Drug Monograph

A - Drug Name

riTUXimab (subcut)

COMMON TRADE NAME(S): Rituxan® SC

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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. The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20) to increase dispersion and absorption.

Absorption	Bioavailability	71% (follicular NHL patients)
Distribution	Binds to lymphoid tissues with little or no binding to non-lymphoid tissues. Rituximab subcut fixed dosing results in higher exposure to rituximab than at recommended IV dosing.	
Metabolism	The metabolism of rituximab is not fully understood. Active metabolites Inactive metabolites	 no no

Elimination	Half-life	34.1 days (follicular lymphoma) 32 days (CLL)

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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.

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D - Adverse Effects

Emetogenic Potential: Minimal

The adverse effects below are those reported for rituximab IV unless the subcutaneous formulation was associated with a relevant difference in incidence.

(*incidence based on rituximab subcut)

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	E
	Myelosuppression ± infection (26%) * (including opportunistic infections, bleeding)	E
Hypersensitivity	Administration-related reactions (48%) * (3% severe including hypersensitivity; cutaneous 23%)	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)

In general, higher incidences of local cutaneous reactions (23% vs 13%) and neutropenia (severe; 26% vs 21%) were observed in patients treated with rituximab subcut as compared to the IV formulation. Anaphylaxis, severe hypersensitivity reactions, cytokine release syndrome or tumour lysis syndrome appeared to be less common, which is expected given the most common time for many acute reactions is in cycle 1, when it is always given as the IV formulation. However, anaphylaxis is the most common with the second cycle.

Adverse effects are more frequent in older patients, and in patients with high bulk disease.

In clinical trials with rituximab IV, there was a higher incidence of severe neutropenia in rituximab-containing arms as compared to the chemotherapy-only arms.

Acute reactions:

- **Drug-related reactions**, 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 treatment and may be fatal. The majority of serious reactions were observed with the first rituximab dose, in which approximately 80% of fatal reactions were reported. The incidence decreases with subsequent doses. These 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 doses. These may not be clinically distinguishable from drug-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 dose, while pneumonitis may appear 1-4 weeks after.
- Signs and symptoms of **tumour lysis syndrome** (TLS) have been reported to occur within 1

to 2 hours after the first treatment. 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 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 administration and in the immediate post-administration period. Rituximab should be discontinued in serious or life-threatening cardio-pulmonary events.

Administration-related reactions with subcutaneous rituximab:

Most local cutaneous reactions were mild to moderate and resolved without any specific treatment. These included pain, swelling, induration, hemorrhage, erythema, pruritus and rash. Local cold compresses and topical steroids may be helpful.

Other adverse effects:

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

Refer to protocol by which patient is being treated.

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

Rituximab (any formulation) 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 rituximab-related reactions.

Since transient hypotension has occurred during rituximab treatment, consideration should be given to withhold antihypertensive medication 12 hours prior to and during the rituximab administration.

Pre-medication:

Administer 30 minutes prior to subcut rituximab (prophylaxis for drug-related reactions described above):

- 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.

- In patients who experienced adverse effects with pre-medications, the omission of pre-medications can be considered.

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

Other supportive care:

- Prophylaxis for tumour lysis (high bulk disease, WBC > 25 x 10^9/L)
- 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:

Patients must receive rituximab as IV infusion during the first cycle, so any infusion-related reactions can be managed by slowing or stopping the infusion.

The subcutaneous formulation **must only** be given at the second or subsequent cycles, and only if the patient has received at least one full rituximab IV dose at the previous cycle. If a patient is unable to receive the full IV rituximab dose, continue subsequent cycles with rituximab IV until a full IV dose can be successfully given.

Setting	**Induction Treatment** **(Cycle 1)**	**Induction treatment** **Fixed dose** **(subsequent cycles, only if rituximab IV full dose tolerated)**	**Maintenance Fixed dose** **(after response to induction therapy)**
Low Grade/Follicular			
With CVP or CHOP(1)	375 mg/m^2 **IV** day 1 (2)	If IV rituximab is tolerated: 1400 mg **Subcut** day 1 q3w for up to 6-8(6) cycles (including cycles given as IV infusion)	Previously untreated: 1400 mg **Subcut** every 2-3 (3) months until disease progression or up to maximum 2 years (maximum of 8 cycles including any IV maintenance cycles)

Setting	Treatment (Cycle 1)	Treatment Fixed dose (subsequent cycles, only if rituximab IV full dose tolerated)
Diffuse Large B Cell		
With CHOP(1)	375 mg/m^2 **IV** day 1 (2)	1400 mg **Subcut** day 1 q3w for 6 to 8 cycles (including cycles given as IV infusion)
CLL		
With FC	375 mg/m^2 **IV** day 1 (1, 2, 4, 5)	1600 mg **Subcut** day 1 q3w for up to 6 cycles (1, 5) (including cycles given as IV infusion)

[1] Give rituximab on day 1 POST-steroid (if applicable) and PRE-cytotoxic regimen.

[2] if patient is unable to receive the full rituximab IV dose and is appropriate for patient to continue with rituximab, give rituximab as IV in the next cycle. Refer to rituximab DM for dosing information.

[3] Hematology disease site group guideline recommends q3m dosing as a reasonable schedule. NDFP funds up to a maximum of 8 doses (over 2 years).

[4] Consider split dose over 2 days for cycles where bulky disease or lymphocyte counts > 25 x 10^9/L.

[5] Consider methylprednisolone IV where bulky disease or lymphocyte counts > 25 x 10^9/L.

[6] 8 cycles for CVP

Dosage with Toxicity:

Toxicity	Rituximab Dose* / Rate
Myelosuppression	No adjustment required.
Severe administration-related or pulmonary	• Hold administration if possible. Discontinue if hypersensitivity, pulmonary-related or based on physician discretion. • Manage appropriately; monitor patient until complete resolution.
Other grade 3 toxicity	Delay treatment until ≤ grade 2

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.	

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

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

Rituximab **subcutaneous** dosing:

- 1400 mg subcut **fixed dose** (non-Hodgkin lymphoma)
- 1600 mg subcut **fixed dose** (CLL)

Refer to Safety Considerations for the Implementation of Subcutaneous Rituximab Formulation

- 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 drug-related reactions.
- For details on rituximab IV administration, refer to the "rituximab" drug monograph.
- Rituximab (subcut) must not be self-administered.
- Rituximab (subcut) is given subcutaneously into the abdominal wall only. Do not give in areas where the skin is red, tender, hard, bruised, or where there are moles or scars.
- Non-Hodgkin's lymphoma: Give subcutaneously over approximately 5 minutes
- CLL: Give subcutaneously approximately over 7 minutes.
- Observe for at least 15 minutes after administration.
- If there are other subcutaneous medications, they should be given at separate sites.
- Compatible with polypropylene or polycarbonate syringes.
- Keep vials refrigerated in the outer carton; do not freeze. Protect from light.

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 IIV 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 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 (subcut). The following are based on known interactions with rituximab IV.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Antihypertensive agents	potentiation of hypotension with infusion	Additive effects	consider withholding temporarily (12 hours before and during administration)
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
Administration-related and hypersensitivity reactions	During and for at least 15 minutes after each injection, longer in patients at higher risk of hypersensitivity reactions.
Clinical assessment of tumour lysis syndrome, infection (including viral, opportunistic), 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

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K - References

Burrows, S. H., Akinbobuyi, O., Rule, S. & Crosbie, N. Subcutaneous rituximab can be safely administered without pre-medication. Br. J. Haematol 2018;181:836-7.

Prescribing information (US): Rituxan Hycela®. Genentech Inc., March 2018.

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

Product Monograph: Rituxan® SC (rituximab). Roche Canada, March 28, 2018 and June 2023.

Personal Communication: Rituxan Hycela Administration-Related Reactions. Roche Canada, June 2018.

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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