riTUXimab S/C, cycloPHOSphamide, DOXOrubicin, vinCRIStine and prednisoLONE (R-CHOP) Therapy – 21 Days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of Non-Hodgkin's Lymphoma (NHL)	C85	00667a	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.

Treatment consists of R-CHOP administered every 21 days for 6 cycles followed by riTUXimab administered for an additional 2 cycles or until disease progression or unacceptable toxicity develops.

Note:

- Patient must have previously received a full dose of intravenous riTUXimab before being switched to subcutaneous (S/C) formulation.
- Patients who have previously received a full dose of intravenous riTUXimab may consider commencing therapy with this regimen using S/C riTUXimab from Cycle 1. Consideration should be given to the length of time since last full dose of intravenous riTUXimab **(Refer to local policy).**

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[1]	500ml 0.9% NaCl at a maximum rate of 400mg/hr[1]	**1 (only)**
1	**riTUXimab**	**1400mg (fixed dose in 11.7ml)**	**Subcutaneous injection (S/C) over 5 minutes into abdominal wall[2,3,4]**	**n/a**	**2-8**
1	DOXOrubicin[5]	50mg/m^2	IV Bolus	Into the side arm of a fast running 0.9% NaCl infusion	1-6
1	vinCRIStine[6]	1.4mg/m^2 (Max 2mg)	IV infusion	50ml 0.9% NaCl minibag over 15 minutes	1-6
1	cycloPHOSphamide	750mg/m^2	IV infusion[7]	250ml 0.9% NaCl over 30 minutes	1-6
1-5	prednisoLONE	100mg(**)	PO		1-6
[1]See table 1: Guidance for administration of riTUXimab**.**					
[2]Patient must have previously received a full dose of intravenous riTUXimab before being switched to subcutaneous formulation.					
[3]During treatment with subcutaneous riTUXimab, administer other subcutaneous drugs at alternative injection sites whenever possible.					

[4]Patients should be observed for at least 15 minutes following riTUXimab subcutaneous administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.
[5]Lifetime cumulative dose of DOXOrubicin is 450mg/m^2. **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below [i]and to the age of the patient**.
[6]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 Here
[7]cycloPHOSphamide may also be administered as an IV bolus over 5-10mins.
**Alternative steroid regimens may be used at consultant discretion.

Table 1: Guidance for administration of IV 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 [ii]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
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, cycloPHOSphamide, vinCRIStine sulphate, prednisoLONE, riTUXimab or any of the excipients
- A cumulative life-long dose of 450mg/m^2 of DOXOrubicin should only be exceeded with extreme caution as there is as risk of irreversible congestive heart failure
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Patients in a severely immunocompromised state
- Pregnancy or lactation

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
- ECG
- MUGA or ECHO should be considered prior to the administration of DOXOrubicin
- LDH, Uric acid, SPEP
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV*
  *See Adverse Effects/Regimen Specific Complications

Regular tests:

- FBC, renal and liver profile and LDH prior to each cycle
- Evaluate for peripheral neuropathy prior to each cycle
- MUGA or ECHO as clinically indicated

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 in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
< 1	and/or	< 75	Delay treatment until recovery. Consider treatment delay and/or add G-CSF adding G-CSF.

Renal and Hepatic Impairment:

Table 3: Recommended dose modification in 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%				
DOXOrubicin	No dose reduction required. Clinical decision in severe impairment.		**Bilirubin (micromol/L)**		**Dose**	
			20-51		50%	
			51-85		25%	
			>85		Omit	
			If AST 2-3 x ULN give 75% dose If AST > 3 x ULN give 50% dose			
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

Management of adverse events:

Table 4: Recommended dose modification based on adverse events

Adverse reactions		Recommended dose modification
riTUXimab		
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.
vinCRIStine		
Neurotoxicity*	Grade 1	100%
	Grade 2	Hold until recovery then reduce dose by 50%
	Grade 3-4	Omit

*Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

riTUXimab: Minimal **(Refer to local policy)**

DOXOrubicin/cycloPHOSphamide: High **(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 dose of riTUXimab .

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

Drugs	Dose	Route
Paracetamol	1g	PO 60 minutes prior to riTUXimab infusion
Chlorphenamine	10mg	IV bolus 60 minutes prior to riTUXimab infusion
Ensure glucocorticoid component of the treatment regimen (prednisoLONE 100mg) is given at least 30 minutes prior to riTUXimab infusion.		

Table 6: Suggested pre-medications prior to S/C riTUXimab :

Drugs	Dose	Route
Paracetamol	1g	PO 30 minutes prior to riTUXimab administration
Chlorphenamine	4mg	PO 30 minutes prior to riTUXimab administration
Ensure glucocorticoid component of the treatment regimen (prednisoLONE 100mg) is given at least 30 minutes prior to riTUXimab infusion.		

OTHER SUPPORTIVE CARE:

- Prophylactic regimen against vinCRIStine- induced constipation is recommended **(Refer to local policy).**
- G-CSF prophylaxis may be required.
- Tumour lysis syndrome prophylaxis **(Refer to local policy).**
- Anti-viral prophylaxis **(Refer to local policy).**
- Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRIStine **(Refer to local policy).**
- Proton-pump inhibitor during steroid treatment **(Refer to local policy).**
- PJP propylaxis **(Refer to local policy).**
- Patients should have an increased fluid intake of 2-3 litres on day 1 and 2 to prevent haemorrhagic cystitis associated with cycloPHOSphamide.

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.

riTUXimab

- **Hypersensitivity/Infusion Reactions/Severe Cytokine Release Syndrome**: Close monitoring is required throughout the first IV infusion **(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. Before starting riTUXimab subcutaneous injections, all patients must always have received at least one full dose of riTUXimab by intravenous infusion, using riTUXimab intravenous formulation. The highest risk of experiencing an administration related reaction is generally observed at cycle one. Beginning the therapy with riTUXimab intravenous infusion would allow a better handling of the administration reactions by slowing or stopping the intravenous infusion.
  If patients were not able to receive one full riTUXimab intravenous infusion dose prior to the switch, they should continue the subsequent cycles with riTUXimab intravenous formulation until a full intravenous dose is successfully administered. Therefore, the switch to riTUXimab subcutaneous formulation can only occur at the second or subsequent cycles of treatment.
  Administration related reactions have been observed in up to 50% of patients treated with riTUXimab subcutaneous formulation in clinical trials but the majority of reactions were mild or moderate and resolved without any specific treatment.
- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely while on riTUXimab.
- **Severe Mucocutaneous Reactions:** These include Steven-Johnson syndrome and Toxic Epidermal Necrolysis. Discontinue 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. The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of. If a patient develops PML, the dosing of riTUXimab must be permanently discontinued.
- **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 which may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis.
- **Vaccines:** 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 or whilst peripherally B cell depleted. Patients treated with riTUXimab may receive non-live vaccinations.

vinCRIStine

- **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. 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 and DOXOrubicin cause pain and possible tissue necrosis if extravasated **(Refer to local policy).**

DRUG INTERACTIONS:

- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-Flourouracil, cycloPHOSphamide or PACLItaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3A4 inhibitors/inducers.

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Version	Date	Amendment	Approved By
1	27/07/2021		NCCP Lymphoid Clinical Advisory Group
2	01/11/2023	Reviewed. Updated order of administration and number of cycles. Updated emetogenic potential section.	Prof Maccon Keane, Prof Elisabeth Vandenberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.
Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient

[ii] 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.