R-CEOP Therapy – 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Treatment of Non Hodgkin CD20 positive Lymphoma for patients not suitable for anthracycline therapy	C85	00510a	Hospital

TREATMENT:

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

Treatment is administered every 21 days as described in the treatment table below.
Patients with limited stage disease receive 3-4 cycles of chemotherapy with or without radiation therapy; patients with advanced stage disease receive 6 cycles of chemotherapy unless disease progression or unacceptable toxicity develops.
Facilities to treat anaphylaxis MUST be present when therapy is administered

Day	Drug	Dose	Route	Diluent & Rate
1	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[1]
1	Cyclophosphamide	750mg/m^2	IV infusion[2]	250mL 0.9% NaCl over 30minutes
1	Etoposide	50mg/m^2	IV infusion	500ml 0.9% NaCl over 60minutes
1	vinCRIStine[3]	1.4mg/m^2 (Max 2mg)	IV infusion	50ml minibag 0.9% NaCl over 15minutes
2-3	Etoposide	100mg/m^2	PO	Take on an empty stomach. Round dose to the nearest 50mg.
1-5	Prednisolone	100mg(*)	PO	
[1] See table 1:Guidance for administration of riTUXimab				
[2] Cyclophosphamide may also be administered as an IV bolus over 5-10mins				
[3]vinCRIStine is a neurotoxic chemotherapeutic agent. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer. https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf				
*Alternative steroid regimens may be used at consultant discretion				

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

EXCLUSIONS:

- Hypersensitivity to cyclophosphamide, riTUXimab, vinCRIStine sulphate, etoposide or any of the excipients.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, blood glucose, Uric Acid, B2M, Immunoglobulins and SPEP
- Consider cardiac function tests
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV.
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile prior to each cycle
- LDH prior to each cycle
- Evaluate for peripheral neuropathy prior to each cycle.

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.
- Consider vinCRIStine dose reduction in elderly patients

Haematological:

Table 2: Dose modification for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
<1	and/or	<75	Dose modification not generally indicated. Consider treatment delay and/or add G-CSF

Renal and Hepatic Impairment:

Table 3: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
riTUXimab	No dose adjustment necessary		No dose adjustment necessary			
Cyclophosphamide	**CrCl (ml/min)**	**Dose**	Severe impairment: Clinical Decision			
	>20	100%				
	10-20	75%				
	<10	50%				
VinCRIStine	**No dose reduction required**		**Bilirubin (micromol/L)**		**AST/ALT**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit
Etoposide	**Cr Cl (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**		**AST**	**Dose**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent doses should be based on clinical response					

Neurotoxicity:

Table 4: Dose modification of vinCRIStine based on neurotoxicity (CTCAE v4.0)

Symptom	Dose of VinCRIStine
Grade 1	100%
Grade 2	Hold until recovery then reduce dose by 50%
Grade 3,4	Omit

Table 5: Dose modification schedule of riTUXimab based on adverse events

Adverse reactions	Discontinue	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. Consider coverage with steroids for those who are not already receiving steroids.
Second occurrence	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)**
Cyclophosphamide: Moderate **(Refer to local policy)**
Etoposide (IV): Low **(Refer to local policy)**
Etoposide (oral): Minimal to low **(Refer to local policy)**
Vincristine: Minimal **(Refer to local policy)**

PREMEDICATIONS:

- Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of riTUXimab.

Table 5: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to riTUXimab infusion
Chlorphenamine	10mg	IV bolus 60minutes prior to riTUXimab infusion
Ensure glucocorticoid component of the treatment regimen (Prednisolone) is given at least 30 minutes prior to riTUXimab infusion		

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor**(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRIStine (2)) **(Refer to local policy)**
- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy)**.
- G-CSF prophylaxis may be required, please discuss with consultant

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **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.
- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely while on riTUXimab.
- **Neuropathy:** VinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months.
- **Constipation:** A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.
- **Extravasation**: VinCRIStine causes pain and possible tissue necrosis if extravasated. **(Refer to local policy).**
- **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 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.

- **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.
- **Please Refer to NCCP regimen 00542 RiTUXimab 375 mg/m^2 Combination Therapy-21 day for detailed information on adverse reactions/Regimen Specific Complications associated with RiTUXimab Therapy**

DRUG INTERACTIONS:

- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3A4 inhibitors/inducers

REFERENCES:

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3. VinCRIStine Summary of Product Characteristics Accessed Jan 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-232-001_15102020091031.pdf
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Version	Date	Amendment	Approved By
1	29/01/2019		Dr Derville O'Shea
2	03/02/2021	Updated treatment (etoposide infusion volume), dose modification in hepatic impairment, vinCRIStine dose modification in neurotoxicity, emetogenic potential, adverse effects (hepatitis B reactivation)	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.