Regimen Monograph

A - Regimen Name

RITU(MNT) Regimen

riTUXimab (Maintenance)

Disease Site

Hematologic
Lymphoma - Non-Hodgkin's Low Grade

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

Single agent maintenance therapy of patients with indolent histology, CD20 positive B-cell lymphomas (excluding small lymphocytic lymphoma, CLL), who have responded to induction treatment with combination chemotherapy and/or rituximab. To be considered for NDFP funding, patients must be rituximab naïve prior to induction therapy for indolent histology lymphoma.

Supplementary Public Funding

riTUXimab
New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC - Maintenance Treatment - Lymphoma)

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B - Drug Regimen

Note: Different rituximab products are NOT INTERCHANGEABLE.

riTUXimab	375 mg /m²	IV

Maintenance rituximab should be started within 8 weeks of completion of the induction regimen (2015 guidelines). Funded by NDFP if maintenance rituximab is started within 6 months of the last dose of induction therapy.

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C - Cycle Frequency

If patient responds to induction therapy:

EVERY 3 MONTHS*
For maximum two years (8 doses total)* of maintenance treatment, unless disease progression or unacceptable toxicity

*Refer to Hematology disease site group guidelines and NDFP form for details.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal (infusion-related events)

Other Supportive Care:

- **Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.
- If high volume disease, consider steroids and prophylaxis for tumour lysis.

Pre-medication (prophylaxis for infusion reactions)

Administer at least 30 minutes prior to IV rituximab :

- 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.

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E - Dose Modifications

Screen patients for hepatitis B prior to starting treatment. See premedication and monitoring sections for supportive care, screening and monitoring recommendations

Doses should be modified according to the protocol by which the patient is being treated.

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 / RPLS	Discontinue
Missed or delayed doses may be administered at a later time point, based on physician's discretion.	

Management of Infusion 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.	• Re-challenge at 50% of the administration rate at which the IR occurred and with pre-medications. • Consider adding oral montelukast ± oral acetylsalicylic acid.

	Restart: • After symptoms have resolved, restart at 50% of the rate at which the IR occurred.	
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Consider clinical benefit and risks of further treatment. Consider patient factors, severity and nature of the IR and availability of the suitable alternative treatment • Consider desensitization for patients with recurrent reactions despite pre-medications and a slower infusion rate.

Hepatic Impairment

No adjustment required; stop if evidence of hepatitis.

Renal Impairment

No 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).

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F - Adverse Effects

Refer to riTUXimab drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Infusion reactions (may be severe and include hypersensitivity)	N/A	• Fatigue • Nausea, vomiting • Paresthesia • Headache • Rash (may be severe) • Myelosuppression +/- infection (including atypical, viral reactivation), bleeding (may be severe) • Hypotension • Flu-like symptoms	• Arrhythmia, cardiotoxicity • Arterial/venous thromboembolism • Bowel obstruction/perforation • Pneumonitis • RPLS / PRES, PML • Optic and cranial nerve disorder • Tumour lysis syndrome • Nephrotoxicity • Vasculitis • Hemolysis • Hyperviscosity • Secondary malignancy (with chemotherapy)

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G - Interactions

Refer to riTUXimab drug monograph(s) for additional details

- Consider withholding antihypertensive medication 12 hours prior to and during rituximab administration.

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H - Drug Administration and Special Precautions

Refer to riTUXimab drug monograph(s) for additional details

Administration

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:**
  - 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
    - Consider delaying rituximab treatment until chemotherapy has reduced the lymphocyte count.
- First infusion: 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:**
- 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).
- Published data suggest that a 90 minute infusion (20% of the dose in the first 30 min then the remaining 80% over 60 min) can be used for second and subsequent infusions, if no reaction occurred with the first infusion.

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

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.

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.

Pregnancy/lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Unknown

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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

- 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 24h after the dose
- Clinical assessment of hypersensitivity reactions, tumour lysis syndrome, hypotension, infection, bleeding, GI, pulmonary, skin, CNS, cardiovascular side effects; regular

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

Suggested Clinical Monitoring

- Monitor closely for cardiovascular symptoms for patients who have cardiac conditions or recurrent cardiac events with rituximab

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J - Administrative Information

Approximate Patient Visit	3 to 5 hours
Pharmacy Workload (average time per visit)	20.946 minutes
Nursing Workload (average time per visit)	54.167 minutes

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K - References

Buske C, Hoster E, Dreyling M, et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treatment failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). Leukemia 2009;23(1):153-61.

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Lenz G, Dreyling M, Hoster E, et al. Immunochemotherapy with rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone significantly improves response and time to treatment failure, but not long-term outcome in patients with previously untreated mantle cell lymphoma: results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). J Clin Oncol 2005;23(9):1984-92.

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Rituximab drug monograph, Cancer Care Ontario.

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;77:338–40.

Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. Lancet 2011;377(9759):42-51.

Sehn LH, Donaldson J, Filewich A, et al. Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safely be delivered in the community setting. Blood 2007;109(10):4171-3.

van Oers MH, Van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. J Clin Oncol 2010;28(17):2853-8.

PEBC Advice Documents or Guidelines

- Rituximab in Lymphoma and Chronic Lymphocytic Leukemia

November 2023 Modified Pregnancy/breastfeeding section

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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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