(*riTUXimab) cycloPHOSphamide, DOXOrubicin, vinCRIStine and prednisoLONE (*R)-CHOP Therapy – 14 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of Non Hodgkin's Lymphoma (NHL)*	C85	00409	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 consists of R-CHOP administered every 14 days for 6 cycles followed by riTUXimab administered for an additional 2 cycles or until disease progression or unacceptable toxicity develops.

G-CSF support (using standard or pegylated form) is required with all cycles of R-CHOP-14 days.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) 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% NaCl at a maximum rate of 400mg/hr[1]	1-8
1	DOXOrubicin[2]	50mg/m^2	IV Bolus	Into the side arm of a fast running 0.9% NaCl infusion	1-6
1	vinCRIStine[3]	1.4mg/m^2 (Max 2mg)	IV infusion	50ml minibag 0.9% NaCl over 15 minutes	1-6
1	cycloPHOSphamide	750mg/m^2	IV infusion[4]	250 ml 0.9% NaCl over 30 minutes	1-6
1-5	prednisoLONE	100mg(**)	PO		1-6
G-CSF support (using standard or pegylated form) is required with all cycles of R-CHOP-14 days.					
[1] See Table 1: Guidance 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 outlined 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 5-10mins.					
**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 [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 riTUXimab, DOXOrubicin, cycloPHOSphamide, vinCRIStine sulphate, prednisoLONE, 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 a 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 a consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Blood glucose
- 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	Dose modification not generally indicated. Consider treatment delay.

Renal and Hepatic Impairment:

Table 3: Recommended dose modification in Renal and Hepatic Impairment:

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td>riTUXimab</td><td colspan="2">No dose adjustment necessary.</td><td colspan="4">No dose adjustment necessary.</td></tr>
<tr><td rowspan="4">cycloPHOSphamide</td><td>CrCL (ml/min)</td><td>Dose</td><td colspan="4" rowspan="4">Severe impairment: Clinical decision.</td></tr>
<tr><td>>20</td><td>100%</td></tr>
<tr><td>10-20</td><td>75%</td></tr>
<tr><td><10</td><td>50%</td></tr>
<tr><td rowspan="5">DOXOrubicin</td><td colspan="2" rowspan="5">No dose reduction required.
Clinical decision in severe impairment.</td><td colspan="2">Bilirubin (micromole/L)</td><td colspan="2">Dose</td></tr>
<tr><td colspan="2">20-51</td><td colspan="2">50%</td></tr>
<tr><td colspan="2">51-85</td><td colspan="2">25%</td></tr>
<tr><td colspan="2">>85</td><td colspan="2">Omit</td></tr>
<tr><td colspan="4">If AST 2-3 x ULN give 75% dose
If AST > 3 x ULN give 50% dose</td></tr>
<tr><td rowspan="4">vinCRIStine</td><td colspan="2" rowspan="4">No dose reduction required.</td><td>Bilirubin (micromol/L)</td><td></td><td>AST/ALT</td><td>Dose</td></tr>
<tr><td>26-51</td><td>or</td><td>60-180</td><td>50%</td></tr>
<tr><td>>51</td><td>and</td><td>Normal</td><td>50%</td></tr>
<tr><td>>51</td><td>and</td><td>>180</td><td>Omit</td></tr>
</table>

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:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting linked here

riTUXimab: Minimal **(Refer to local policy)**
DOXOrubicin/cycloPHOSphamide: High **(Refer to local policy)**
vinCRIStine: Minimal **(Refer to local policy)**
Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

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 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 riTUXi infusion		

OTHER SUPPORTIVE CARE:

- Prophylactic regimen against vincristine-induced constipation is recommended **(Refer to local policy)**.
- G-CSF prophylaxis is required, please discuss with consultant
- 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 prophylaxis **(Refer to local policy).**
- Patients should have an increased fluid intake of 2-3 litres on day 1and 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.
- **Extravasation:** vinCRIStine and DOXOrubicin causes pain and possible tissue necrosis if extravasated **(Refer to local policy).**

riTUXimab:

- **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, 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 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.
- **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.

DOXOrubicin:

- **Cardiotoxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

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.

REFERENCES:

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Version	Date	Amendment	Approved By
1	15/03/2017		Prof Maccon Keane
2	27/03/2019	Updated to new NCCP regimen template Updated baseline tests and supportive care Updated dosing modifications in hepatic impairment	Prof Maccon Keane
3	31/12/2019	Updated recommendation for hepatic impairment	Prof Maccon Keane
4	04/10/2021	Reviewed. Amended emetogenic potential, added to adverse effects (DOXOrubicin)	Prof Maccon Keane
5	27/10/2023	Updated treatment table and emetogenic potential	Prof Maccon Keane, Prof Elisabeth Vandenberghe
5a	05/07/2024	Updated information in the Emetogenic Potential section.	NCCP

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.