(R*)- miniCHOP Therapy – 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of Non Hodgkin Lymphoma in patients aged greater than 80 or with significant co-morbidities*	C85	00436a	riTUXimab: Hospital cycloPHOSphamide: Hospital DOXOrubicin: Hospital vinCRIStine: Hospital

* riTUXimab to be included in all CD20 positive patients

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 for a **maximum of 6 cycles** or until disease progression or unacceptable toxicity develops.

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

Day	Drug	Dose	Route	Diluent & Rate
1	riTUXimab (CD20+ patients only)	375mg/m^2	IV infusion[1] Observe post infusion[1]	500ml 0.9% NaCl at a maximum rate of 400mg/hr[1]
1	DOXOrubicin[2]	25mg/m^2	IV Bolus over 15 mins	Into the side arm of a fast running 0.9% NaCl infusion
1	vinCRIStine[3]	1mg	IV infusion	50ml minibag 0.9% NaCl over 15 minutes
1	cycloPHOSphamide	400mg/m^2	IV infusion[4]	250ml 0.9% NaCl over 30 minutes
1-5	prednisoLONE	40mg/m^2(**)	PO	
[1] See table 1 for administration of riTUXimab				
[2]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 below[i] and to the age of the patient**				
[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]cycloPHOSphamide may also be administered as an IV bolus over 5-10 mins				
** 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[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
- ECOG 0-2
- Patients over the age of 80 years, or with significant co-morbidities

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, cycloPHOSphamide, riTUXimab, vinCRIStine sulphate 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

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:

- Blood, renal and liver profile
- LDH, blood glucose, Uric Acid, SPEP
- ECG
- MUGA or ECHO
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV

***See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation**

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Regular tests:

- Blood, renal and liver profile prior to each cycle
- 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

Haematological:

Table 2: Dose modification for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
<1.0	and/or	<100	Consider treatment delay until count recovery to ANC ≥1.0 x 10^9/L and platelets ≥100x 10^9/L with a max of 28 days between 2 consecutive cycles Consider primary prophylaxis with 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%				
DOXOrubicin	Dose reduce in severe renal impairment		**Total Bilirubin (micromol/L)**	**Dose**		
			20-51	50%		
			51-85	25%		
			>85	Omit		
			If AST 2-3 x normal, give 75% dose.			
			If AST >3x 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

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Neurotoxicity:

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

Symptom	Dose of vinCRIStine
Grade 1	100%
Grade 2	Discuss reducing or withholding vinCRIStine with Consultant

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).**
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 infusion of riTUXimab.

Table 6: 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 40mg/m^2) is given at least 30 minutes prior riTUXimab infusion		

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OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump inhibitor **(Refer to local policy)**
- Consider PJP 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)**
- 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.

riTUXimab

- **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.
- **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.
- **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.
- **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.
- **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.

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- **Progressive multifocal leukoencephalopathy (PML)**: Use of riTUXimab may be associated with an increased risk of PML. If a patient develops PML, the dosing of riTUXimab must be permanently discontinued.
- **Immunisations**:
  - 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

vinCRIStine and DOXOrubicin

- **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**: DOXOrubicin and vinCRIStine 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 CYP3AR inhibitors/inducers.

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2. Chaganti S et al. BSH Guidelines for the management of diffuse large B- cell Lymphoma. BJH 2016; 174(1):43-56
3. Vinca alkaloids + Azoles. Stockley's Drug Interactions 11th Edition
4. Krens S D, Lassche,Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Onco/2019; 20:e201-08. https://doi.org/10.1016/S1470-2045(19)30145-7
5. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at:

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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

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Version	Date	Amendment	Approved By
1	05/11/2018		Dr Ezzat Elhassadi Prof Maccon Keane
2	28/07/2021	Regimen review Updated management of hepatic impairment for cyclophosphamide Updated wording regarding management of hepatitis B reactivation Updated adverse events/regimen specific complications with regards to riTUXimab Updated emetogenic potential	Prof Ezzat Elhassadi Prof Maccon Keane
3	15/02/2023	Amended emetogenic potential. Standardised pre-medications table.	Prof Maccon Keane
4	01/11/2023	Updated administration order in treatment table.	Prof Ezzat Elhassadi Prof Maccon Keane

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.

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