapy. HBV reactivation is defined as an abrupt increase in HBV DNA levels or detection of HBsAg in a patient who was previously HBsAg negative and anti-HBc positive. Reactivation also has occurred in patients who appear to have resolved HBV 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 levels or detection of HBsAg in a patient who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication following 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 TRUXIMA. For patients who show evidence of prior hepatitis treatment, discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

5.6 Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab product-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue TRUXIMA for serious infections and institute appropriate anti-infective therapy [see Adverse Reactions (6.2, 6.3)]. TRUXIMA is not recommended for use in patients with severe, active infections.

5.7 Cardiovascular Adverse Reactions

Cardiac adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock may occur in patients receiving rituximab products. Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of TRUXIMA for patients who develop clinically significant arrhythmias, or who have a history of arrhythmias or angina [see Adverse Reactions (6.1)].

5.8 Renal Toxicity

Severe, including fatal, renal toxicity can occur after rituximab product administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and TRUXIMA is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue TRUXIMA in patients with a rising serum creatinine or oliguria [see Warnings and Precautions (5.7)].

5.9 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving rituximab products in combination with chemotherapy.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days after final rituximab infusion. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

5.10 Immunization

The safety of immunization with live viral vaccines following rituximab product therapy has not been studied and vaccination with live virus vaccines is not recommended during rituximab therapy. For patients treated with TRUXIMA, physicians should review the patient’s vaccination status and screens for HIV and hepatitis B and C infection. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

5.11 Embryo-Fetal Toxicity

Based on human data, rituximab products can cause fetal harm due to B-cell lymphocytopenia, as well as leukopenia and thrombocytopenia in utero. Advise pregnant women of the risk to the fetus. In 16 exposed women, 7 had live births; 6 were normal and 1 resulted in spontaneous abortion. There were no exposed infants reported with congenital anomalies. There were also reports of fetal deaths. In preclinical studies, rituximab caused lymphocytopenia in rats and rabbits. There are no adequate and well-controlled studies in pregnant women. Therefore, TRUXIMA should be used during pregnancy only if the potential benefit justifies potential risk to the fetus.

5.12 Concomitant Use With Other Biologic Agents and DMARDs other than Methotrexate in RA, GPA and NMFA

Limited data is available on the safety of the use of biologic agents or disease-modifying antirheumatic drugs (DMARDs) other than methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not been evaluated in rituximab or methotrexate patients exhibiting peripheral B-cell depletion following treatment with rituximab products.

5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

While the efficacy of rituximab was assessed in randomized controlled trials in patients with RA with rituximab plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the rituximab plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%). A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with rituximab plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on rituximab plus MTX vs. 70% of patients on MTX alone).

Most patients in the rituximab-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

• Infusion-related reactions [see Warnings and Precautions (5.1)]
• Severe mucocutaneous reactions [see Warnings and Precautions (5.2)]
• Hepatitis B reactivation with fulminant hepatitis [see Warnings and Precautions (5.3)]
• Progressive multifocal leukoencephalopathy [see Warnings and Precautions (5.4)]
• Tumor lysis syndrome [see Warnings and Precautions (5.5)]
• Infections [see Warnings and Precautions (5.6)]
• Cardiovascular adverse reactions [see Warnings and Precautions (5.7)]
• Renal toxicity [see Warnings and Precautions (5.8)]
• Bowel obstruction and perforation [see Warnings and Precautions (5.9)]

6.1 Clinical Adverse Events in Lymphoid Malignancies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. The data described below reflect exposure to rituximab in 2783 patients, with exposures ranging from a single infusion up to 2 years. Rituximab was studied in both single-arm and controlled trials (n=1561 and n=1222, respectively). The population included 1180 patients with low grade or follicular lymphoma, 927 patients with DLBCL, and 676 patients with CLL. Most NHL patients received rituximab as an infusion of 375 mg/m² per infusion, given as a single agent weekly for up to 6 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received rituximab as an intravenous infusion followed by 500 mg/m² for up to 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of rituximab-based therapy.

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with NHL were: infusion-related reactions and neutropenia.

6.2 Infectious Malignancies

In the majority of patients with NHL, infusion-related reactions consisting of fever, chills, rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first rituximab infusion and resolved with slowing or interruption of the rituximab infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion-related reactions was highest during the first infusion (77%) and decreased with each subsequent infusion [see Warnings and Precautions (5.1)]. In patients with previously untreated follicular NHL or previously untreated DLBCL, who did not experience a Grade 3 or 4 infusion-related reaction in Cycle 1 and received a 90-minute infusion of rituximab at Cycle 2, the incidence of Grade 3-4 infusion-related reactions on the day of, or day after the infusion was 1.1% (95% CI [0.3%, 2.9%]). For Cycles 2-6, the incidence of Grade 3-4 infusion-related reactions on the day of as day after the infusion that was 2.8% (95% CI [1.3%, 5.0%]) [see Warnings and Precautions (5.1), Clinical Studies (14.4)].

6.3 Gastrointestinal System

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with CLL were: infusion-related reactions and neutropenia.

6.4 Hematologic Malignancies

In patients with NHL receiving rituximab monotherapy, NCI-CTCAE Grade 3 and 4 infections were reported in 48% of patients. These included lymphopenia (40%), fever (37%), and infections (15%). In patients with previously untreated follicular NHL or previously untreated DLBCL, who did not experience a Grade 3 or 4 infusion-related reaction in Cycle 1 and received a 90-minute infusion of rituximab at Cycle 2, the incidence of Grade 3-4 infusion-related reactions on the day of, or day after the infusion was 1.1% (95% CI [0.3%, 2.9%]). For Cycles 2-6, the incidence of Grade 3-4 infusion-related reactions on the day of as day after the infusion that was 2.8% (95% CI [1.3%, 5.0%]) [see Warnings and Precautions (5.1), Clinical Studies (14.4)].

In randomized, controlled studies where rituximab was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection occurred during the single-arm studies. A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with rituximab plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the rituximab plus MTX group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

6.5 Respiratory Malignancies

A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with rituximab plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on rituximab plus MTX vs. 70% of patients on MTX alone). Most patients in the rituximab-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

6.6 Gynecologic Malignancies

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with NHL were: infusion-related reactions and neutropenia.

6.7 Special Senses

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with NHL were: infusion-related reactions and neutropenia.

6.8 Skin

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with NHL were: infusion-related reactions and neutropenia.

6.9 Oncology nurse

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with NHL were: infusion-related reactions and neutropenia.

6.10 Metabolic and Nutritional System

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with NHL were: infusion-related reactions and neutropenia.

6.11 Other Adverse Reactions

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with NHL were: infusion-related reactions and neutropenia.

6.12 Laboratory Abnormalities

The most common adverse reactions of rituximab (incidence ≥25%) observed in the clinical trials of patients with NHL were: infusion-related reactions and neutropenia.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

In CLL Study 1, the following Grade 3 and 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion-related reactions (9% in R-FC arm), neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and pancytopenia (3% vs. 1%).

In CLL Study 2, the following Grade 3 or 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion-related reactions (7% in R-FC arm), neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%), hypotension (2% vs. 0%), and hepatitis B (2% vs. <1%). Fifty-nine percent of R-FC-treated patients experienced an infusion-related reaction of any severity.

6.2 Clinical Trials Experience in Rheumatoid Arthritis

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The data presented below reflect the experience in 2578 RA patients treated with rituximab in controlled and long-term studies1 with a total exposure of 5014 patient-years. Among all exposed patients, adverse reactions reported in greater than 10% of patients include infusion-related reactions, upper respiratory tract infection, nasopharyngitis, urinai tract infection, and bronchitis.

In placebo-controlled studies, patients received 2 x 500 mg or 2 x 1000 mg intravenous infusions of rituximab or placebo, in combination with methotrexate, during a 24-week period. From these studies, 938 patients treated with rituximab (2 x 1000 mg) or placebo have been pooled (see Table 2). Adverse reactions reported in ≥5% of patients were hypertension, nausea, upper respiratory tract infection, arthralgia, pyrexia and pruritus (see Table 2). The rates and types of adverse reactions in patients who received rituximab 2 x 500 mg were similar to those observed in patients who received rituximab 2 x 1000 mg.

Table 2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Placebo + MTX</th>
<th>Rituximab + MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthenia</td>
<td>23 (5%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11 (2%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>16 (3%)</td>
<td>14 (2%)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>10 (2%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>14 (4%)</td>
<td>16 (3%)</td>
</tr>
<tr>
<td>Hypothyroidity</td>
<td>22 (5%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (5%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Nervous System</td>
<td>23 (6%)</td>
<td>26 (6%)</td>
</tr>
<tr>
<td>Numbness</td>
<td>12 (3%)</td>
<td>12 (3%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (1%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (2%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Rash, pruritic</td>
<td>5 (1%)</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (2%)</td>
<td>12 (2%)</td>
</tr>
<tr>
<td>Vomiting, nausea</td>
<td>10 (2%)</td>
<td>10 (2%)</td>
</tr>
</tbody>
</table>

*These data are based on 938 patients treated in Phase 2 and 3 studies of rituximab (2 x 1000 mg) or placebo administered in combination with methotrexate.

1 Coded using MedDRA.

Infusion-Related Reactions

In the rituximab RA pooled placebo-controlled studies, 32% of rituximab-treated patients experienced an adverse reaction during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the 24-hour period following the second infusion, rituximab or placebo, decreased to 11% and 13%, respectively. Acute infusion-related reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of rituximab-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion-related reactions following the second infusion of rituximab or placebo decreased to 9% and 11%, respectively. Serious acute infusion-related reactions were experienced by <1% of patients in either treatment group. Acute infusion-related reactions required dose modification (stopping, slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion-related reactions decreased with subsequent courses of rituximab. The administration of intravenous glucocorticoids prior to rituximab infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of glucocorticoids for the prevention of acute infusion-related reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to rituximab infusions.

Infections

In the pooled, placebo-controlled studies, 39% of patients in the rituximab group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, bronchitis, and sinusitis.
The incidence of serious infections was 2% in the rituximab-treated patients and 1% in the placebo group. In the experience with rituximab in 2578 RA patients, the rate of serious infections was 4.31 per 100 patient years. The most common serious infections (≥0.5%) were pneumonia or lower respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included pneumonia, sepsis, and colitis. Rates of serious infection remained stable in patients receiving subsequent courses. In 185 rituximab-treated RA patients with active disease, subsequent treatment with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per 100 patient years) after exposure.

### Cardiovascular Reactions

In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular reactions was 1.7% and 1.3% in the rituximab and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/789 = 0.4%) as compared to none in the placebo treatment group (0/399).

In the experience with rituximab in 2578 RA patients, the rate of serious cardiac reactions was 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years (28 events in 26 patients), which is consistent with MI rates in the general RA population. These rates did not increase over three courses of rituximab.

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the treatment period. The primary analysis was at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine (15, followed by a 500 mg intravenous infusion every 6 months for 18 months). Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine (15, followed by a 500 mg intravenous infusion every 6 months for 18 months). In the experience with rituximab in RA patients, newly-occurring hypophosphatemia was observed in 21% (528/2570) of patients and newly-occurring hyperuricemia was observed in 2% (58/2570) of patients. The majority of the observed hypophosphatemia occurred at the time of the infusions and was transient.

### Infusion-Related Reactions

The incidence of infusion-related reactions was 1.7% and 1.3% in the rituximab and placebo treatment groups, respectively. These rates did not increase over three courses of rituximab. However, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion-related reactions.

### Adverse Reactions

The data presented below from GPA/MPA Study 1 (NCT00104299) reflect the experience in 197 adult patients with active GPA and MPA treated with rituximab or cyclophosphamide in a single controlled study, which was conducted in two phases: a 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and an additional 12 month remission maintenance phase [see Clinical Studies (14.6), and Dosage and Administration (2.5)].

### Clinical Trials Experience in Granulomatosis with Polyangitis (GPA)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### Retreatment in Patients with RA

In the experience with rituximab in RA patients, 2578 patients have been exposed to rituximab and have received up to 10 courses of rituximab in RA clinical trials, with 1890, 1045, and 425 patients having received at least two, three, and four courses, respectively. Most of the patients who received additional courses did so 24 weeks or more after the previous course and none were retreated sooner than 16 weeks. The rates and types of adverse reactions reported for subsequent courses of rituximab were similar to rates and types seen for a single course of rituximab.

In RA Study 2, where all patients initially received rituximab, the safety profile of patients who retreated with rituximab was similar to those who were retreated with placebo [see Clinical Studies (14.6), and Dosage and Administration (2.5)].

### 6.3 Clinical Trials Experience in Granulomatosis with Polyangitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangitis (MPA)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

### Induction Treatment of Adult Patients with Active GPA/MPA (GPA/MPA Study 1)

The data presented below from GPA/MPA Study 1 (NCT00104299) reflect the experience in 197 adult patients with active GPA and MPA treated with rituximab or cyclophosphamide in a single controlled study, which was conducted in two phases: a 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and an additional 12 month remission maintenance phase [see Clinical Studies (14.7)]. In the 6-month remission induction phase, 197 patients with GPA and MPA were randomized to either rituximab 375 mg/m² once weekly for 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily (adjusted for renal function, white blood cell count, and other factors) plus glucocorticoids to induce remission. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The rituximab group did not receive additional therapy to maintain remission. The primary analysis was at the end of the 6 month remission induction period and the safety results for this period are described below.

### Adverse Reactions

The incidence of Adverse Reactions Occurring in ≥10% of rituximab-treated Patients with active GPA and MPA in the GPA/MPA Study 1 Up to Month 6* is depicted in the following table.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=199</td>
<td>N=98</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (3%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Infections</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Malignancies</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

* The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

### Infusion-Related Reactions

Infusion-related reactions in GPA/MPA Study 1 were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Among the 99 patients treated with rituximab, 12% experienced at least one infusion-related reaction, compared with 11% of the 98 patients in the cyclophosphamide group.

### Infusions

In GPA/MPA Study 1, 62% (61/99) of patients in the rituximab group experienced an infection of any type compared to 47% (46/98) patients in the cyclophosphamide group by Month 6. The most common infections in the rituximab group were upper respiratory tract infections, urinary tract infections, and herpes zoster.

The incidence of serious infections was 11% in the rituximab-treated patients and 10% in the cyclophosphamide treated patients, with rates of approximately 25 and 28 per 100 patient-years, respectively. The most common serious infection was pneumonia.

### Hypogammaglobulinemia

Hypogammaglobulinemia (IgG, IgM, IgM below the lower limit of normal) has been observed in patients with GPA and MPA treated with rituximab in GPA/MPA Study 1. At 6 months, in the rituximab group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46% in the cyclophosphamide group.

### Follow up Treatment of Adult Patients with GPA/MPA who have Achieved Disease Control with Induction Treatment (GPA/MPA Study 2)

In GPA/MPA Study 2 (NCT00748644), an open-label, controlled, clinical study [see Clinical Studies (14.7)], evaluating the efficacy and safety of non-U.S.-licensed rituximab versus azathioprine as follow up treatment in adult patients with GPA, MPA or renal-limited ANCA-associated vasculitis who had achieved disease control after induction treatment with cyclophosphamide, a total of 57 GPA and MPA patients in disease remission received follow up treatment with two 500 mg intravenous infusions of non-U.S.-licensed rituximab, separated by two weeks on Day 1 and Day 15, followed by a 500 mg intravenous infusion every 6 months for 18 months.

The safety profile was consistent with the safety profile for rituximab in RA and GPA and MPA.

### Infusion-Related Reactions

In GPA/MPA Study 2, 757 (12%) patients in the non-U.S.-licensed rituximab arm reported infusion-related reactions. The incidence of IRR symptoms was highest during or after the first infusion (93%) and decreased with subsequent infusions (≤4%). One patient had two serious IRRs, two IRRs led to a dose modification, and no IRRs were severe, fatal, or led to withdrawal from the study.

### Infusions

In GPA/MPA Study 2, 30/57 (53%) patients in the non-U.S.-licensed rituximab arm and 33/58 (57%) in the azathioprine arm reported infections. The incidence of all grade infections was similar between the arms. The incidence of serious infections was similar in both arms (12%). The most commonly reported serious infection in the group was mild or moderate bronchitis.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

Long-term, Observational Study with Rituximab in Patients with GPA/MPA (GPA/MPA Study 3)

In a long-term observational safety study (NCT01613599), 97 patients with GPA or MPA received treatment with rituximab (mean of 8 infusions [range 1-28]) for up to 4 years, according to physician standard practice and discretion. Majority of patients received doses ranging from 500 mg to 1000 mg, approximately every 6 months. The safety profile was consistent with the safety profile for rituximab in RA and GPA and MPA.

6.4 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other rituximab products may be misleading.

Using an ELISA assay, anti-rituximab antibody was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent rituximab. Three of the four patients had an objective clinical response.

A total of 237/99 (23%) rituximab-treated adult patients with GPA and MPA developed anti-rituximab antibodies at any time during treatment. Anti-rituximab antibody positivity was not associated with increased rates of infusion-related reactions or other adverse events. Upon further treatment, the proportions of patients with infusion-related reactions were similar between anti-rituximab antibody positive and negative patients, and most reactions were mild to moderate. Four anti-rituximab antibody positive patients had rash and one had a mild infusion reaction, and the temporal relationship between anti-rituximab antibody positivity and infusion-related reaction was variable.

A total of 23/99 (23%) rituximab-treated adult patients with GPA and MPA developed anti-rituximab antibodies by 18 months in GPA/MPA Study 1. The clinical relevance of anti-rituximab antibody formation in rituximab-treated adult patients is unclear.

6.5 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of rituximab. Because these reactions are voluntarily reported by patients and by physicians, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity: Pancytopenia, marrow hypoplasia, Grade 3-4 prolonged or late-onset neutropenia, hypercoagulability syndrome in Waldenström's macroglobulinemia, prolonged hypogammaglobulinemia [see Warnings and Precautions (5.6)].

Cardiac: Fatal cardiac failure.

Immunologic: Uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.

Infection: Viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections [see Warnings and Precautions (5.6)].

Neoplasia: Disease progression of Kaposi's sarcoma.

Skin: Severe maculopapular reactions, pyoderma gangrenosum (including infection), tenosynovitis.

Gastrointestinal: Bowel obstruction and perforation.

Pulmonary: Fatal bronchiolitis obliterans and fatal interstitial lung disease.


7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with rituximab products. In patients with CLL, rituximab did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on human data, rituximab products can cause adverse developmental outcomes including B-cell lymphocytopenia in infants exposed in-utero [see Clinical Considerations]. In animal reproduction studies, intravenous administration of rituximab to pregnant cynomolgus monkeys during the period of organogenesis [post coitum days 20 through 50] resulted in a decrease of 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed fetuses did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.

A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing 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 78. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

There are no data on the presence of rituximab products in human milk, the effect on the breastfed child, or the effect on milk production. However, rituximab is detected in the milk of lactating cynomolgus monkeys, and IgG is present in human milk. Since many drugs are excreted in human milk, advise lactating women not to breastfeed while receiving rituximab products.

8.2 Pediatric Use

Prolonged or late-onset neutropenia, hyperviscosity syndrome in patients receiving R-FC who were 70 years or older compared to younger patients for 6.5 Postmarketing Experience.

8.3 Females and Males of Reproductive Potential

Rituximab products can cause fetal harm [see Use in Specific Populations (8.1)].

Contraception

Females of childbearing potential should use effective contraception while receiving TRUXIMA and for 12 months following treatment.

8.4 Pediatric Use

The safety and effectiveness of rituximab products have not been established in pediatric patients with NHL, CLL, or RA.

The safety and effectiveness of rituximab was not studied in pediatric patients with polycystic juvenile idiopathic arthritis (PJIA) due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system.

8.5 Geriatric Use

Diffuse Large B-Cell NHL

Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients received rituximab in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac reaction adverse events, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonitis and pneumonitis.

Low-Grade or Follicular Non-Hodgkin's Lymphoma

Patients with previously untreated follicular lymphoma evaluated in NHL Study 5 were randomized to rituximab as single-agent maintenance therapy (n=505) or observation (n=513) after achieving a response to rituximab in combination with chemotherapy. Of these, 123 (24%) patients in the rituximab arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of rituximab in low-grade or follicular, CD20-positive, B-Cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

Chronic Lymphocytic Leukemia

Among patients with CLL evaluated in two randomized active-controlled trials, 243 of 676 rituximab-treated patients (36%) were 65 years of age or older; of these, 100 rituximab-treated patients (15%) were 70 years of age or older.

In exploratory analyses defined by age, there was no observed benefit from the addition of rituximab to fludarabine and cyclophosphamide among patients 70 years of age or older in CLL Study 1 or in CLL Study 2; there was also no observed benefit from the addition of rituximab to fludarabine and cyclophosphamide among patients 65 years of age or older in CLL Study 2 [see Clinical Studies (14.5)]. Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients, regardless of the addition of rituximab. In CLL Study 1, the dose intensity of rituximab was similar in older and younger patients, however in CLL Study 2 older patients received a lower dose intensity of rituximab.

The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (CLL Study 1); 56% vs. 39% (CLL Study 2)], febrile neutropenia [16% vs. 6% (NHL Study 10 [NCT00719472])], anemia [5% vs. 2% (CLL Study 1); 21% vs. 10% (CLL Study 2)], thrombocytopenia [19% vs. 8% (CLL Study 2)], pancytopenia [7% vs. 2% (CLL Study 1); 7% vs. 2% (CLL Study 2)] and infections [30% vs. 14% (CLL Study 2)].

Rheumatoid Arthritis

Among the 2758 patients in global RA studies completed to date, 12% were 65-75 years old and 2% were 75 years old and over. The incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older patients.
11 DESCRIPTION

Rituximab-abbs is genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab-abbs has an approximate molecular weight of 145 kD.

TRUXIMA (rituximab-abbs) injection is a sterile, clear to opalescent, colorless to pale yellow, preservative-free solution for intravenous infusion. TRUXIMA is supplied at a concentration of 10 mg/ml in a 10 ml vial. Each ml of solution contains 10 mg of rituximab-abbs, polysorbate 80 (0.7 mg), sodium chloride (9 mg), tri-sodium citrate dihydrate (7.35 mg), and Water for Injection, USP. The pH is 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rituximab-abbs is a monoclonal antibody. Rituximab products target the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab products mediate B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic syndromes. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

12.2 Pharmacodynamics

Non-Hodgkin's Lymphoma (NHL)

In NHL patients, administration of rituximab resulted in depletion of circulating and tissue-based B cells. Among 166 patients in NHL Study 1 (NCT00168740), circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment.

In a multicenter, single-arm study of 37 patients with relapsed or refractory, low-grade or follicular, B-cell NHL who received 375 mg/m2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone. Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive B-cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

In GPA and MPA patients in GPA/MPA Study 1, peripheral blood CD19 B-cells depleted to less than 10 cells/μl following the first two infusions of rituximab, and remained at that level in most (84%) patients through Month 6. By Month 12, the majority of patients (81%) still showed signs of B-cell return with counts >10 cells/μl. By Month 18, most patients (87%) had counts >10 cells/μl.

In GPA/MPA Study 2 where patients received non-U.S.-licensed rituximab as two 500 mg intravenous infusions separated by two weeks, followed by a 500 mg intravenous infusion at Month 6, 12, and 18, 70% (30 out of 43) of the rituximab-treated patients with peripheral B cells evaluated post-baseline had undetectable CD19+ peripheral B cells at Month 24. At Month 24, all 37 patients with evaluable baseline CD19+ peripheral B cells and Month 24 measurements had lower CD19+ B cells relative to baseline.

12.3 Pharmacokinetics

Non-Hodgkin’s Lymphoma (NHL)

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m2 rituximab weekly by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 500 mg/m2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive B-cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis

Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days).

Rheumatoid Arthritis

Following administration of 2 doses of rituximab in patients with RA, the mean (± S.D.; % CV) concentrations after the first infusion (Cmax first) and second infusion (Cmax second) were 157 (± 46; 29%) and 183 (± 55; 30%) mcg/mL and 318 (± 86; 27%) and 381 (± 98; 26%) mcg/mL for the 2 x 500 mg and 2 x 1000 mg doses, respectively.

Based on a population pharmacokinetic analysis of data from 2005 RA patients who received rituximab, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days). Age, weight and gender had no effect on the pharmacokinetics of rituximab in RA patients.

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

The PK parameters in adult patients with GPA/MPA receiving 375 mg/m2 intravenous rituximab once weekly for four doses are summarized in Table 4.

Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Statistic</th>
<th>Adult GPA/MPA (GPA/MPA Study 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Number of Patients</td>
<td>97</td>
</tr>
<tr>
<td>Terminal Half-life (days)</td>
<td>Median</td>
<td>25 (11 to 52)</td>
</tr>
<tr>
<td>AUC_{1000} (mcg/mL*day)</td>
<td>Median</td>
<td>2702 (3653 to 21874)</td>
</tr>
<tr>
<td>Clearance (L/day)</td>
<td>Median</td>
<td>0.279 (0.113 to 0.663)</td>
</tr>
<tr>
<td>Volume of Distribution (L)</td>
<td>Median</td>
<td>3.12 (2.42 to 3.91)</td>
</tr>
</tbody>
</table>

The population PK analysis in adults with GPA and MPA showed that male patients and patients with higher BSA or positive anti-rituximab antibody levels have higher clearance. However, further dose adjustment based on gender or anti-drug antibody status is not necessary.

Specific Populations

The pharmacokinetics of rituximab products have not been studied in children and adolescents with NHL, CLL, or RA. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab products.

Drug Interactions

Formal drug interaction studies have not been performed with rituximab products.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of rituximab products or to determine potential effects on fertility in males or females.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of rituximab in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

NHL Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory, low-grade or follicular, B-cell NHL who received 375 mg/m2 of rituximab given as an intravenous infusion weekly for 4 doses. Patients with tumor masses >10 cm or with >5000 lymphocytes/μL in the peripheral blood were excluded from the study.

Results are summarized in Table 5. The median time to onset of response was 50 days. Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

NHL Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m2 of rituximab weekly for 8 doses. Results are summarized in Table 5.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

**NHL Study 2**
In a multicenter, single-arm study, 60 patients received 375 mg/m² of rituximab weekly for 4 doses. All patients had relapsed or refractory, low-grade or follicular, B-cell NHL and had achieved an objective clinical response to rituximab administered 3.8–35.6 months (median 14.5 months) prior to retreatment with rituximab. Of these 60 patients, 5 received more than one additional course of rituximab. Results are summarized in Table 5.

**Bulky Disease**
In pooled data from studies 1 and 3, 39 patients with bulky (single lesion >10 cm in diameter) and relapsed or refractory, low-grade NHL received rituximab 375 mg/m² weekly for 4 doses. Results are summarized in Table 5.

### Table 5
Summary of Rituximab Efficacy Data in NHL by Schedule and Clinical Setting

<table>
<thead>
<tr>
<th>NHL Study</th>
<th>Number of Patients</th>
<th>Weekly × 4</th>
<th>Weekly × 8</th>
<th>Weekly × 4 and Weekly × 8</th>
<th>Retreatment, Weekly × 4</th>
<th>N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response Rate</td>
<td>48%</td>
<td>57%</td>
<td>36%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>6%</td>
<td>14%</td>
<td>3%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Duration of Response (Mo)</td>
<td>11.2</td>
<td>13.4</td>
<td>6.9</td>
<td>15.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Resistant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response Rate</td>
<td>6%</td>
<td>14%</td>
<td>3%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Duration of Response (Mo)</td>
<td>1.9 to 42.1</td>
<td>2.5 to 36.5</td>
<td>2.8 to 25.0</td>
<td>3.0 to 25.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Six of these patients are included in the first column. Thus, data from 296 intent-to-treat patients are presented in this table.

† Kaplan-Meier projected with observed range.

### 14.2 Previously Untreated, Low-Grade or Follicular, CD20-positive, B-Cell NHL

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

**NHL Study 4**
A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with rituximab 375 mg/m² on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome measure of the study was progression-free survival (PFS) defined as the time from randomization to the first of progression, relapse, or death. Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 6. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

### Table 6
Efficacy Results in NHL Study 4

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>R-CVP</th>
<th>CVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=162</td>
<td>N=160</td>
<td></td>
</tr>
<tr>
<td>Median PFS (years)</td>
<td>2.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.44 (0.29, 0.65)</td>
<td></td>
</tr>
</tbody>
</table>

*p <0.0001, two-sided stratified log-rank test.

† Estimates of Cox regression stratified by center.

### NHL Study 5

An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to rituximab in combination with chemotherapy. Patients were randomized to rituximab as single-agent maintenance therapy, 375 mg/m² every 8 weeks for up to 12 doses or to observation. Rituximab was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization to the event of progression, relapse, or death, as determined by independent review. Of the randomized patients, 40% were ≥60 years of age, 70% had Stage IV disease, 96% had ECOG performance status (PS) 0–1, and 42% had FLIPI scores of 3–5. Prior to randomization to maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response and 28% had a partial response.

### NHL Study 7

A total of 632 patients age ≥60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOEP or R-CHOP. Patients received 6 or 8 cycles of CHOEP each cycle lasting 21 days. All patients in the CHOEP arm received 4 doses of rituximab 375 mg/m² on Days –7 and –3 (prior to Cycle 1) and 48–72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOEP also received rituximab prior to Cycle 7. The main outcome measure of the study was progression-free survival, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive rituximab or no further therapy. Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores ≥2, 86% had ECOG performance status of ≤2, 57% had elevated LDH levels, and 36% had or two or more extranodal sites involved. Efficacy results are presented in Table 7. These results reflect a statistical approach which allows for an evaluation of rituximab administered in the induction setting that excludes any potential impact of rituximab given after the second randomization.

### 14.3 Diffuse Large B-Cell NHL (DLBCL)

The safety and effectiveness of rituximab were evaluated in three randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1,854 patients. Patients with previously untreated diffuse large B-cell NHL received rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

**NHL Study 7**
A total of 399 patients with DLBCL, age ≥60 years, were randomized in a 1:1 ratio to receive CHOEP or R-CHOP. All patients received up to eight 3-week cycles of CHOEP induction; patients in the R-CHOP arm received rituximab 375 mg/m² on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease. 60% of patients had an age-adjusted IPI ≥2, 80% had ECOG performance status scores <2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 7.

### NHL Study 8

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with rituximab. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≥1, 99% had ECOG performance status of ≤2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement. Efficacy results are presented in Table 7.
Across both studies, 243 of 676 rituximab-treated patients (36%) were 65 years of age or older and 100 rituximab-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in elderly patients are presented in Table 9.

### Table 7: Efficacy Results in NHL Studies 7, 8, and 9

<table>
<thead>
<tr>
<th>NHL Study 7</th>
<th>NHL Study 8</th>
<th>NHL Study 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=632)</td>
<td>(n=399)</td>
<td>(n=823)</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>R-CHOP</td>
<td>R-Chemo</td>
</tr>
<tr>
<td>CHOP</td>
<td>CHOP</td>
<td>Chemo</td>
</tr>
<tr>
<td><strong>Main outcome measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression-free survival (years)</strong></td>
<td>3.1 (0.3, 4.3)</td>
<td>3.2 (0.3, 4.3)</td>
</tr>
<tr>
<td><strong>Event-free survival (years)</strong></td>
<td>1.6 (0.9, 2.4)</td>
<td>1.6 (0.9, 2.4)</td>
</tr>
<tr>
<td><strong>Time to death (years)</strong></td>
<td>2.9 (1.8, 4.0)</td>
<td>2.9 (1.8, 4.0)</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
<td>0.69*</td>
<td>0.60*</td>
</tr>
<tr>
<td><strong>Overall survival at 2 years</strong></td>
<td>74% (63%), 58% (86%)</td>
<td>69% (58%), 85% (95%)</td>
</tr>
<tr>
<td><strong>Hazard ratio</strong></td>
<td>0.72*</td>
<td>0.68*</td>
</tr>
</tbody>
</table>

* Significant at p<0.05, 2-sided.
† Kaplan-Meier estimates.
‡ R-CHOP vs. CHOP.

In NHL Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

### 14.4 Ninety-Minute Infusions in Previously Untreated Follicular NHL and DLBCL

In NHL Study 10, a total of 363 patients with previously untreated follicular NHL (n=113) or DLBCL (n=250) were evaluated in a prospective, open-label, multicenter, single-arm trial for the safety of 90-minute rituximab infusions. Patients with follicular NHL received rituximab 375 mg/m² plus CHOP chemotherapy. Patients with DLBCL received rituximab 375 mg/m² plus CHOP chemotherapy. Patients with clinically significant cardiovascular disease were excluded from the study. Patients were eligible for a 90-minute infusion at Cycle 2 if they did not experience a Grade 3-4 infusion-related adverse event with Cycle 1 and had a circulating lymphocyte count <5000/µL before Cycle 2. All patients were pre-medicated with acetaminophen and an antihistamine and received the glucocorticoid component of their chemotherapy prior to rituximab infusion. The main outcome measure was the development of Grade 3-4 infusion-related reactions on the day of, or day after, the 90-minute infusion at Cycle 2 (see Adverse Reactions (6.1)).

Eligible patients received their Cycle 2 rituximab infusion over 90 minutes as follows: 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes (see Dosage and Administration (2.1)).

### Table 8: Efficacy Results in CLL Studies 1 and 2

<table>
<thead>
<tr>
<th>CLL Study 1*</th>
<th>CLL Study 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Previously untreated)</td>
<td>(Previously treated)</td>
</tr>
<tr>
<td>R-FC</td>
<td>n = 408</td>
</tr>
<tr>
<td>FC</td>
<td>39.8</td>
</tr>
<tr>
<td><strong>Median PFS (months)</strong></td>
<td>21.7</td>
</tr>
<tr>
<td><strong>Hazard ratio (95% CI)</strong></td>
<td>0.56 (0.43, 0.71)</td>
</tr>
<tr>
<td><strong>P value (Log-Rank test)</strong></td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Response rate (95% CI)</strong></td>
<td>86% (62%, 91%)</td>
</tr>
</tbody>
</table>

* As defined in 1996 National Cancer Institute Working Group guidelines.

### Table 9: Efficacy Results in CLL Studies 1 and 2 Subgroups Defined by Age*

<table>
<thead>
<tr>
<th>CLL Study 1</th>
<th>CLL Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>Hazard Ratio for PFS (95% CI)</td>
</tr>
<tr>
<td>(n=409)</td>
<td>(n=408)</td>
</tr>
<tr>
<td>Age &lt; 65 yrs</td>
<td>572</td>
</tr>
<tr>
<td>Age 65 yrs</td>
<td>245</td>
</tr>
<tr>
<td>Age &gt; 70 yrs</td>
<td>736</td>
</tr>
</tbody>
</table>

* From exploratory analyses.

### 14.6 Rheumatoid Arthritis (RA)

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

The efficacy and safety of rituximab were evaluated in two randomized, double-blind, placebo-controlled studies of adult patients with moderately to severely active RA who had a prior inadequate response to at least one TNF inhibitor. Patients were 18 years of age or older, diagnosed with active RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints.

In RA Study 1 (NCT00480612), patients were randomized to receive either rituximab 2 x 1000 mg + MTX or placebo + MTX for 24 weeks. Further courses of rituximab 2 x 1000 mg + MTX were administered in an open label extension study at a frequency determined by clinical evaluation, but no sooner than 16 weeks after the preceding course of rituximab. In addition to the intravenous premedication, glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the placebo-controlled period are shown in Table 10.

In RA Study 2 (NCT00266227), all patients received the first course of rituximab 2 x 1000 mg + MTX. Patients who experienced ongoing disease activity were randomized to receive a second course of either rituximab 2 x 1000 mg + MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at Week 48, after treatment, are shown in Table 10.

### Table 10: ACR Responses in RA Study 1 and RA Study 2 (Percent of Patients)

<table>
<thead>
<tr>
<th>RA Study 1 24 Week Placebo-Controlled (Week 24)</th>
<th>RA Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Rituximab</td>
<td>Placebo</td>
</tr>
<tr>
<td>MTX</td>
<td>MTX</td>
</tr>
<tr>
<td>Placebo-Controlled (Week 24)</td>
<td>Placebo-Controlled Retreatment (Week 24 and Week 48)</td>
</tr>
<tr>
<td>Placebo + Rituximab</td>
<td>n = 201</td>
</tr>
<tr>
<td>Placebo</td>
<td>n = 192</td>
</tr>
<tr>
<td><strong>ACR20</strong></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>18%</td>
</tr>
<tr>
<td>Week 24</td>
<td>45%</td>
</tr>
<tr>
<td>Week 24</td>
<td>26%</td>
</tr>
</tbody>
</table>

* In RA Study 2, all patients received a first course of rituximab 2 x 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either rituximab 2 x 1000 mg + MTX or placebo + MTX at or after Week 24.

† Since all patients received a first course of rituximab, no comparison between Placebo + MTX and rituximab + MTX is made at Week 24.
‡ For RA Study 1, weighted difference stratified by region (US, rest of the world) and rheumatoid factor (RF) status (positive ≥20 IU/mL, negative <20 IU/mL) at baseline; For RA Study 2, weighted difference stratified by RF status at baseline and ≥20% improvement from baseline in both SJC and TJC at Week 24 (Yes/No).

Improvement was also noted for all components of ACR response following treatment with rituximab, as shown in Table 11.

### Table 11: Inadequate Response to TNF Antagonists

<table>
<thead>
<tr>
<th>RA Study 24 Week Placebo-Controlled (Week 24)</th>
<th>RA Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo + Rituximab</td>
<td>Placebo</td>
</tr>
<tr>
<td>MTX</td>
<td>MTX</td>
</tr>
<tr>
<td>Placebo-Controlled (Week 24)</td>
<td>Placebo-Controlled Retreatment (Week 24 and Week 48)</td>
</tr>
<tr>
<td>Placebo + Rituximab</td>
<td>n = 201</td>
</tr>
<tr>
<td>Placebo</td>
<td>n = 192</td>
</tr>
<tr>
<td><strong>ACR20</strong></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>18%</td>
</tr>
<tr>
<td>Week 24</td>
<td>45%</td>
</tr>
<tr>
<td>Week 24</td>
<td>26%</td>
</tr>
</tbody>
</table>

* In RA Study 2, all patients received a first course of rituximab 2 x 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either rituximab 2 x 1000 mg + MTX or placebo + MTX at or after Week 24.

† Since all patients received a first course of rituximab, no comparison between Placebo + MTX and rituximab + MTX is made at Week 24.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

Following 2 years of treatment with rituximab + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of rituximab + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with rituximab + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the rituximab + MTX treated patients who had no progression in the first year also had no progression in the second year.

Lesser Efficacy of 500 Vs. 1000 mg Treatment Courses for Radiographic Outcomes RA Study 3 (NCT00299104) is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX compared to rituximab 2 x 500 mg + MTX and rituximab 2 x 1000 mg + MTX treatment courses in MTX-naive RA patients with moderately to severely active disease. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by Week 8 in all three treatment arms. After a minimum of 24 weeks, patients with ongoing disease activity were eligible to receive retreatment with rituximab + MTX from Week 16 onward.

In RA Study 1 and its open-label extension, 70% of patients initially randomized to rituximab + MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As shown in Table 12, progression of structural damage in rituximab + MTX patients was further reduced in the second year of treatment.

Table 11

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo + MTX (n = 201)</th>
<th>Rituximab + MTX (n = 298)</th>
<th>Placebo + MTX (Baseline)</th>
<th>Rituximab + MTX (Baseline)</th>
<th>Placebo + MTX (Wk 24)</th>
<th>Rituximab + MTX (Wk 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Joint Count</td>
<td>31.0</td>
<td>27.0</td>
<td>33.0</td>
<td>13.0</td>
<td>31.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
<td>20.0</td>
<td>19.0</td>
<td>21.0</td>
<td>9.5</td>
<td>20.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Physician Global Assessment*</td>
<td>71.0</td>
<td>69.0</td>
<td>71.0</td>
<td>36.0</td>
<td>71.0</td>
<td>69.0</td>
</tr>
<tr>
<td>Patient Global Assessment*</td>
<td>73.0</td>
<td>68.0</td>
<td>71.0</td>
<td>41.0</td>
<td>73.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Pain*</td>
<td>39.0</td>
<td>38.0</td>
<td>70.0</td>
<td>38.5</td>
<td>39.0</td>
<td>38.0</td>
</tr>
<tr>
<td>Disability Index (HAQ)‡</td>
<td>2.0</td>
<td>1.9</td>
<td>1.9</td>
<td>1.5</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.4</td>
<td>2.5</td>
<td>2.6</td>
<td>0.9</td>
<td>2.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Visual Analogue Scale: 0 = best, 100 = worst.
‡ Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.

Table 12

Inadequate Response to TNF Antagonists

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo + MTX (n = 201)</th>
<th>Rituximab + MTX (n = 298)</th>
<th>Placebo + MTX (Baseline)</th>
<th>Rituximab + MTX (Baseline)</th>
<th>Placebo + MTX (Wk 24)</th>
<th>Rituximab + MTX (Wk 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change during</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSS</td>
<td>0.66</td>
<td>1.77</td>
<td>1.11</td>
<td>(0.47, 1.75)</td>
<td>0.66</td>
<td>1.77</td>
</tr>
<tr>
<td>ES</td>
<td>0.44</td>
<td>1.19</td>
<td>0.75</td>
<td>(0.32, 1.19)</td>
<td>0.44</td>
<td>1.19</td>
</tr>
<tr>
<td>JSN Score</td>
<td>0.22</td>
<td>0.58</td>
<td>0.36</td>
<td>(0.10, 0.62)</td>
<td>0.22</td>
<td>0.58</td>
</tr>
<tr>
<td>Second Year*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSS</td>
<td>0.48</td>
<td>1.04</td>
<td>-</td>
<td>-</td>
<td>0.48</td>
<td>1.04</td>
</tr>
<tr>
<td>ES</td>
<td>0.28</td>
<td>0.62</td>
<td>-</td>
<td>-</td>
<td>0.28</td>
<td>0.62</td>
</tr>
<tr>
<td>JSN Score</td>
<td>0.20</td>
<td>0.42</td>
<td>-</td>
<td>-</td>
<td>0.20</td>
<td>0.42</td>
</tr>
</tbody>
</table>

* Based on radiographic scoring following 104 weeks of observation.

The same patients may not have responded at each time point.

Radiographic Response

In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. Rituximab + MTX slowed the progression of structural damage compared to placebo + MTX after 1 year as shown in Table 12.

Table 13

Improvement from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 24 in RA Study 4

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo + MTX</th>
<th>Rituximab 2 x 1000 mg + MTX</th>
<th>Placebo + MTX n = 172</th>
<th>Rituximab 2 x 1000 mg + MTX n = 170</th>
<th>Placebo + MTX (Baseline)</th>
<th>Rituximab 2 x 1000 mg + MTX (Baseline)</th>
<th>Placebo + MTX (Wk 24)</th>
<th>Rituximab 2 x 1000 mg + MTX (Wk 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Improvement from Baseline</td>
<td>0.19</td>
<td>0.42</td>
<td>0.23</td>
<td>(0.11, 0.34)</td>
<td>0.19</td>
<td>0.42</td>
<td>0.23</td>
<td>(0.11, 0.34)</td>
</tr>
<tr>
<td>Percent of patients with “Improved” score</td>
<td>48%</td>
<td>58%</td>
<td>11% (0%, 21%)</td>
<td></td>
<td>48%</td>
<td>58%</td>
<td>11% (0%, 21%)</td>
<td></td>
</tr>
</tbody>
</table>

* Minimal Clinically Important Difference: MCID for HAQ = 0.22.
† Adjusted difference stratified by region (US, rest of the world) and rheumatoid factor (RF) status (positive ≥20 IU/mL, negative < 20 IU/mL) at baseline.

14.7 Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

Induction Treatment of Adult Patients with Active Disease (GPA/MPA Study 1) A total of 197 adult patients with active, severe GPA and MPA (two forms of ANCA Associated Vasculitides) were treated in a randomized, double-blind, active-controlled, multicenter, non-inferiority study, conducted in two phases—a 6 month remission induction phase and a 12 month remission maintenance phase. Patients were 15 years of age or older, diagnosed with GPA (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a Birmingham Vasculitis Activity Score for Granulomatosis with Polyangiitis (BVAS/GPA) ≥3, and their disease was severe, with at least one major item on the BVAS/GPA. Ninety-six (49%) of patients had new disease and 101 (51%) of patients had relapsing disease. Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive either rituximab 375 mg/m² once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg/day for 3 to 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and acetaminophen prior to rituximab infusion. Following intravenous corticosteroid administration, all patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The rituximab group did not receive additional therapy to maintain remission. The main outcome measure for both GPA and MPA patients was achievement of complete remission at 6 months defined as a BVAS/GPA of 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. As shown in Table 14, the study demonstrated non-inferiority of rituximab to cyclophosphamide for complete remission at 6 months.

Table 14

Inadequate Response to TNF Antagonists

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rituximab 2 x 1000 mg + MTX</th>
<th>Placebo + MTX</th>
<th>Treatment Difference</th>
<th>Placebo - Rituximab</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change during</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSS</td>
<td>0.50</td>
<td>0.63</td>
<td>-0.13</td>
<td>(0.34, 0.05)</td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>0.28</td>
<td>0.42</td>
<td>-0.14</td>
<td>(0.26, 0.00)</td>
<td></td>
</tr>
<tr>
<td>JSN Score</td>
<td>0.42</td>
<td>0.52</td>
<td>-0.10</td>
<td>(0.16, 0.04)</td>
<td></td>
</tr>
<tr>
<td>Change during</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSS</td>
<td>0.43</td>
<td>0.57</td>
<td>-0.14</td>
<td>(0.22, 0.05)</td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>0.29</td>
<td>0.47</td>
<td>-0.18</td>
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<tr>
<td>JSN Score</td>
<td>0.50</td>
<td>0.61</td>
<td>-0.11</td>
<td>(0.17, 0.06)</td>
<td></td>
</tr>
</tbody>
</table>

* Based on radiographic scoring following 104 weeks of observation.
† Patients received up to 2 years of treatment with rituximab + MTX.
‡ Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with rituximab + MTX from Week 16 onward.
The observed cumulative incidence rate of first major relapse during the 28 months was 3 patients (5%) in the non-U.S.-licensed rituximab group and 17 patients (29%) in the azathioprine group. By month 28, major relapse occurred in 3 patients (5%) in the non-U.S.-licensed rituximab group and 21 patients (36%) in the azathioprine group.

Table 14

Complete Remission at 6 Months (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Rituximab (n = 99)</th>
<th>Cyclophosphamide (n = 98)</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>64%</td>
<td>53%</td>
</tr>
<tr>
<td>95.1% CI (54%, 73%)</td>
<td>(43%, 63%)</td>
<td></td>
</tr>
<tr>
<td>(Rituximab – Cyclophosphamide)</td>
<td>(-3%, 24%)</td>
<td></td>
</tr>
</tbody>
</table>

* non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (-3% > -20%).

† The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Complete Remission (CR) at 12 and 18 months

In the rituximab group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment of Flares with Rituximab

Based upon investigator judgment, 15 patients received a second course of rituximab therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the induction treatment course of rituximab.

Follow Up Treatment of Adult Patients with GPA/MPA who have achieved disease control with other Immunosuppressant (GPA/MPA Study 2)

A total of 115 patients (86 with GPA, 24 with MPA, and 5 with renal-limited ANCA-associated vasculitis) in disease remission were randomized to receive azathioprine (56 patients) or non-U.S.-licensed rituximab (57 patients) in this open-label, prospective, multi-center, randomized, active-controlled study. Eligible patients were 21 years and older and had either newly diagnosed (80%) or relapsing disease (20%). A majority of the patients were ANCA-positive. Remission of active disease was achieved using a combination of glucocorticoids and cyclophosphamide. Within a maximum of 1 month after the last cyclophosphamide dose, eligible patients (based on BVAS of 0), were randomized in a 1:1 ratio to receive either non-U.S.-licensed rituximab or azathioprine.

The non-U.S.-licensed rituximab was administered as two 500 mg intravenous infusions separated by two weeks (on Day 1 and Day 15) followed by a 500 mg intravenous infusion every 6 months for 18 months. Azathioprine was administered orally at a dose of 2 mg/kg/day for 12 months, then 1.5 mg/kg/day for 6 months, and finally 1 mg/kg/day for 4 months; treatment was discontinued after 22 months. Prednisone treatment was tapered and then kept at a low dose (approximately 5 mg per day) for at least 12 months after randomization. Prednisone dose tapering and the decision to stop prednisone treatment after month 18 were left at the investigator’s discretion.

Planned follow-up was until month 28 (10 or 6 months, respectively, after the last non-U.S.-licensed rituximab infusion or azathioprine dose). The primary endpoint was the occurrence of major relapse (defined by the reappearance of clinical and/or laboratory signs of vasculitis activity that could lead to organ failure or damage, or could be life threatening) through month 28.

By month 28, major relapse occurred in 3 patients (5%) in the non-U.S.-licensed rituximab group and 17 patients (29%) in the azathioprine group.

The observed cumulative incidence rate of first major relapse during the 28 months was lower in patients on non-U.S.-licensed rituximab relative to azathioprine (Figure 3).

Figure 3

Cumulative Incidence Over Time of First Major Relapse in Patients with GPA/MPA

![Graph showing cumulative incidence over time of first major relapse](image)

No. of Subjects with Major Relapse

<table>
<thead>
<tr>
<th>Azathioprine</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
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No. of Subjects at Risk

<table>
<thead>
<tr>
<th>Azathioprine</th>
<th>Rituximab</th>
</tr>
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<td>34</td>
<td>34</td>
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</tbody>
</table>

16 HOW SUPPLIED/STORAGE AND HANDLING

TRUXIMA (rituximab-abbs) injection is a sterile, clear to opalescent, colorless to pale yellow, preservative-free solution for intravenous infusion supplied as a carton containing one 100 mg/10 mL (10 mg/mL) single-dose vial (NDC 63459-103-10) or a carton containing one 500 mg/50 mL (10 mg/mL) single-dose vial (NDC 63459-104-50).

Store TRUXIMA vials refrigerated at 2°C to 8°C (36°F to 46°F). TRUXIMA vials should be protected from direct sunlight. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Infusion-Related Reactions

Inform patients about the signs and symptoms of infusion-related reactions. Advise patients to contact their healthcare provider immediately to report symptoms of infusion-related reactions including urticaria, hypotension, angioedema, sudden cough, breathing problems, weakness, dizziness, palpitations, or chest pain [see Warnings and Precautions (5.1)].

Severe Mucocutaneous Reactions

Advise patients to contact their healthcare provider immediately for symptoms of severe mucocutaneous reactions, including painful sores or ulcers on the mouth, blisters, peeling skin, rash, and pustules [see Warnings and Precautions (5.2)].

Hepatitis B Virus Reactivation

Advise patients to contact their healthcare provider immediately for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes [see Warnings and Precautions (5.3)].

Progressive Multifocal Leuкоencephalopathy (PML)

Advise patients to contact their healthcare provider immediately for symptoms of PML, including new or changes in neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, or vision problems [see Warnings and Precautions (5.4)].

Tumor Lysis Syndrome (TLS)

Advise patients to contact their healthcare provider immediately for symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy [see Warnings and Precautions (5.5)].

Cardiovascular Adverse Reactions

Advise patients of the risk of cardiovascular adverse reactions, including ventricular fibrillation, myocardial infarction, and cardiogenic shock. Advise patients to contact their healthcare provider immediately to report chest pain and irregular heartbeats [see Warnings and Precautions (5.6)].

Renal Toxicity

Advise patients of the risk of renal toxicity. Inform patients of the need for healthcare providers to monitor kidney function [see Warnings and Precautions (5.7)].

Bowel Obstruction and Perforation

Advise patients to contact their healthcare provider immediately for symptoms of bowel obstruction and perforation, including severe abdominal pain or repeated vomiting [see Warnings and Precautions (5.9)].

Embryo-Fetal Toxicity

Advise a pregnant woman of the potential risk to a fetus. Advise female patients that rituximab products can cause fetal harm if taken during pregnancy and to use effective contraception during treatment with TRUXIMA and for at least 12 months after the last dose of TRUXIMA. Advise patients to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.11) and Use in Specific Populations (8.1, 8.3)].

Lactation

Advise women not to breastfeed during treatment with TRUXIMA and for 6 months after the last dose [see Use in Specific Populations (8.2)].

TRUXIMA® (rituximab-abbs) injection, for intravenous use

TRUXIMA® (rituximab-abbs) injection, for intravenous use

TRUXIMA® is a registered trademark of CELLTRION, Inc.

Manufactured by: CELLTRION, Inc
20, Academy-ro 51 beon-gil,
Yeounsu-gu, Incheon
22014, Republic of Korea
US License Number 1996
Marketed by: Teva Pharmaceuticals USA, Inc.
North Wales, PA 19454
What is the most important information I should know about TRUXIMA?

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

- **Infusion-related reactions.** Infusion-related reactions are very common side effects of TRUXIMA treatment. Serious infusion-related reactions can happen during your infusion or within 24 hours after your infusion of TRUXIMA. Your healthcare provider should give you medicines before your infusion of TRUXIMA to decrease your chance of having a severe infusion-related reaction.
  
  Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an infusion of TRUXIMA:
  - hives (red itchy welts) or rash
  - itching
  - swelling of your lips, tongue, throat or face
  - sudden cough
  - shortness of breath, difficulty breathing or wheezing
  - weakness
  - dizziness or feel faint
  - palpitations (feel like your heart is racing or fluttering
  - chest pain

- **Severe skin and mouth reactions.** Tell your healthcare provider or get medical help right away if you get any of these symptoms at any time during your treatment with TRUXIMA:
  - painful sores or ulcers on your skin, lips or in your mouth
  - blisters
  - peeling skin
  - rash
  - pustules

- **Hepatitis B virus (HBV) reactivation.** Before you receive your TRUXIMA treatment, your healthcare provider will do blood tests to check for HBV infection. If you have had hepatitis B or are a carrier of hepatitis B virus, receiving TRUXIMA could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. You should not receive TRUXIMA if you have active hepatitis B liver disease. Your healthcare provider will monitor you for hepatitis B infection during and for several months after you stop receiving TRUXIMA.
  
  Tell your healthcare provider right away if you get worsening tiredness or yellowing of your skin or white part of your eyes, during treatment with TRUXIMA.

- **Progressive Multifocal Leukoencephalopathy (PML).** PML is a rare, serious brain infection caused by a virus that can happen in people who receive TRUXIMA. People with weakened immune systems can get PML. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.
  
  Tell your healthcare provider right away if you have any new or worsening symptoms or if anyone close to you notices these symptoms:
  - confusion
  - dizziness or loss of balance
  - difficulty walking or talking
  - decreased strength or weakness on one side of your body
  - vision problems

See “What are the possible side effects of TRUXIMA?” for more information about side effects.

What is TRUXIMA?

TRUXIMA is a prescription medicine used to treat adults with:

- Adults with Non-Hodgkin's Lymphoma (NHL): alone or with other chemotherapy medicines.
- Adults with Chronic Lymphocytic Leukemia (CLL): with the chemotherapy medicines fludarabine and cyclophosphamide.
- Adults with Rheumatoid Arthritis (RA): with another prescription medicine called methotrexate, to reduce the signs and symptoms of moderate to severe active RA in adults, after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well enough.
- Adults with Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA): with glucocorticoids, to treat GPA and MPA.

TRUXIMA is not indicated for treatment of children.

Before you receive TRUXIMA, tell your healthcare provider about all of your medical conditions, including if you:

- have had a severe reaction to TRUXIMA or another rituximab product
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system.
- have or have had any severe infections including:
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
  - Parvovirus B19
  - Varicella zoster virus (chickenpox or shingles)
  - West Nile Virus
• have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or during treatment with TRUXIMA.

• are pregnant or plan to become pregnant. Talk to your healthcare provider about the risks to your unborn baby if you receive TRUXIMA during pregnancy.

Females who are able to become pregnant should use effective birth control (contraception) during treatment with TRUXIMA and for 12 months after the last dose of TRUXIMA. Talk to your healthcare provider about effective birth control.

Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with TRUXIMA.

• are breastfeeding or plan to breastfeed. It is not known if TRUXIMA passes into your breast milk. Do not breastfeed during treatment and for at least 6 months after your last dose of TRUXIMA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take or have taken:

• a Tumor Necrosis Factor (TNF) inhibitor medicine
• a Disease Modifying Anti-Rheumatic Drug (DMARD)

If you are not sure if your medicine is one listed above, ask your healthcare provider.

How will I receive TRUXIMA?

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

• Your healthcare provider may prescribe medicines before each infusion of TRUXIMA to reduce infusion side effects such as fever and chills.

• Your healthcare provider should do blood tests regularly to check for side effects to TRUXIMA.

• Before each TRUXIMA treatment, your healthcare provider or nurse will ask you questions about your general health. Tell your healthcare provider or nurse about any new symptoms.

What are the possible side effects of TRUXIMA?

TRUXIMA can cause serious side effects, including:

• See “What is the most important information I should know about TRUXIMA?”

• Tumor Lysis Syndrome (TLS). TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:
  ◦ kidney failure and the need for dialysis treatment
  ◦ abnormal heart rhythm

  TLS can happen within 12 to 24 hours after an infusion of TRUXIMA. Your healthcare provider may do blood tests to check you for TLS. Your healthcare provider may give you medicine to help prevent TLS.

  Tell your healthcare provider right away if you have any of the following signs or symptoms of TLS:
  ◦ nausea
  ◦ vomiting
  ◦ diarrhea
  ◦ lack of energy

• Serious infections. Serious infections can happen during and after treatment with TRUXIMA, and can lead to death. TRUXIMA can increase your risk of getting infections and can lower the ability of your immune system to fight infections. Types of serious infections that can happen with TRUXIMA include bacterial, fungal, and viral infections. After receiving TRUXIMA, some people have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these people with low antibody levels developed infections. People with serious infections should not receive TRUXIMA. Tell your healthcare provider right away if you have any symptoms of infection:
  ◦ fever
  ◦ cold symptoms, such as runny nose or sore throat that do not go away
  ◦ flu symptoms, such as cough, tiredness, and body aches
  ◦ earache or headache
  ◦ pain during urination
  ◦ cold sores in the mouth or throat
  ◦ cuts, scrapes or incisions that are red, warm, swollen or painful

• Heart problems. TRUXIMA may cause chest pain, irregular heartbeats, and heart attack. Your healthcare provider may monitor your heart during and after treatment with TRUXIMA if you have symptoms of heart problems or have a history of heart problems. Tell your healthcare provider right away if you have chest pain or irregular heartbeats during treatment with TRUXIMA.

• Kidney problems, especially if you are receiving TRUXIMA for NHL. TRUXIMA can cause severe kidney problems that lead to death. Your healthcare provider should do blood tests to check how well your kidneys are working.

• Stomach and serious bowel problems that can sometimes lead to death. Bowel problems, including blockage or tears in the bowel can happen if you receive TRUXIMA with chemotherapy medicines. Tell your healthcare provider right away if you have any severe stomach-area (abdomen) pain or repeated vomiting during treatment with TRUXIMA.

Your healthcare provider will stop treatment with TRUXIMA if you have severe, serious or life-threatening side effects.

The most common side effects of TRUXIMA include:

◦ infusion-related reactions (see “What is the most important information I should know about TRUXIMA?”)
◦ infections (may include fever, chills)
◦ body aches
◦ tiredness
◦ nausea

In adult patients with GPA or MPA the most common side effects of TRUXIMA also include:

◦ low white and red blood cells
◦ swelling
◦ diarrhea
◦ muscle spasms

continued
Other side effects with TRUXIMA include:
  ◦ aching joints during or within hours of receiving an infusion
  ◦ more frequent upper respiratory tract infection
These are not all of the possible side effects with TRUXIMA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of TRUXIMA.**
Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about TRUXIMA that is written for healthcare professionals.

**What are the ingredients in TRUXIMA?**
**Active ingredient:** rituximab-abbs
**Inactive ingredients:** polysorbate 80, sodium chloride, tri-sodium citrate dihydrate, and Water for Injection, USP.

Manufactured by: CELLTRION, Inc. 20, Academy-ro 51 beon-gil, Yeonsu-gu, Incheon, 22014 Republic of Korea
U.S. License Number 1996
Marketed by: Teva Pharmaceuticals USA, Inc, North Wales, PA 19454
For more information, go to www.TRUXIMA.com or call 1-888-483-8279.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 12/2019

teva

RIX-40199