Drug Monograph

A - Drug Name

riTUXimab

COMMON TRADE NAME(S): Rituxan®; Truxima™; Riximyo™; Ruxience™; Riabni™

- Different rituxumab products are **not interchangeable**.
- For additional information on biosimilars, refer to:
  - Position Statements for the Clinical Operational Implementation of Oncology Biosimilars from the pan-Canadian Clinical Operations Working Group
  - Clinician Fact Sheet

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B - Mechanism of Action and Pharmacokinetics

Rituximab is a chimeric mouse-human monoclonal IgG1κ antibody. It binds to the CD20 antigen (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein, which is expressed on B-lymphocytes and on > 90% of B cell non-Hodgkin's lymphomas. CD20 is not shed from the cell surface and does not internalize upon antibody binding. Rituximab is thought to deplete CD20-positive cells via antibody-dependent cell-cytotoxicity and complement-mediated cell lysis.

Distribution	Binds to lymphoid tissues with little or no binding to non-lymphoid tissues. Pharmacokinetics are dose proportional. Circulating B-cells were observed to be depleted within the first 3 doses in most patients and sustained for up to 6-9 months post-treatment; levels started to recover at 6 months after treatment and median B-cell levels returned to normal by 12 months after treatment completion.	
	Cross blood brain barrier?	no information found
	PPB	no information found

Metabolism	The metabolism of rituximab is not fully understood.	
	Active metabolites	no
	Inactive metabolites	no
Elimination	Clearance of rituximab decreases markedly with accumulation of the drug which occurs after multiple infusions. Detectable in serum for 3 to 6 months after completion of treatment.	
	Half-life	60 hours (after 1st infusion) 174 hours (after 4th infusion)
	Urine	no information found

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C - Indications and Status

Health Canada Approvals:

- Non-Hodgkin lymphoma (NHL)
- Chronic lymphocytic leukemia (CLL)

Refer to the product monograph for a full list and details of approved indications.

Other Uses:

- Relapsed or refractory hairy cell leukemia
- Acute lymphoblastic leukemia

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

Side effects in the table below are from monotherapy with rituximab, or severe/life-threatening events from other uses.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (1%)	I
	Arterial thromboembolism (1-2%)	E
	Cardiotoxicity (rare)	E
	Hypertension (5%)	I E
	Hypotension (10%)	I
	Venous thromboembolism (3%)	E
Dermatological	Alopecia (1-10%)	E
	Rash (11%) (may be severe)	I E
Gastrointestinal	Abdominal pain (7%)	I E
	Anorexia, weight loss (3%)	E
	Constipation (1%)	I
	Diarrhea (4%)	I
	Dyspepsia (3%)	E
	GI obstruction (<1%)	E D
	GI perforation (<1%)	E D
	Mucositis (1%)	E
	Nausea, vomiting (17%)	I
General	Edema (5%)	E
	Fatigue (18%)	I
	Flu-like symptoms (>10%)	I E
Hematological	Hemolysis (<1%)	E
	Hyperviscosity (Waldenstrom's; rare)	I E
	Immunosuppression (± opportunistic infections, ≥ 10%)	E
	Myelosuppression ± infection, bleeding (11%) (higher incidence with chemotherapy, may be severe)	E
Hypersensitivity	Hypersensitivity (77%) (7% severe; with first infusion)	I
Immune	Antibody response (1%) (antichimeric antibodies)	E

	Other Viral reactivation (including hepatitis B; rare)	D
Metabolic / Endocrine	Abnormal electrolyte(s) (2%)	E
	Hyperglycemia (5%)	E
	Tumor lysis syndrome (<1%)	I
Musculoskeletal	Musculoskeletal pain (8%) (or stiffness)	I E
Neoplastic	Secondary malignancy (5%) (with chemotherapy)	L
Nervous System	Anxiety (2%)	E
	Dizziness (7%)	E
	Headache (13%)	I E
	Leukoencephalopathy (PML - rare)	E
	Neuropathy (rare, peripheral or cranial)	E D
	Paresthesia (16%)	E
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
	Sleep disorder (2%)	E
Ophthalmic	Conjunctivitis (1%)	E
	Optic nerve disorder (rare)	E
	Watering eyes (3%)	E
Renal	Nephrotoxicity (1-10%)	E
Respiratory	Cough, dyspnea (8%)	I E
	Pneumonitis (rare)	I E
Vascular	Vasculitis (rare)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common adverse effects are **infusion-related symptoms, fatigue, headache, rash, neutropenia and infections.** Adverse effects are more frequent in older patients, and in patients with high bulk disease. In clinical trials, there was a higher incidence of severe neutropenia in rituximab-containing arms as compared to the chemotherapy-only arms.

Acute reactions:

- **Infusion-related symptoms**, which may be related to cytokine release, include fever and chills/rigors, urticaria, bronchospasm, ARDS, angioedema, hypotension and flushing; they usually occur 30 minutes to 2 hours after the start of the first infusion and may be fatal. The majority of serious infusion reactions were observed with the first infusion, in which approximately 80% of fatal infusion reactions were reported. The incidence decreases with subsequent infusions. Infusion reactions are more common in patients with high tumour burdens and are fatal in up to 0.07% of patients. Autoimmune diseases or other co-morbidities may have contributed to the fatal outcome.
- **Anaphylaxis** (including fatalities) may occur, usually with the second or subsequent infusion. These may not be clinically distinguishable from infusion-related reactions.
- Severe **pulmonary reactions** with dyspnea, bronchospasm, hypoxia, and pulmonary infiltrates or edema have been reported, and are more common in patients with pulmonary involvement or disease. Acute symptoms appear within 1-2 hours of the initiation of the first infusion, while pneumonitis may appear 1-4 weeks after the infusion.
- Signs and symptoms of **tumour lysis syndrome** (TLS) have been reported to occur within 1 to 2 hours after the first infusion. Patients at risk (high tumour burden) should be closely monitored and prophylaxis considered.
- Symptoms of these acute reactions usually resolve with slowing or interruption of the rituximab infusion and aggressive treatment (IV saline, diphenhydramine and acetaminophen ± bronchodilators, IV corticosteroids or epinephrine). However, deterioration may occur after initial improvement of pulmonary or severe infusion-related symptoms and patients should be carefully monitored until complete symptom resolution. TLS should be excluded.
- Patients with pre-existing **cardiac** conditions, including arrhythmias and angina, should be carefully monitored throughout the infusion and in the immediate post-infusion period. Infusions should be discontinued in serious or life-threatening cardio-pulmonary events.

Serious Reactions:

Arterial thromboembolism, such as stroke, has been described in elderly patients who received rituximab especially in combination. Patients with cardiovascular disease or risk factors should be carefully monitored for signs of cerebral ischemia.

Severe **mucocutaneous reactions** (Stevens-Johnson syndrome, toxic epidermal necrolysis, paraneoplastic pemphigus, lichenoid dermatitis or vesiculobullous dermatitis) have been described and may be fatal. The onset of these reactions can vary from days to several months following exposure to rituximab.

Bowel obstruction and perforation (some fatal cases) have been reported. The mean time of onset for these GI symptoms is 6 days.

Infections are common, including opportunistic infections. **Reactivation** of tuberculosis or hepatitis B virus (HBV) infection may occur during treatment, with fulminant hepatitis, hepatic failure and death, including in patients with normal hepatitis B surface antigen but who are seropositive. The risk is increased in patients receiving steroids and/or chemotherapy. Patients should be screened (hepatitis B surface antigen, HbsAg and hepatitis B core antibody, HbcAb status) prior to treatment. HBsAg positive patients should receive antiviral prophylaxis during and after rituximab. HBsAg

negative, but HBcAb positive patients should be considered for antiviral prophylaxis and be closely monitored for viral reactivation by an HBV expert (2015 rituximab guidelines).

Cases of Pneumocystis Jiroveci Pneumonia (PJP) have been reported. Infections have been reported in some patients with prolonged hypogammaglobulinemia (>11 months after rituximab exposure).

There have been isolated reports of JC virus reactivation in NHL patients, resulting in fatal **progressive multifocal leukoencephalopathy** (PML). Rituximab should be held at first signs or symptoms suggestive of PML, which may progress over days to weeks and can include progressive unilateral weakness, clumsiness of limbs, confusion, cognitive or personality changes. Patients suspected of having PML should be investigated with MRI and lumbar puncture to evaluate JC viral DNA.

Posterior reversible leukoencephalopathy syndrome (PRES) has been reported rarely; brain imaging confirms diagnosis. Risk factors include hypertension and concomitant immunosuppressive therapy.

Other **viral infections** (including fatal cases), such as CMV, herpes simplex, varicella, hepatitis C, West Nile, etc. have been reported up to one year following rituximab cessation. Patients who are HIV-positive with Kaposi's sarcoma have been reported to have rapid Kaposi's sarcoma progression.

Patients who develop human anti-murine antibodies (HAMA) or human anti-chimeric antibodies for rituximab (HACA) may have allergic or hypersensitivity reactions when treated with rituximab or other murine or chimeric monoclonal antibodies.

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E - Dosing

Note: Different rituximab products are **not interchangeable.**

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Refer to protocol by which patient is being treated. Rituximab infusion should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions. **Rituximab must not be administered as an IV bolus or push.**

Since transient hypotension may occur during rituximab infusion, consideration should be given to withhold antihypertensive medication 12 hours prior to and throughout the rituximab infusion.

Pre-medication:

Administer at least 30 minutes prior to IV rituximab (prophylaxis for infusion reactions):

- Oral antipyretic (e.g. acetaminophen)
- H1-receptor antagonist (e.g. diphenhydramine)
- Corticosteroid (e.g. methylprednisolone 80 mg IV) in patients with high bulk disease or pulmonary involvement if no corticosteroids are already being given as part of the chemotherapy regimen.

Other supportive care:

- Prophylaxis for tumour lysis (high bulk disease)
- HBsAg positive patients should receive antiviral prophylaxis during and after rituximab. HBsAg negative, but HBcAb positive patients should be considered for antiviral prophylaxis and be closely monitored for viral reactivation by an HBV expert.

Adults:

<table>
<tr><th>Setting</th><th>Initial treatment (IV)</th><th colspan="2">Maintenance (after response to induction therapy) (IV)</th></tr>
<tr><td colspan="4">Low Grade/Follicular</td></tr>
<tr><td>Single Agent</td><td>375 mg/m^2 q1w x 4 doses</td><td rowspan="2">Previously untreated with advanced high-tumour burden: 375mg/m^2 q 2-3 months, for max 12 doses (2 years)[2]</td><td rowspan="2">Previously treated patients: 375 mg/m^2 q 3 months until disease progression (max 2 years)</td></tr>
<tr><td>With CVP[1]

With CHOP[1,2]</td><td>►375 mg/m^2 q3w x 8 cycles

►375 mg/m^2 q3w x 6-8 cycles</td></tr>
<tr><td colspan="4">Diffuse Large B Cell</td></tr>
<tr><td>With CHOP[1]</td><td>375 mg/m^2 q3w x 6-8 cycles[2]</td><td colspan="2">Not applicable</td></tr>
</table>

Setting	Initial treatment (IV)	Maintenance (after response to induction therapy) (IV)
CLL		
With FC	Cycle 1: 375 mg/m^2 day 1 (3) then Cycles 2-6: 500 mg/m^2 day 1 (3)	Not applicable
[1] Give on day 1 POST-steroid and PRE-cytotoxic regimen. [2] Hematology disease site group guideline recommends q3 month dosing as a reasonable schedule. NDFP funds up to a maximum of 8 doses (over 2 years). [3] Consider methylprednisolone IV ± slower infusion or split dose over 2 days for cycles where bulky disease or lymphocyte counts > 25 x 10^9/L.		

Dosage with Toxicity:

Toxicity	Rituximab Dose* / Infusion Rate
Myelosuppression	No adjustment required.
Other grade 3 toxicity	Delay infusion until ≤ grade 2
• Any pulmonary toxicity • Other grade 4 toxicity • Severe mucocutaneous toxicity • Serious/life-threatening cardio-pulmonary events • Reactivation of tuberculosis or hepatitis B • Evidence of active hepatitis • PML / PRES	Discontinue
*Missed or delayed doses may be administered at a later time point, based on physician's discretion.	

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • Once symptoms have resolved, restart at 50% of the rate at which the IR occurred.	• Re-challenge at 50% of the administration rate at which the IR occurred and with pre-medications. • Consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Consider clinical benefit and risks of further treatment. Consider patient factors, severity and nature of the IR and availability of suitable alternative treatment. • Consider desensitization for patients with recurrent reactions despite pre-medications and a slower infusion rate.

Dosage with Hepatic Impairment:

No dosage adjustment required; stop if evidence of hepatitis.

Dosage with Renal Impairment:

No dosage adjustment required.

Dosage in the elderly:

No dose adjustment required. Exercise caution as older patients are more likely to experience serious adverse events (including cardiac, pulmonary, or other grade 3/4 toxicity).

Children:

Safety and effectiveness in children have not been established. Hypogammaglobulinemia has been observed in pediatric patients and may be severe, requiring long-term immunoglobulin substitution therapy.

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F - Administration Guidelines

Note: Different rituximab products are **not interchangeable.**

Rituximab IV and Subcutaneous formulations are not interchangeable. The dosing and concentrations of these products are different.

For details on rituximab subcut administration, refer to rituximab (subcut) drug monograph.

Rituximab should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions.

- DO NOT administer as an IV push or bolus.
- Dilute to a final concentration of 1-4 mg/mL in normal saline or D5W.
- To avoid foaming, gently invert the bag to mix the solution.
- Do not admix with other drugs.
- Administer rituximab through a dedicated line.
- Compatible with PVC or polyethylene bags.
- Keep vials refrigerated; do not freeze. Protect from light.

Infusion rates:

First infusion:

- Recommended to be administered over a graduated rate: initial rate of 50 mg/h, then escalate rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h (about 4.25 hours in total).

Subsequent infusions:

- If no severe infusion reaction (grade 3 or 4) occurred with the first cycle, a rapid infusion of IV rituximab over a total of 90 minutes can be initiated with cycle 2 (20% of the dose in the first 30 min then the remaining 80% over 60 min).
- OR initial rate of 100 mg/h, then escalate rate in 100 mg/h increments every 30 minutes, to a maximum of 400 mg/h as tolerated (about 3.25 hours in total).
- Alternatively, subcutaneous administration of rituximab can be considered starting with cycle 2.

When bulky disease present or WBC > 25-50 x 10^9/L, consider:

- A slower infusion rate, or
- Split dosing over days 1-2, or
- Delaying rituximab treatment until chemotherapy has reduced the lymphocyte count

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients with known hypersensitivity and anaphylactic reactions to proteins of similar mouse or human origin, to Chinese Hamster Ovary (CHO) cell proteins or to any component of this product.
- Patients who have or have had PML, have active and/or severe infections, active hepatitis B, or severely immunocompromised (e.g. AIDS patients with very low CD4 or CD8 counts).
- Avoid the use of live vaccines.

Other Warnings/Precautions:

- Exercise caution in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection. Patients may have increased risk of infection following rituximab treatment.
- Prior to starting rituximab in HBV seropositive patients, consultation with a liver disease expert is recommended to determine ongoing monitoring of HBV reactivation and its management.
- Exercise caution in patients with neutrophil counts < 1.5 x 10^9/L and/or platelets < 75 x 10^9/L due to limited experience in this patient group.
- Use with *extreme caution* in patients with pre-existing cardiovascular disease or in patients with high tumour burden. Consider steroids ± slow infusions or infusions split over 2 days for patients with bulky disease or > 25 x 10^9/L circulating malignant cells.
- Use with caution in patients with pulmonary insufficiency or lung tumour infiltration, and in patients with myelosuppression.
- Reduced immunogenicity may occur with the use of vaccines.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Teratogenicity: No
- Mutagenicity: Unknown
- Fetotoxicity: Unknown
  Rituximab is not recommended for use during pregnancy. IgGs are known to pass the placental barrier. There have been reports of infants with transient B-cell depletion and lymphocytopenia. Adequate contraception should be used by patients and their partners during treatment, and for **12 months** after the last dose.
- Breastfeeding: Not recommended
  IgG is excreted into breast milk. Breastfeeding is not recommended during treatment and for **6 months** after the last dose.
- Fertility effects: Unknown

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H - Interactions

Formal drug interaction studies have not been performed with rituximab.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Antihypertensive agents	potentiation of hypotension with infusion	Additive effects	consider withholding temporarily (12 hours before and during infusion)
cisplatin	renal failure	Unknown	use with extreme caution; monitor renal function closely

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	baseline and at each visit
LFTs	baseline and at each visit
Renal functions tests	baseline and at each visit
Close observation for tumour lysis syndrome, treatment-related reactions, pulmonary and skin toxicities	for 24 hours after the dose
Clinical assessment of infusion-related reactions, tumour lysis syndrome, infection, bleeding, GI, pulmonary, skin, CNS, cardiovascular side effects	at each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Monitor cardiovascular symptoms in patients who have cardiac conditions or recurrent cardiac events with rituximab	At each visit

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Rituximab (Biosimilar IV) and Rituximab SC in Combination with Chemotherapy - Indolent B-cell Lymphoma
- Rituximab (Biosimilar IV) and Rituximab SC - Second Line - Chronic Lymphocytic Leukemia
- Rituximab (Biosimilar IV) and Rituximab SC - Retreatment - Indolent Lymphoma
- Rituximab (Biosimilar IV) and Rituximab SC - Retreatment - Aggressive Histology Lymphoma
- Rituximab (Biosimilar IV) and Rituximab SC - Previously Untreated Chronic Lymphocytic Leukemia
- Rituximab (Biosimilar IV) and Rituximab SC - Maintenance Treatment - Lymphoma
- Rituximab (Biosimilar IV) and Rituximab SC - In Combination with Venetoclax - Relapsed Chronic Lymphocytic Leukemia
- Rituximab (Biosimilar IV) and Rituximab SC - HIV-Related Aggressive Histology B-cell Lymphoma
- Rituximab (Biosimilar IV) and Rituximab SC - Aggressive Histology Lymphoma
- Rituximab (Biosimilar IV) - Single Agent - Indolent Lymphoma
- Rituximab (Biosimilar IV) - In Combination with Idelalisib - Relapsed Chronic Lymphocytic Leukemia
- Rituximab (Biosimilar IV) - As Part of the MATRix Regimen in Newly Diagnosed Previously Untreated PCNSL
- Polatuzumab Vedotin with Bendamustine and Rituximab (Biosimilar) - Relapsed or Refractory Diffuse Large B-cell Lymphoma

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K - References

McEvoy GK, editor. AHFS Drug Information 2013. Bethesda: American Society of Health-System Pharmacists, p. 1181-9.

Product Monograph: Rituxan® (rituximab). Roche Canada, October 2016 and June 2023.

Sehn LH, Donaldson J, Filewich A, et al. Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization. Blood

2004; 104(11): A1407.

Salar A, Casao D, Cervera M, et al. Rapid infusion of rituximab with or without steroid-containing chemotherapy: 1-yr experience in a single institution. Eur J Haematol 2006: 77: 338–340.

CCO Practice Guideline: Rituximab in Lymphoma and Chronic Lymphocytic Leukemia

October 2023 Modified Indications and Pregnancy/lactation sections

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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