(*riTUXimab)-Gemcitabine Cyclophosphamide vinCRIStine and PrednisoLONE (*R)-GCVP) Therapy–21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of high-grade non-Hodgkin Lymphoma in patients who are unsuitable for R-CHOP due to impaired cardiac function or other co-morbidities*	C85	00737a	Hospital

*riTUXimab to be included in CD20 positive patients

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 is repeated at 21 day intervals for up to 6 cycles or until disease progression or unacceptable toxicity develops.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	riTUXimab **(CD20+ patients only)**	375mg/m^2	IV infusion[1] Observe post infusion[1]	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[1]	Every 21 days for 6 cycles
1	Cyclophosphamide	750mg/m^2	IV infusion[2]	250 ml 0.9% NaCl over 30 minutes	Every 21 days for 6 cycles
1	vinCRIStine[3]	1.4mg/m^2 (Max 2mg)	IV infusion	50ml minibag 0.9% NaCl over 15 minutes	Every 21 days for 6 cycles
1, 8	Gemcitabine[4]	750mg/m^2	IV infusion	250 ml 0.9% NaCl over 30 minutes	Cycle 1
1, 8	Gemcitabine	875mg/m^2	IV infusion	250 ml 0.9% NaCl over 30 minutes	Cycle 2
1, 8	Gemcitabine	1000mg/m^2	IV infusion	250 ml 0.9% NaCl over 30 minutes	Cycle 3 and onwards
1-5	PrednisoLONE	100mg(**)	PO		Every 21 days for 6 cycles
9 onwards	G-CSF[5]	5mcg/kg	SC (Round to nearest whole syringe)	Daily injection until ANC >1x10^9/L for 7 consecutive days	

[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 here

[4] The gemcitabine dose is escalated to 875 mg/m^2 for Cycle 2 and then 1000 mg/m^2 for successive cycles if no toxicity is observed.

[5] G-CSF support is required with this regimen (**Refer to local policy** or see suggested support above).

**Alternative steroid regimens may be used at consultant discretion.

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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
- Adequate haematological, renal and liver status

EXCLUSIONS:

- Hypersensitivity to cyclophosphamide, vinCRIStine sulphate, prednisolone, riTUXimab, gemcitabine or any of the excipients
- Marked persisting myelosuppression and/or severe stomatitis induced by previous treatment with other cytotoxic agents and/or radiation
- 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.

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TESTS:

Baseline tests:

- FBC, renal and liver profile
- Cardiac function if clinically indicated*
- 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
- Diabetic patients should increase frequency of monitoring of blood glucose whilst taking high dose steroids
- Cardiac function 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)	Cyclophosphamide and vinCRIStine dose	Gemcitabine dose
≥ 1.0	and	≥ 75	100%	100%
0.5 - < 1.0	and	50 - <75	75%	75%
<0.5	and	<50	Delay until ANC ≥1 and platelets ≥ 75, then 100% dose.	Day 1: Delay until ANC ≥1 and platelets ≥ 75, then 100% dose. Day 8: Omit dose
Dose modifications due to haematological toxicities should only be made according to the blood count on the day of treatment.				
Febrile neutropenia			Delay until recovery. If recurrent, then 75% dose in subsequent courses.	Delay until recovery. If recurrent, then 75% dose in subsequent courses.
Haemorrhage with thrombocytopenia			Delay until recovery, then 75% dose in subsequent courses.	Delay until recovery, then 75% dose in subsequent courses.

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Renal and Hepatic Impairment:

Table 3: 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%				
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
Gemcitabine	**CrCl (ml/min)**	**Dose**	If bilirubin ≥27 micromol/L, either start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring.			
	≥ 30	100%				
	< 30	Consider dose reduction/Clinical decision				

Management of adverse events:

Table 4: Dose Modification for Adverse Events

Adverse reactions		**Recommended dose modification**
Grade 3		75% in subsequent courses.
Grade 4		Delay until recovery, then 50% in subsequent courses.
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.

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SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

riTUXimab: Minimal **(Refer to local policy)**
Cyclophosphamide: Moderate **(Refer to local policy)**
vinCRIStine: Minimal **(Refer to local policy)**
Gemcitabine: Low **(Refer to local policy)**

PREMEDICATIONS:

- None for GCVP portion.
- 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 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		

OTHER SUPPORTIVE CARE:

- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy)**
- G-CSF prophylaxis is required with this regimen **(Refer to local policy)**
- 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)**
- Patients should have an increased fluid intake of 2-3 litres on day 1 and 2 to prevent haemorrhagic cystitis associated with cyclophosphamide.

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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:

- **Hepatitis B Reactivation**: This has been reported in patients receiving riTUXimab including fulminant hepatitis with fatal outcome.
- **Hypersensitivity/Infusion Reactions:** Close monitoring is required throughout the first 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.
- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely while on 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, hyperphosphataemia, 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 normalised.
- **Severe Mucocutaneous Reactions:** These include Stevens-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.

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- **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.
- **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 if extravasated **(Refer to local policy).**

Gemcitabine:

- **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
- **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.
- **Irreversible renal failure** associated with haemolytic uraemic syndrome may occur rarely with gemcitabine. Use caution with pre-existing renal impairment.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.
- 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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Version	Date	Amendment	Approved By
1	12/09/2022		NCCP Lymphoid Clinical Advisory Group

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.

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