RiTUXimab and Bendamustine Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of patients with previously untreated indolent CD20-positive, stage III-IV non-hodgkin lymphoma (NHL)	C82	00345a	Hospital
Treatment of patients with previously untreated CD20-positive, stage III-IV mantle cell lymphoma (MCL), ineligible for autologous stem cell transplant	C83	00345b	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Bendamustine is administered on day 1 and day 2 and riTUXimab on day 1 of a 28 day cycle for up to 6 cycles or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when riTUXimab therapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	RiTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[1]	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[1]	1-6
1 and 2	Bendamustine	90mg/m^2	IV infusion	500 mL 0.9% sodium chloride over 1 hour	1-6
[1] See table 1:Guidance for administration of riTUXimab					

Table 1: Guidance for administration of riTUXimab

The recommended initial rate for infusion is 50 mg/hr; after the first 30 minutes, it can be escalated in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. Subsequent infusions can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr. Development of an allergic reaction may require a slower infusion rate. See Hypersensitivity/Infusion reactions under Adverse Effects/Regimen Specific Complications below. Any deviation from the advised infusion rate should be noted in local policies.
Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies
RiTUXimab should be diluted to a final concentration of 1-4mg/ml.
Rapid rate infusion schedule[i] **See NCCP guidance here.** If patients did **not** experience a serious infusion related reaction with their first or subsequent infusions of a dose of riTUXimab administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions. Initiate at a rate of 20% of the total dose for the first 30 minutes and then 80% of the dose for the next 60 minutes (total infusion time of 90 minutes). If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions. Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to riTUXimab, should not be administered the more rapid infusion.

ELIGIBILITY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to bendamustine, riTUXimab or any of the excipients or to murine proteins.
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Patients in a severely immunocompromised state.
- AST or ALT greater than 2.5 x upper limit of normal and total bilirubin greater than 1.5 x upper limit of normal
- Creatinine clearance (CrCl) < 40 mL/min
- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to < 3 x 10^9/L or < 75x 10^9/L, respectively)

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist or by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH
- ECG
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV*
  *See Adverse Effects/Regimen Specific Complications

Regular tests:

- FBC, renal and liver profile, LDH prior to each cycle
- ECG as clinically indicated*
  *See Adverse Events/Regimen Specific Complications

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- No dose reductions of riTUXimab are recommended.

Haematological:

Table 1: Recommended dose modification of bendamustine in haematological toxicity

ANC (x 10^9/L)		Platelets(x 10^9/L)	Dose of Bendamustine
≥1	and	≥75	100%
< 1	or	< 75	Delay until recovery

Renal and Hepatic Impairment:

Table 2: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
Bendamustine	**Cr Cl (ml/min)**	**Dose**	**serum bilirubin (micromol/L)**	**Dose**
	>10	No dose adjustment necessary	< 21	No dose adjustment necessary
	Experience in patients with severe renal impairment is limited.		21-51	30% dose reduction
			>51	No data available
riTUXimab	No dose adjustment necessary		No dose adjustment necessary	

Management of adverse events:

Table 3: Dose Modification of riTUXimab based on Adverse Events

Adverse reactions	Recommended dose modification
Severe infusion related reaction (e.g dyspnoea, bronchospasm, hypotension or hypoxia) First occurrence	Interrupt infusion immediately. Evaluate for cytokine release/tumour lysis syndrome (appropriate laboratory tests) and pulmonary infiltration (chest x -ray). Infusion may be restarted on resolution of all symptoms, normalisation of laboratory values and chest x-ray findings at no more than one-half the previous rate.
Second occurrence	Consider coverage with steroids for those who are not already receiving steroids. Consider discontinuing treatment
Mild or moderate infusion-related reaction	Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

RiTUXimab: Minimal **(Refer to local policy).**
Bendamustine: Moderate **(Refer to local policy)**

PREMEDICATIONS:

Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of riTUXimab. Premedication with glucocorticoids should be considered if riTUXimab is not given in combination with glucocorticoid containing chemotherapy for treatment of NHL.

Table 4: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to riTUXimab infusion
Chlorpheniramine	10mg	IV bolus 60minutes prior to riTUXimab infusion
Hydrocortisone	100mg	IV bolus 60 minutes prior to riTUXimab infusion

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Proton Pump Inhibitor **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**

  Note: All patients who receive bendamustine should receive irradiated blood products throughout their chemotherapy and for life

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Hepatitis B Reactivation**: Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.
- **Hypersensitivity/Infusion Reactions:** Close monitoring is required throughout the first infusion of riTUXimab. (Refer to local policy) RiTUXimab can cause allergic type reactions during the IV infusion such as hypotension, wheezing, rash, flushing, pruritis, sneezing, cough, fever or faintness. Bendamustine can cause allergic type reactions during IV infusion such as fever, chills, pruritus and rash. Severe anaphylactic and anaphylactoid reactions have occurred rarely, particularly in the second and subsequent cycles of therapy. If an allergic reaction occurs, stop the infusion and the physician in charge should determine a safe time and rate to resume the infusion. Consider pre-treatment with antihistamines, antipyretics and corticosteroids for patients experiencing Grade 1 or 2 infusion reactions; consider discontinuing treatment for patients experiencing Grade 3 or 4 infusion reactions
- **Cardiac Disorders**: Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely. During treatment with bendamustine hydrochloride the concentration of potassium in the blood must be closely monitored and potassium supplement must be given when K+ < 3.5 mEq/l, and ECG measurement must be performed. Fatal cases of myocardial infarction and cardiac failure have been reported with bendamustine hydrochloride treatment.
- **Skin reactions:** A number of skin reactions have been reported with bendamustine therapy. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, bendamustine should be withheld or discontinued. For severe skin reactions where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued
- **Severe Cytokine Release syndrome:** Usually occurs within 1 to 2 hours of initiating the first infusion. This syndrome may be associated with some features of cytokine release/tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphatemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death.
  - Pulmonary interstitial infiltrates or oedema visible on chest x-ray may accompany acute respiratory failure.

  - For severe reactions, stop the infusion immediately and evaluate for tumour lysis syndrome and pulmonary infiltration. Aggressive symptomatic treatment is required. The infusion can be resumed at no more than one-half the previous rate once all symptoms have resolved, and laboratory values and chest x-ray findings have normalized.
- **Severe Mucocutaneous Reactions**: These include Stevens-Johnson syndrome and Toxic Epidermal Necrolysis. Discontinue riTUXimab in patients who develop a severe mucocutaneous reaction. The safety of readministration has not been determined.
- **Progressive multifocal leukoencephalopathy (PML):** Use of riTUXimab may be associated with an increased risk of PML. Patients must be monitored for any new or worsening neurological symptoms. Cases of PML including fatal ones have been reported following the use of bendamustine mainly in combination with rituximab or obinutuzumab. Consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms. If PML is suspected then appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. (7)
- **Infections:** RiTUXimab should not be administered to patients with an active, severe infection. Caution should be exercised when considering the use of riTUXimab in patients with a history of recurring or chronic infections or with underlying conditions that may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis.
  Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia and opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV). Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/microlitre) and low CD4-positive T-cell (T-helper cell) counts (< 200/microlitre) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections. In case of low CD4-positive T-cell counts (< 200/microlitre) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. All patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections.
- **Tumour lysis syndrome:** Tumour lysis syndrome associated with bendamustine treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of bendamustine and, without intervention, may lead to acute renal failure and death. Preventive measures include adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. The use of allopurinol during the first one to two weeks of bendamustine therapy can be considered but not necessarily as standard. However, there have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol were administered concomitantly.
- **Vaccines:** Vaccination should be completed at least 4 weeks prior to first administration of riTUXimab. The safety of immunisation with live viral vaccines following riTUXimab therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst on rituximab**.** Patients treated with riTUXimab may receive non-live vaccinations
- **Fertility:** Women of childbearing potential must use effective methods of contraception both before and during bendamustine therapy. Men being treated with bendamustine are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to

therapy with bendamustine.

- **Non-melanoma skin cancers:** In clinical studies, an increased risk for non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) has been observed in patients treated with bendamustine-containing therapies. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer. (7)

DRUG INTERACTIONS:

- Antihypertensives: Additive effect of hypotension during rituximab infusion. Consider withholding antihypertensives 12 hours before and during rituximab infusion.
- Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme, Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exists.
- Current drug interaction databases should be consulted for more information

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Version	Date	Amendment	Approved By
1	05/04/2017		Prof E Vandenberghe Prof Maccon Keane
2	01/05/2019	Updated to new NCCP template layout. Standardised treatment table. Updated emetogenic potential updated supportive care with requirement for irradiated blood products with bendamustine and riTUXimab. Updated adverse events for bendamustine by Inclusion of safety update on risk of infections	Prof Maccon Keane
3	28/04/2021	Reviewed. Updated exclusion criteria. Updated adverse effects (including Hep B reactivation and also in line with SPC update).	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i]The rapid infusion is an unlicensed means of administration of riTUXimab for the indications described above, in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.