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

Indications and Usage (1.1, 1.2, 1.3, 1.4) 12/2019

• 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 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, 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 rituximab and 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) with or without microscopic polyangiitis (MPA) in adult patients with GPA and MPA who have achieved disease control with induction treatment, in combination with glucocorticoids (1.4).

Dosage and Administration (2.2.1) 12/2019

• Administer only as an intravenous infusion (2.2.1).
• Do not administer as an intravenous push or bolus (2.2.1).

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 (2.2.1).

• The dose for NHL is 375 mg/m² once weekly for 4 weeks. The follow up dose for adult patients with NHL who have achieved disease control with induction treatment, in combination with glucocorticoids is 375 mg/m² once weekly for 4 weeks (2.3).

• The dose for CLL is 250 mg/m² (2.4).

Contraindications None (4)

Warnings and Precautions (5.10, 5.12, 5.13) 12/2019

• 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 case 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).

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

• Lactation: Advise not to breastfeed (5.2).

Use in Specific Populations

• Lactation: Advise not to breastfeed (8.2).

Revised: 05/2020

Full Prescribing Information: Contents*

Warning: Fatal Infusion-Related Reactions, Severe Mucocutaneous Reactions, Hepatitis B Virus Reactivation and Progressive Multifocal Leukoencephalopathy (PML)

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SEE 17 FOR PATIENT COUNSELING INFORMATION and Medication Guide.

Bioimilar 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 for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

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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), including fatal PML, can occur in patients receiving rituximab products [see Warnings and Precautions (5.4) and Adverse Reactions (6.1)].

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, and 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 Infusion [see Dosage and Administration (2.8)].

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

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.
• Treatment 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.

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.

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 course. During treatment with TRUXIMA in combination with chemotherapy, 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.
• First Infusion: Initiate infusion 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 infusion 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 treatment (through Cycle 6 or 8). 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.

2.6 Administration:
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)].

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*Sections or subsections omitted from the full prescribing information are not listed.*
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: administer 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 for Pneumocystis jirovecii pneumonia (PCP) and herpetic infections for patients with CLL during treatment and for up to 12 months following treatment as appropriate [see Warnings and Precautions (5.6)].

PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months following the last TRUXIMA infusion.

2.8 Administration and Storage

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. TRUXIMA should be a clear to opalescent, colorless to pale yellow solution. Do not use vial if particulates or discoloration is present.

**Administration**

Withdraw the necessary amount of TRUXIMA and dilute to a final concentration of 1 mg/mL to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

**Storage**

Diluted TRUXIMA solutions for infusion may be stored at 2°C to 8°C (36°F to 46°F) for 24 hours. Diluted TRUXIMA solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since TRUXIMA solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C to 8°C). No incompatibilities between TRUXIMA and polyvinylchloride or polyethylene bags have been observed.

3 DOSAGE FORMS AND STRENGTHS

**Injection:** TRUXIMA is a clear to opalescent, colorless to pale yellow solution for intravenous infusion.

- 100 mg/10 mL (10 mg/mL) in a single-dose vial
- 500 mg/50 mL (10 mg/mL) in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

Rituximab products can cause severe, including fatal, infusion-related reactions. Severe reactions typically occur during the first infusion with time to onset of 1 to 120 minutes. Rituximab product-induced infusion-related reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with acetaminophen and acetaminophen prior to dosing. For RA, GPA and MPA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion-related reactions as needed. Depending on the severity of the infusion-related reaction and the required interventions, the clinician may consider permanently discontinue TRUXIMA. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (>25,000/mm³) [see Warnings and Precautions (5.7)].

5.2 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab products. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable during clinical trials. The combination of cisplatin and TRUXIMA is not approved for use in patients with severe, active infections.

5.3 Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation has occurred in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab products. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increased 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 B infection, then anti-HBc positive and HBsAg negative but anti-HBc positive, consult with physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy before and/or during TRUXIMA treatment.

5.4 Progressive Multifocal Leuкоencephalopathy (PML)

JC virus infection resulting in PML and death can occur in rituximab product-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent 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 or neuropathologist. Discontinue TRUXIMA and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.5 Tumor Lysis Syndrome (TLS)

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia may occur within 1-24 hours of the first infusion of rituximab products in patients with NHL. A high number of circulating malignant cells (>25,000/mm³) or high tumor burden, confers a greater risk of TLS.

Acute aggressive intravenous hydration and anti-hyperemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated [see Warnings and Precautions (5.8)].

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 (6.1, 6.2)]. 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 TRUXIMA 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 arrhythmia or angina [see Adverse Reactions (6.1)].

5.8 Renal Toxicity

Renal toxicity, 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 discontinuation of TRUXIMA is recommended in patients with a rising serum creatinine or oliguria [see Warnings and Precautions (5.5)].

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.
In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range: 1–77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

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 before or during treatment.

For patients treated with TRUXIMA, physicians should review the patient’s vaccination status and patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating TRUXIMA and administer non live vaccines at least 4 weeks prior to a course of TRUXIMA. The effect of rituximab on immune responses was assessed in a randomized, controlled study in patients with RA treated with rituximab and methotrexate (MTX) compared to patients treated with MTX alone.

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 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.

11 Embryo-Fetal Toxicity
Based on animal data, rituximab products can cause fetal harm due to B-cell lymphoproliferative disease and lymphoma. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving TRUXIMA and for at least 12 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

12 Concomitant Use with Other Biologic Agents and DMARDS other than Methotrexate (MTX), GPA and MPA
Limited data are 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. The potential impact of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA patients exhibiting peripheral B-cell depletion following treatment with rituximab products.

13 Use in RA Patients Who Have Not Had Prior Inadequate Response to TNF-blocking Antagonists (TNF Ab)
While the efficacy of rituximab was supported in four controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDS, and in a controlled trial in MTX-naive patients, a favorable risk-benefit relationship has not been established in these populations. The use of TRUXIMA in patients with RA who have not had prior inadequate responses to one or more TNF antagonists is not recommended [see Clinical Studies (14.6)].

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 Trials Experience 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=356 and n=2427). 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 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received rituximab 375 mg/m² as an initial 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 clinical trials of patients with NHL were: infusion-related reactions and neutropenia.

6.1.1 Infusion-related Reactions
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, diaphoresis, or hypertension occurred during the first rituximab infusion and resolved within 30 to 120 minutes of beginning the first infusion and resolved with slow 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%, 2.8%]). For Cycles 2-6, the incidence of Grade 3-4 infusion-related reactions on the day of, or day after the infusion was 2.4% (95% CI [1.3%, 5.0%]) [see Warnings and Precautions (5.1), Clinical Studies (14.4)].

6.1.2 Infections
Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%) [see Warnings and Precautions (5.6)].

In randomized, controlled studies where rituximab was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection in clinical trials of patients who received rituximab. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received rituximab.

6.1.3 Cytopenias and Hypogammaglobulinemia
In patients with NHL receiving rituximab monotherapy, NCI-CTCAE Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (7%), thrombocytopenia (6%), and anemia (4%). The median duration of lymphopenia was 14 days (range, 1−588 days) and of neutropenia was 13 days (range, 2−116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy occurred during the single-arm studies.

In studies of monotherapy, rituximab-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients. In CLL trials, the frequency of prolonged neutropenia and late-onset neutropenia was higher in patients treated with R-FC compared to patients treated with FC. Prolonged neutropenia was defined as neutropenia that has not resolved between 24 and 42 days after the last dose of study treatment. Late-onset neutropenia is defined as Grade 3-4 neutropenia starting at least 42 days after the last treatment dose. In patients with previously untreated CLL, the frequency of prolonged neutropenia was 24% in patients treated with rituximab plus methotrexate (MTX), and decreased with each subsequent cycle.

6.1.4 Hypogammaglobulinemia
Prolonged neutropenia occurred in 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients. In patients with previously untreated CLL, the frequency of prolonged neutropenia was 14.8% of 209 patients who received R-FC and 4.3% of 230 patients who received FC. For patients with previously treated CLL, the frequency of prolonged neutropenia was 24% in patients treated with R-FC (n=274) and 19.1% for patients who received FC (n=389). In patients who did not have prolonged neutropenia, the frequency of late-onset neutropenia was 14.8% of 209 patients who received R-FC and 4.3% of 230 patients who received FC.

6.2 Incidence of Adverse Reactions in ≥5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituximab (N=356)²

<table>
<thead>
<tr>
<th>All Grades (%)</th>
<th>Grade 3 and 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Reactions</td>
<td>99.8</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>86.0</td>
</tr>
<tr>
<td>Fever</td>
<td>53.1</td>
</tr>
<tr>
<td>Chills</td>
<td>33.7</td>
</tr>
<tr>
<td>Infection</td>
<td>31.1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>28.8</td>
</tr>
<tr>
<td>Headache</td>
<td>19.1</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>14.1</td>
</tr>
<tr>
<td>Pain</td>
<td>12.1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>10.1</td>
</tr>
<tr>
<td>TheT. Irritation</td>
<td>9.3</td>
</tr>
<tr>
<td>Flushing</td>
<td>5.0</td>
</tr>
<tr>
<td>Hematologic System</td>
<td>48.7</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>48.7</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>14.4</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14.4</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12.3</td>
</tr>
<tr>
<td>Anemia</td>
<td>8.8</td>
</tr>
</tbody>
</table>

1 continued
table 2

* These data are based on 936 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 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, rigor, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypertension or hypotension) 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 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 placebo group.

Infection-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the rituximab group, the proportion of patients experiencing an infection-related reaction was 12%, 5%, and 1% following the first, second, and third infusions, respectively. Patients were pre-medicated with antihistamine and acetaminophen before each rituximab infusion and were on oral corticosteroids which may have mitigated or masked an infusion-related reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion-related reactions.

Infections
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.

Hypogammaglobulinemia
Hypogammaglobulinemia (IgA, IgG or 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, the efficacy and safety of non-U.S.-licensed rituximab versus azathioprine as follow up treatment in adult patients with GPA, MPA or renal and/or 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, 7/57 (12%) patients in the non-U.S.-licensed rituximab arm reported infusion-related reactions. The incidence of IRRs was highest during the first infusion (9%) 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.

Infections
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.

6.3.3 Clinical Trials Experience in Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (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 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 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 presented below in Table 3 were adverse events which occurred at a rate of greater than or equal to 10% in the rituximab group. This table reflects experience in 99 GPA patients treated with rituximab, with a total of 471 patient-years of observation and 98 GPA and MPA patients treated with cyclophosphamide, with a total of 47.0 patient-years of observation. Infection was the most common category of adverse events reported (47-62%) and is discussed below.

Table 3

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=99</td>
<td>N=98</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (18%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (17%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Headache</td>
<td>17 (17%)</td>
<td>19 (19%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>17 (17%)</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>16 (16%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>16 (16%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (14%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Cough</td>
<td>13 (13%)</td>
<td>9 (9%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (13%)</td>
<td>21 (21%)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>13 (13%)</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (12%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>11 (11%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 (10%)</td>
<td>11 (11%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (10%)</td>
<td>26 (26%)</td>
</tr>
<tr>
<td>Rash</td>
<td>10 (10%)</td>
<td>17 (17%)</td>
</tr>
</tbody>
</table>

6

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

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, urinary tract infections, 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 rituximab 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 Adverse 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 (0/398).

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 0.58 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 infusion and TRUXIMA® should be discontinued in the event of a serious or life-threatening cardiac event.

Hypophosphatemia and hyperuricemia
In the pooled, placebo-controlled studies, newly-occurring hypophosphatemia (<2.0 mg/dl) was observed in 12% (67/540) of patients on rituximab versus 10% (39/398) of patients on placebo. Hypophosphatemia was more common in patients who received corticosteroids. Newly-occurring hyperuricemia (>10 mg/dl) was observed in 1.5% (8/540) of patients on rituximab versus 0.3% (1/398) of patients on placebo.

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% (56/2570) of patients. The majority of the observed hypophosphatemia occurred at the time of the infusions and was transient.

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 1990, 1043, 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 were retreated with rituximab was similar to those who were retreated with placebo [see Clinical Studies (14.6), and Dosage and Administration (2.5)].
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 273/2578 (11%) patients with RA tested positive for anti-rituximab antibodies at any time after receiving rituximab. 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 serious infusion-related reactions, 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 within 8 to 255 months (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 reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, Grade 3-4 prolonged or late-onset neutropenia, hyperglycemia syndrome in Waldenström's macroglobulinemia, prolonged hypogammaglobulinemia [see Warnings and Precautions (6.2)].
- Cardiac: fatal cardiac failure.
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infusion-related reactions, 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 (5.8)].
- Neuropathy: disease progression of Kaposi's sarcoma.
- Skin: severe mucocutaneous reactions, pyoderma gangrenosum (including genital presentation).
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.
- Nervous system: posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS).

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 caused lymphoid B-cell depletion in the newborn offspring at doses resulting in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Advise pregnant women of the risk to a fetus.

Adverse outcome: frequency occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated populations is unknown. The estimated background rate in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Clinical Considerations
Fetal/Neonatal Adverse Reactions
Observe newborns and infants for signs of infection and manage accordingly.

Data
Human data
Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in utero. Rituximab was detected postnatally in the serum of infants exposed in utero.

Animal Data
An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post coitum days 20 through 50). Rituximab was administered as loading doses on post coitum (PC) Days 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring 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 doses of 15 or 37.5 mg/kg or 0, 20, or 100 mg/kg/ dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. 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.

8.2 Lactation
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 nursing mothers. Based on animal data, drugs that may inhibit human milk function should not be used in breastfeeding women who are taking rituximab products.

8.3 Females and Males of Reproductive Potential
Contraception
Rituximab products can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Females
Advise females of reproductive potential to use effective contraception during treatment with TRUXIMA and for at least 6 months after the last dose.

8.4 Pediatric Use
The safety and effectiveness of rituximab products have not been established in pediatric patients with NHL, CLL, or RA. Rituximab was not studied in pediatric patients with polycystic juvenile idiopathic arthritis (PJJ/A) 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, 116 of 475 patients receiving rituximab in combination with chemotherapy. Of these, 396 (83%) were age 65 or greater and 123 (26%) were age 75 or greater. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-Grade or Follicular Non-Hodgkin’s Lymphoma
Patients with previously untreated follicular NHL evaluated in NHL Study 5 were randomized to rituximab as single-agent maintenance therapy (n=505) or observation (n=495). Among patients receiving a response to rituximab in combination 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 responded 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.

8.6 Use in Specific Populations
8.6.1 Pregnancy
Risk Summary
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 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 of age or older receiving a response to rituximab in combination 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 responded differently from younger subjects.

Rheumatoid Arthritis
Among the 2578 patients in global RA studies completed to date, 12% were 65–75 years old and 2% were 75 years old and older. 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 a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Rituximab-abbs has an approximately molecular weight of 145 kD.

Rituximab-abbs is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium.

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 either 100 mg/10 mL or 500 mg/50 mL single-dose vials. Each mL of solution contains 10 mg 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 the absence of chronic B-cell stimulation, 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 (NCT00166740), 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.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

Rheumatoid Arthritis

In RA patients, treatment with rituximab induced depletion of peripheral B lymphocytes, with the majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/µL) within 2 weeks after receiving rituximab. There was no correlation of patients who failed to achieve B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. At Week 24 of the first course of rituximab treatment, small proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the experience with rituximab in RA patients during repeated rituximab treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below LLN at any time after receiving rituximab, respectively. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with rituximab are unclear.

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.
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 |
|------------------|---------------|-------------------|------------------|
| Study Arm        | Rituximab     | CVP               | Rituximab Treatment |
|                  | Weekly x4     | Weekly x8         | Weekly x4        |
| N               | N=166         | N=37              | N=39*            |
| N=60            |               |                   |                  |
| Overall Response | 48%           | 57%               | 36%              |
| Response Rate    | 6%            | 14%               | 9%               |
| Median Duration of Response (Months) | 11.2          | 13.4              | 15.0             |
| [Range] 1, 6; 1.9 to 42.1; 2.5 to 36.5; 2.8 to 25.0; 3.0 to 25.1 |

† Estimates of Cox regression stratified by center.

### 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 CVPH 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 56% had an IPI score of ≥2, 86% had ECOG performance status of ≤2, 57% had elevated LDH levels, and 18% had extranodal involvement in at least two sites. Efficacy results are presented in Table 6. 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. Analysis of results after the second randomization in NHL Study 7 demonstrates that for patients randomized to R-CHOP, additional rituximab exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

### 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 1,654 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 632 patients age ≥60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 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 CHOP 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 of ≥2, 57% had elevated LDH levels, and 30% had two or more extranodal diseases 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.

Analysis of results after the second randomization in NHL Study 7 demonstrates that for patients randomized to R-CHOP, additional rituximab exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

### NHL Study 8
A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP 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. Among all enrolled patients, 86% had Stage III or IV disease, 60% of patients had an age-adjusted IPI ≥2, 86% had ECOG performance status of ≤2, 57% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 7.

### NHL Study 9
A total of 399 patients with DLBCL, age ≥60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP 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 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.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

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

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>CHOP</td>
<td>R-CHOP</td>
</tr>
<tr>
<td>Progression-free survival (years)</td>
<td>Event-free survival (years)</td>
<td>Time to treatment failure (years)</td>
</tr>
<tr>
<td>Main outcome</td>
<td>Median of</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td></td>
<td>main outcome measure</td>
<td></td>
</tr>
<tr>
<td>R-CHOP</td>
<td>CHOP</td>
<td>R-CHOP</td>
</tr>
<tr>
<td>3.1</td>
<td>1.6</td>
<td>2.9</td>
</tr>
<tr>
<td>0.69*</td>
<td>0.60*</td>
<td>0.45*</td>
</tr>
<tr>
<td>0.72*</td>
<td>0.68*</td>
<td>0.40*</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 CVP 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/mm3 before Cycle 2. All patients were pre-medicated with acetaminophen and an antihistamine and received the glucocorticoid component of their chemotherapy

14.5 Chronic Lymphocytic Leukemia (CLL)

The effectiveness and safety of rituximab were evaluated in two randomized (1:1) multicenter open-label studies comparing FC alone or in combination with rituximab for up to 6 cycles in patients with previously untreated CLL (CLL Study 1 (n=817)) or previously treated CLL (CLL Study 2 (n=532)). Patients received fludarabine 25 mg/m2/day and cyclophosphamide 250 mg/m2/day on days 1, 2 and 3 of each cycle, with or without rituximab. In both studies, seventy-one percent of CLL patients were eligible for a 90-minute infusion at Cycle 2 if they did not experience a Grade 3-4 infusion-related reaction at 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 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)). Patients who tolerated the 90-minute rituximab infusion at Cycle 2 continued to receive subsequent rituximab infusions at the 90-minute infusion rate for the remainder of the treatment regimen (through Cycle 6 or Cycle 8). The incidence of Grade 3-4 infusion-related reactions at Cycle 2 was 1.1% (95% CI [0.3%, 2.8%]) among all patients, 3.5% (95% CI [1.0%, 8.8%]) for those patients treated with R-CPV, and 0.0% (95% CI [0.0%, 1.5%]) for those patients treated with R-CHOP. For Cycles 2-8, the incidence of Grade 3-4 infusion-related reactions was 2.8% (95% CI [1.3%, 5.0%]). No acute fatal infusion-related reactions were observed.

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 (NCT00486854), 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 re-treatment, are shown in Table 10.

Table 8
Efficacy Results in CLL Studies 1 and 2

<table>
<thead>
<tr>
<th>CLL Study 1* (Previously untreated)</th>
<th>CLL Study 2* (Previously treated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-FC</td>
<td>FC</td>
</tr>
<tr>
<td>N=408</td>
<td>N=409</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>39.8</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.56 (0.43, 0.71)</td>
</tr>
<tr>
<td>P-value (Log-Rank test)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Response rate (95% CI)</td>
<td>86%</td>
</tr>
</tbody>
</table>
| *As defined in 1996 National Cancer Institute Working Group guidelines.

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

<table>
<thead>
<tr>
<th>CLL Study 1</th>
<th>CLL Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age subgroup</td>
<td>Number of Patients</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>738</td>
</tr>
<tr>
<td>Age ≥ 70 yrs</td>
<td>81</td>
</tr>
</tbody>
</table>

* From exploratory analyses.

RA Study 1

In RA Study 1, all patients received a first course of rituximab 2 x 1000 mg + MTX or placebo + 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 re-treatment, are shown in Table 10.

Table 10
ACR Responses in RA Study 1 and RA Study 2 (Percent of Patients) (Modified Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>RA Study 1</th>
<th>RA Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-Controlled (Week 24)</td>
<td>Placebo-Controlled Retreatment (Week 24 and Week 48)</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td><strong>Response</strong></td>
</tr>
<tr>
<td>Placebo + MTX</td>
<td>Rituximab + MTX</td>
</tr>
<tr>
<td>n = 201</td>
<td>n = 298</td>
</tr>
<tr>
<td>Treatment Difference (Rituximab - Placebo)</td>
<td>Treatment Difference (Rituximab - Placebo)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>ACR20 Week 24 18% 51% 33%</td>
<td>ACR20 Week 24 48% 45% NA</td>
</tr>
<tr>
<td>Week 48 45% 54% 11%</td>
<td>Week 48 26% 29% 4%</td>
</tr>
<tr>
<td>ACR50 Week 24 5% 27% 21%</td>
<td>ACR50 Week 24 27% 21% NA</td>
</tr>
<tr>
<td>Week 48 26% 29% 4%</td>
<td>Week 48 13% 14% 1%</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 RF status at baseline; for RA Study 2, 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 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.
TRUXIMA® (rituximab-abbs) injection, for intravenous use

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>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Joint Count</td>
<td>31.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Swollen Joint Count</td>
<td>20.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Physician Global Assessment*</td>
<td>71.0</td>
<td>69.0</td>
</tr>
<tr>
<td>Patient Global Assessment*</td>
<td>73.0</td>
<td>68.0</td>
</tr>
<tr>
<td>Pain†</td>
<td>38.0</td>
<td>38.0</td>
</tr>
<tr>
<td>Disability Index (HAQ)‡</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* The same patients may not have responded at each time point.
† Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.
‡ Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with rituximab + MTX from Week 16 onward.

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 12

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Rituximab 2 x 1000 mg + MTX†</th>
<th>Placebo + MTX‡</th>
<th>Treatment Difference (Placebo – Rituximab)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change during</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Year</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 (0.47, 1.75)</td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>0.44</td>
<td>1.19</td>
<td>0.75 (0.32, 1.19)</td>
<td></td>
</tr>
<tr>
<td>JSN Score</td>
<td>0.22</td>
<td>0.58</td>
<td>0.36 (0.10, 0.62)</td>
<td></td>
</tr>
<tr>
<td>Change during</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second Year‡</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>
</tr>
<tr>
<td>ES</td>
<td>0.28</td>
<td>0.62</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>JSN Score</td>
<td>0.20</td>
<td>0.42</td>
<td>-</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.

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 daily 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 13

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Difference (Rituximab – Placebo)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Improvement from Baseline</td>
<td>0.19</td>
</tr>
<tr>
<td>Percent of patients with “Improved” score (Change from Baseline &gt;MCID)*</td>
<td>48%</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.
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

<table>
<thead>
<tr>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 99)</td>
<td>(n = 98)</td>
<td>(Rituximab – Cyclophosphamide)</td>
</tr>
<tr>
<td>Rate 64%</td>
<td>53%</td>
<td>11%</td>
</tr>
<tr>
<td>95.1% CI</td>
<td>(54%, 73%)</td>
<td>(-3%, 24%)</td>
</tr>
</tbody>
</table>

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

1 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 (58 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 18 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 requiring hospitalization) or death.

**Table 14**
Percentage of Patients with GPA/MPA Who Achieved Complete Remission at 6 Months (Intent-to-Treat Population)

<table>
<thead>
<tr>
<th>Rituximab</th>
<th>Cyclophosphamide</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 99)</td>
<td>(n = 98)</td>
<td>(Rituximab – Cyclophosphamide)</td>
</tr>
<tr>
<td>Rate 64%</td>
<td>53%</td>
<td>11%</td>
</tr>
<tr>
<td>95.1% CI</td>
<td>(54%, 73%)</td>
<td>(-3%, 24%)</td>
</tr>
</tbody>
</table>

**Summary**

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).

**17 PATIENT COUNSELING INFORMATION**

Advising patients about the signs and symptoms of infection-related reactions among patients treated with the non-U.S.-licensed rituximab or azathioprine is critical [see Warnings and Precautions (5.2)].

**Severe Mucocutaneous Reactions**

Advising 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**

Advising 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 (5.2)].

**Progressive Multifocal Leuкоencephalopathy (PML)**

Advising patients to contact their healthcare provider immediately for signs and 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 (5.3)].

**Tumor Lysis Syndrome (TLS)**

Advising patients to contact their healthcare provider immediately for signs and symptoms of tumor lysis syndrome such as nausea, vomiting, diarrhea, and lethargy [see Warnings and Precautions (5.4)].

**Benign Thrombotic Microangiopathy**

Advising patients of the risk of avoidable adverse reactions, including those associated with thrombotic microangiopathy [see Warnings and Precautions (5.4)].

**Renal Toxicity**

Advising patients of the risk of renal toxicity. Inform patients of the need for healthcare providers to monitor kidney function [see Warnings and Precautions (5.8)].

**Bowel Obstruction and Perforation**

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

**Embryo-Fetal Toxicity**

Advising pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)].

**Use in Specific Populations (8.2)**

**Advising patients of the risk of effective contraception during treatment with TRUXIMA and for at least 12 months after the last dose [see Use in Specific Populations (8.3)].

**Lactation**

Advising women not to breastfeed during treatment with TRUXIMA and for at least 6 months after the last dose [see Use in Specific Populations (8.2)].
MEDICATION GUIDE
TRUXIMA® (trux-ee'-mah)
(rituximab-abbs)
injection

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 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

continued
• 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 at least 12 months after the last dose of TRUXIMA. Talk to your healthcare provider about effective birth control.
• 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.
  • TRUXIMA treatment, your healthcare provider or nurse will ask you 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
    ◦ 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
    ◦ ear ache 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.

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U.S. License Number 1996
Market by: Teva Pharmaceuticals USA, Inc, North Wales, PA 19454
For more information, go to www.TRUXIMA.com or call 1-888-483-8279.

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