

Regimen Monograph

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A - Regimen Name

BEND+RITU Regimen

Bendamustine-riTUXimab

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

- First-line treatment of patients with indolent CD20 positive non-Hodgkin's lymphoma* or mantle cell lymphoma with ECOG status ≤ 2
- Treatment of patients with relapsed/refractory[†] indolent CD20 positive non-Hodgkin's lymphoma* or mantle cell lymphoma, where the combination of fludarabine-rituximab could previously have been a therapeutic option.

*(excluding small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL))

[†] Patients who previously received rituximab may be eligible for rituximab retreatment, in those who sustained a response and remained disease-free for at least 6 months after the last dose of rituximab

Refer to the NDFP eligibility forms for detailed funding criteria.

**Supplementary
Public Funding**[bendamustine](#)

New Drug Funding Program (Bendamustine - First Line - Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma)

[bendamustine](#)

New Drug Funding Program (Bendamustine - Relapsed_Refractory - Indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma)

[riTUXimab](#)

New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC in Combination with Chemotherapy - Indolent B-cell Lymphoma)

[riTUXimab](#)

New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC - Retreatment - Indolent Lymphoma) (with combination chemotherapy)

[riTUXimab \(subcut\)](#)

New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC in Combination with Chemotherapy - Indolent B-cell Lymphoma)

[riTUXimab \(subcut\)](#)

New Drug Funding Program (Rituximab (Biosimilar IV) and Rituximab SC - Retreatment - Indolent Lymphoma) (with combination chemotherapy)

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B - Drug Regimen

Note: Different rituximab products are NOT INTERCHANGEABLE.

Cycle 1: All patients must receive their first dose of rituximab by IV infusion

<u>riTUXimab</u>	375 mg /m ²	IV	Day 1
<u>bendamustine</u>	90 mg /m ²	IV	Days 1 and 2

Cycle 2 and onwards (For a maximum of 6 cycles including initial IV rituximab cycle(s))

Rituximab IV:

riTUXimab	375 mg /m ²	IV	Day 1
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OR

Rituximab subcutaneous:

The subcutaneous formulation must only be given at the second or subsequent cycles, and only after at least 1 full rituximab IV dose.

riTUXimab (subcut)	1400 mg	Subcut	Day 1
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Plus BEND chemotherapy:

bendamustine	90 mg /m ²	IV	Days 1 and 2
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C - Cycle Frequency

REPEAT EVERY 28 DAYS for a maximum of 6 cycles in the absence of unacceptable toxicity or disease progression.

For patients who responded to induction therapy, and were rituximab-naïve prior to induction, refer to maintenance rituximab regimen - RITU(MNT) or RITU(MNT-SC).

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

- Also refer to [CCO Antiemetic Recommendations](#).
- **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 prophylaxis for tumour lysis.

Pre-medication (prophylaxis for infusion reactions):

Administer at least 30 minutes prior to 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.
- In patients receiving **subcut** rituximab who experienced adverse effects with pre-medications, the omission of pre-medications can be considered.

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E - Dose Modifications

See premedication and monitoring sections for supportive care, screening and monitoring recommendations.

Hypertension should be controlled prior to starting treatment.

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

Dosage with toxicity

Dose levels for bendamustine: 90 mg/m², 60 mg/m². Do not re-escalate after reduction for toxicity.

Rituximab: No dosage reduction recommendation. Dose is either delayed or discontinued due to toxicity.

Toxicity / Counts (x 10⁹/L)	Rituximab (IV) Dose / Infusion Rate	Rituximab (Subcut) Dose	Bendamustine Dose
Grade 4 neutropenia or platelets; thrombocytopenic bleeding	Hold*	Hold*	Hold* then ↓ 1 dose level
Grade 2 clinically significant	Continue		Hold until ≤ grade 1 then reduce by 1 dose level
Other ≥ grade 3 non-hematological/organ toxicity	Hold until ≤ grade 1; considering discontinuing if grade 4		Hold until ≤ grade 1 then reduce by 1 dose level; consider discontinuing if grade 4

<ul style="list-style-type: none"> Any pulmonary toxicity Severe mucocutaneous toxicity Serious/life-threatening cardio-pulmonary events Reactivation of tuberculosis or hepatitis B Evidence of active hepatitis PML / RPLS 	Discontinue
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*Do not start new cycle until toxicities have recovered to \leq grade 1, platelets $\geq 75-100 \times 10^9/L$, and ANC $\geq 1 \times 10^9/L$.

Management of administration-related reactions:

Also refer to the CCO guideline for detailed description of [Management of Cancer Medication-Related Infusion Reactions](#).

Rituximab:

Grade	Management	Re-challenge
1 or 2	<ul style="list-style-type: none"> Stop or slow the infusion. Manage the symptoms. <p>Restart:</p> <ul style="list-style-type: none"> Once symptoms have resolved, restart at 50% of the IV rate at which the IR occurred. 	<ul style="list-style-type: none"> Re-challenge at 50% of the IV administration rate at which the IR occurred and with pre-medications. Consider adding oral montelukast \pm oral acetylsalicylic acid.
3 or 4	<ul style="list-style-type: none"> Stop the infusion. Aggressively manage symptoms. 	<ul style="list-style-type: none"> 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.

Bendamustine:

Toxicity	Management and re-challenge (if applicable)
Grade 1-2 Hypersensitivity/ acute reactions	Hold or slow infusion; premedicate with antipyretic, antihistamine, and corticosteroid before re-challenge and subsequent cycles.
Grade ≥ 3 Hypersensitivity/ acute reactions	Discontinue Manage appropriately; monitor patient until complete resolution.

Hepatic Impairment

Bilirubin		AST or ALT or ALP	Bendamustine Dose	Rituximab Dose
$\leq 1.5 \times \text{ULN}$	OR	$\leq 2.5 \times \text{ULN}$	Caution	No adjustment required; discontinue if evidence of hepatitis
$> 1.5 \times \text{ULN}$	OR	$> 2.5 \times \text{ULN}$	Do not use	

Renal Impairment

Creatinine Clearance (mL/min)	Bendamustine Dose	Rituximab Dose
> 80	100%	No adjustment required
40 - 80	Caution	
< 40	Do not use	

Dosage in the Elderly

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

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F - Adverse Effects

Refer to [riTUXimab](#), [riTUXimab \(subcut\)](#), [bendamustine](#) 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
<ul style="list-style-type: none"> • Infusion or hypersensitivity reactions (may be severe; with rituximab IV) • Nausea, vomiting • Fatigue • Myelosuppression and Immunosuppression (including atypical infections, viral/TB re-activation) 	<ul style="list-style-type: none"> • Diarrhea • Flu-like symptoms • Constipation • Administration-related reactions, including cutaneous (with rituximab subcut) 	<ul style="list-style-type: none"> • Headache • Musculoskeletal pain • Mucositis • Abdominal pain • Anorexia, weight loss • Dyspepsia • Dysgeusia • Cough, dyspnea (may be severe) • Dizziness • Insomnia • Paresthesia • Rash (may be severe) • Edema • Abnormal electrolytes 	<ul style="list-style-type: none"> • Arterial / venous thromboembolism • Arrhythmia, prolonged QTc • Cardiotoxicity • Hypertension • Hepatotoxicity • Tumour lysis syndrome • Nephrotoxicity • Pneumonitis, ARDS • GI obstruction / perforation • PRES / RPLS, PML • Optical and cranial nerve disorder • Hemolysis • Vasculitis • Hyperviscosity • Secondary malignancy

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G - Interactions

Refer to [bendamustine](#), [riTUXimab](#), [riTUXimab \(subcut\)](#) drug monograph(s) for additional details.

- Consider withholding antihypertensive medication 12 hours prior to and during rituximab administration
- CYP1A2 inhibitors may increase bendamustine concentration and toxicity; use with caution
- CYP1A2 inducers (including cigarette smoking) may reduce bendamustine concentration and/or efficacy

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H - Drug Administration and Special Precautions

Refer to [bendamustine](#), [riTUXimab](#), [riTUXimab \(subcut\)](#), drug monograph(s) for additional details.

Note: Different rituximab products are NOT INTERCHANGEABLE.

Administration

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

Refer to [Safety Considerations for the Implementation of Subcutaneous Rituximab Formulation](#).

Rituximab and bendamustine 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 (IV)

- 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 10⁹/L, consider:

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

Rituximab (Subcut)

Refer to [Safety Considerations for the Implementation of Subcutaneous Rituximab Formulation](#)

- 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
- Observe for at least 15 minutes after administration.
- Cold compresses and topical steroids may be helpful for local cutaneous reactions.
- 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.

Bendamustine:

- Non-Hodgkin lymphoma - infuse over 60 minutes
- **DO NOT** administer as an IV push or bolus.
- Dilute to a final concentration of 0.2 - 0.6 mg/mL in 500 mL infusion bag of 0.9% sodium chloride or 2.5% dextrose/0.45% sodium chloride.
- Reconstituted solution must be transferred to infusion bag within 30 minutes of reconstitution.
- Administer bendamustine through a dedicated line.
- Compatible with PVC or polyethylene bags.
- Do not admix with other drugs.

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 rituximab, bendamustine or mannitol.
- 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 live or live-attenuated vaccines, since they may result in serious or fatal infections in patients immunocompromised by BEND+RITU.
- Patients with CrCl < 40 mL/min or moderate/severe hepatic impairment

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 < $1.5 \times 10^9/L$ and/or platelets < $75 \times 10^9/L$ due to limited experience with rituximab in this patient group.

- Use rituximab with *extreme caution* in patients with pre-existing cardiovascular disease or in patients with high tumour burden. Consider steroids \pm slow rituximab infusions or infusions split over 2 days for patients with bulky disease or $> 25 \times 10^9/L$ circulating malignant cells.
- Use rituximab with caution in patients with pulmonary insufficiency or lung tumour infiltration, and in patients with myelosuppression.
- Reduced immunogenicity may occur with the use of inactivated vaccines.
- Avoid bendamustine in patients with relapsed indolent NHL who did not tolerate prior therapies (including other alkylating agents)
- Use bendamustine with caution in patients with hypertension and patients with mild renal and hepatic impairment.

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:
 - Bendamustine: Yes
 - Rituximab: 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

- Blood pressure; baseline and before each dose
- CBC; baseline and before each cycle
- Electrolytes, including sodium, potassium, magnesium and uric acid; baseline and before each cycle
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Monitor patients during and for at least 15 minutes after each rituximab dose, longer in patients at higher risk of hypersensitivity reactions
- Clinical assessment of hypersensitivity/infusion reactions, tumour lysis syndrome, infection (including viral, opportunistic), bleeding, GI, pulmonary, skin, CNS and cardiovascular side effects, secondary malignancies; at each visit
- 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
- ECG; as clinically indicated; periodic in the setting of cardiac disorders and electrolyte imbalances
- Blood glucose; baseline and periodic
- CMV testing in febrile patients; as clinically indicated
- HIV status; baseline

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J - Administrative Information

Approximate Patient Visit	BEND+RITU - 6 hours (first cycle); 1.5 to 4 hours (subsequent cycles); BEND only: 0.5 to 1 hour
Pharmacy Workload (average time per visit)	24.073 minutes
Nursing Workload (average time per visit)	55.417 minutes

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K - References

Bendamustine and rituximab drug monographs, Cancer Care Ontario.

Davies A, Merli F, Mihaljević B, et al. Efficacy and safety of subcutaneous rituximab versus intravenous rituximab for first-line treatment of follicular lymphoma (SABRINA): a randomised, open-label, phase 3 trial. *Lancet Haematol*. 2017 Jun;4(6):e272-e282.

Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. *J Clin Oncol*. 2008 Sep 20;26(27):4473-9.

Rummel MJ, Niederle N, Maschmeyer G, et al.; Study group indolent Lymphomas (StiL). Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013 Apr 6;381(9873):1203-10. doi: 10.1016/S0140-6736(12)61763-2. Epub 2013 Feb 20. Erratum in: *Lancet*. 2013 Apr 6;381(9873):1184.

PEBC Advice Documents or Guidelines

- [Rituximab in Lymphoma and Chronic Lymphocytic Leukemia](#)

November 2024 Updated Hepatic impairment dosing and Pregnancy/breastfeeding sections

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the “Formulary”) is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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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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