Polatuzumab Vedotin, Bendamustine and riTUXimab Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
In combination with bendamustine and riTUXimab for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.	C85	00685a	ODMS 01/12/2021

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.

- riTUXimab and polatuzumab are administered on day one and bendamustine on day two and three of each cycle .
- Due to limited clinical experience in patients treated with 1.8 mg/kg polatuzumab vedotin at a total dose >240 mg, it is recommended not to exceed the dose 240 mg/cycle.

Each cycle is 21 days and treatment is administered for up to 6 cycles, unless disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	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
2	1	Polatuzumab vedotin	1.8mg/kg	IV infusion	100ml 0.9% sodium chloride over 90 minutes[2,3,4]	1-6
1	2 and 3	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.

[2] Polatuzumab vedotin should be diluted to a concentration of 0.72-2.7mg/ml.

[3] Polatuzumab vedotin must be administered using a sterile, non-pyrogenic, low protein binding 0.2 micron or 0.22 micron filter.

[4] The initial dose of polatuzumab vedotin should be administered over 90 minutes. Patients should be monitored during the infusion and for at least 90 minutes following completion of the initial dose. If well tolerated subsequent infusions may be given over 30 minutes and the patients monitored for a further 30 minutes after the end of the infusion.

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 0-2
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to riTUXimab, polatuzumab vedotin, bendamustine or any of the excipients or to murine proteins
- Ongoing corticosteroid use >30 mg per day prednisone or equivalent, for purposes other than lymphoma symptom control
- Primary or secondary CNS lymphoma
- Current Grade >1 peripheral neuropathy
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Patients in a severely immunocompromised state
- AST or ALT > 2.5 x upper limit of normal and total bilirubin > 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) unless due to bone marrow involvement with lymphoma
- Pregnancy
- Breast feeding

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 2: Dose modification of polatuzumab, bendamustine and riTUXimab in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
≥1	100%	≥75	100%
<1	Hold all treatment until ANC recover to >1. • If ANC recovers to ≥1 on or before day 7, resume all treatment without any additional dose reductions. • If ANC recovers to >1 after day 7, restart all treatment, with a dose reduction of bendamustine from 90mg/m^2 to 70mg/m^2 or 70mg/m^2 to 50mg/m^2. • If a bendamustine dose reduction to 50mg/m^2 has already occurred, discontinue all treatment.	<75	Hold all treatment until platelets recover to >75. • If platelets recover to >75 on or before day 7, resume all treatment without any additional dose reductions. • If platelets recover to >75 after day 7, restart all treatment, with a dose reduction of bendamustine from 90mg/m^2 to 70mg/m^2 or 70mg/m^2 to 50mg/m^2. • If a bendamustine dose reduction to 50mg/m^2 has already occurred, discontinue all treatment.

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Renal Impairment			**Hepatic Impairment**	
riTUXimab	No dose adjustment necessary		No dose adjustment necessary	
Polatuzumab vedotin	No dose adjustment is required in patients with CrCl ≥ 30 ml/min. Due to limited data a recommended dose has not been determined for patients with CrCl <30ml/min.		**Mild** (bilirubin greater than upper limit of normal [ULN) to less than or equal to 1.5 × ULN or aspartate transaminase (AST) greater than ULN).	No adjustment in the starting dose is required
			Moderate or severe (bilirubin greater than 1.5 × ULN	Polatuzumab vedotin should be avoided
Bendamustine	**CrCl (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

Management of adverse events:

Table 4: Dose Modification of polatuzumab vedotin for peripheral neuropathy (PN)

Severity of PN on Day 1 of any cycle	**Recommended dose modification**
Grade 2-3	Hold polatuzumab vedotin until improvement to ≤ Grade 1. • If recovered to Grade ≤ 1 on or before day 14, restart polatuzumab vedotin at a permanently reduced dose of 1.4mg/kg. • If a prior dose reduction to 1.4mg/kg has occurred, discontinue polatuzumab vedotin. • If not recovered to Grade ≤1 on or before day 14, discontinue polatuzumab vedotin.
Grade 4	Discontinue polatuzumab vedotin.

Table 5: Dose Modification polatuzumab vedotin for infusion-related reactions (IRRs)

Severity of IRR on Day 1 of any cycle	Recommended dose modification
Grade 1–3 IRR	• Interrupt polatuzumab vedotin infusion and give supportive treatment. • For the first instance of Grade 3 wheezing, bronchospasm, or generalised urticaria, permanently discontinue polatuzumab vedotin. • For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue polatuzumab vedotin. • Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. • For the next cycle, infuse polatuzumab vedotin over 90 minutes. If no infusion related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.
Grade 4 IRR	• Stop polatuzumab vedotin infusion immediately. • Give supportive treatment. • Permanently discontinue polatuzumab vedotin.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: riTUXimab: Minimal **(Refer to local policy).**
Polatuzumab vedotin: Low **(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 and polatuzumab. Please see Table 6 for suggested pre-medications.
- Premedication with glucocorticoids should be considered if riTUXimab is not given in combination with glucocorticoid-containing chemotherapy for treatment of Non Hodgkin Lymphoma (NHL) as outlined in Table 6.

Table 6: Suggested pre-medications prior to infusion of riTUXimab and polatuzumab

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

Polatuzumab vedotin is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

- **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:** Infusion reactions have been reported in patients treated with riTUXimab, polatuzumab vedotin and bendamustine**.** 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. Polatuzumab vedotin can cause IRRs, including severe cases. Delayed IRRs as late as 24 hours after receiving polatuzumab vedotin have occurred. 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 while receiving treatment with both riTUXimab and bendamustine. 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.
- **Infections:** Patients should be monitored for signs and symptoms of bacterial, fungal, or viral infections during treatment with riTUXimab, polatuzumab vedotin and bendamustine. Consideration should be given to the use of antimicrobial prophylaxis.
  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.

Serious, life threatening or fatal infections have been reported in patients treated with polatuzumab vedotin. Reactivation of latent infections has been reported.
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.
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 is associated with polatuzumab vedotin and bendamustine; patient should be closely monitored. 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
- **Progressive multifocal leukoencephalopathy (PML):** PML has been reported with the use of riTUXimab, polatuzumab vedotin and bendamustine. Patients should be monitored closely for new or worsening neurological, cognitive, or behavioural changes suggestive of PML. riTUXimab, polatuzumab vedotin and bendamustine should be withheld if PML is suspected and permanently discontinued if the diagnosis is confirmed.
- **Fertility:** Both polatuzumab vedotin and bendamustine can be harmful to the foetus when administered to a pregnant woman.
    - Women of childbearing potential are advised to use effective contraception during treatment with both polatuzumab vedotin and bendamustine and for at least 9 months after the last dose of polatuzumab vedotin.
    - Male patients with female partners of childbearing potential should be advised to use effective contraception during treatment and for at least 6 months after the last dose of both polatuzumab vedotin and bendamustine.
    - Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with bendamustine.

riTUXimab

- **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.
- **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.

Polatuzumab vedotin

- **Peripheral neuropathy (PN):** PN has been reported in patients treated with polatuzumab vedotin as early as the first cycle of treatment, and the risk increases with sequential doses. Patients with pre-existing PN may experience worsening of this condition. Patients should be monitored for symptoms of PN. Patients experiencing new or worsening PN may require a delay, dose reduction, or discontinuation of polatuzumab vedotin as per Table 4 above.

Bendamustine

- **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 anti-cancer 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
- **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.
- Concomitant use of strong CYP3A4 inhibitors may increase plasma levels of polatuzumab vedotin; therefore caution is advised in the case of concomitant treatment with CYP3A4 inhibitors. Patients receiving concomitant strong CYP3A4 inhibitors should be monitored more closely for signs and toxicities.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Laurie H et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Journal of Clinical Oncology January 1-, 2020 38 (2) 155-165. https://ascopubs.org/doi/pdf/10.1200/JCO.19.00172
2. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drug in patients with renal or hepatic impairment. Lancet Onco/2019; 20:e201-08. https://doi.org/10.1016/S1470-2045(19)30145-7
3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
4. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V4 2022. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
6. European Medicines Agency. Bendamustine hydrochloride: CMDh scientific conclusions and grounds for variation, amendments to the Product Information and timetable for the implementation. Annex II - Amendments to the product information of the nationally authorised medicinal product(s). Last updated 10/11/2020. Available from: https://www.ema.europa.eu/en/documents/psusa/bendamustine-hydrochloride-cmdh-scientific-conclusions-grounds-variation-amendments-product/00003162/202001_en.pdf
7. riTUXimab (MabThera®) Summary of Product Characteristics. Accessed July 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf
8. Polatuzumab vedotin (Polivy®) Summary of Product Characteristics. Accessed July 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/polivy-epar-product-information_en.pdf
9. Bendamustine 25mg powder for concentrate for solution for infusion Summary of Product characteristics. Accessed July 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-077-001_25032021123409.pdf

Version	Date	Amendment	Approved By
1	07/12/2021		NCCP Lymphoid CAG

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.