Nordic Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Mantle Cell Lymphoma	C83	00393a	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 with R-CHOP (21 day cycle) is alternated with riTUXimab and high dose cytarabine (21 day cycle) for a total of 6 cycles (i.e. Cycle 1, 3 and 5 = R-CHOP and Cycle 2, 4, and 6 = riTUXimab and high dose cytarabine). *(Please Note the dosing in R-CHOP in this regimen)*

Cycle	Regimen	Interval
1	R-CHOP	21 days
2	R-High dose cytarabine	21 days
3	R-CHOP	21 days
4	R-High dose cytarabine	21 days
5	R-CHOP	21 days
6	R-High dose cytarabine	21 days

G-CSF (5mcg/kg/day) is administered on days 8-12 of R-CHOP and days 6-12 of R-cytarabine to cover nadir.

The Nordic Therapy regimen may be consolidated with a BEAM PBSCT **(Ref NCCP regimen 00408 BEAM Therapy).**
Consider riTUXimab maintenance every 2 months for 3 years in transplanted Mantle Cell Lymphoma patients.

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

A. **R-CHOP: Cycles 1, 3, 5.**

Day	Drug	Dose	Route	Diluent & Rate
1	riTUXimab	375mg/m^2	IV infusion[a] Observe post infusion[a]	500ml 0.9% NaCl at a maximum rate of 400mg/hr[a]
1	DOXOrubicin[b, c]	75mg/m^2	IV Bolus	Into the side arm of a 250ml 0.9% NaCl infusion
1	vinCRIStine[d]	1.4mg/m^2 (Max 2mg dose)	IV infusion	50ml 0.9% NaCl infused over 15mins
1	cycloPHOSphamide[b]	1200mg/m^2	IV infusion[e]	250ml 0.9% NaCl over 30 mins
1-5	prednisoLONE	100mg	PO	
8-12	G-CSF (Round to nearest whole syringe)	5mcg/kg	SC	

[a] See Table 1: Guidance for administration of riTUXimab.

[b] Consideration could be given to the modification of the standard R-CHOP regimen above to reduce the dose of cycloPHOSphamide to 750mg/m^2 and the dose of DOXOrubicin to 50mg/m^2.

[c] 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.

[d] 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.

[e] cycloPHOSphamide may also be administered as an IV bolus over 2-15 mins.

B. **riTUXimab and High Dose Cytarabine: Cycles 2, 4, 6.**

Day	Drug	Dose	Route	Diluent & Rate
1	riTUXimab	375mg/m^2	IV infusion[a] Observe post infusion[a]	500ml 0.9% NaCl at a maximum rate of 400mg/hr[a]
1, 2 **(4 doses)**	[b]Cytarabine	3000mg/m^2 **BD**	IV infusion	500ml NaCl 0.9% over 1 hour
6-12	G-CSF (Round to nearest whole syringe)	5mcg/kg	SC	

[a] See Table 1: Guidance for administration of riTUXimab

[b] Patients > 60 years of age should receive cytarabine 2000mg/m^2 BD

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 status 0-2

EXCLUSIONS:

- Hypersensitivity to riTUXimab, cycloPHOSphamide, DOXOrubicin, vinCRIStine, prednisoLONE, cytarabine or any of the excipients or to murine proteins.
- 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 experienced in the treatment of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid, SPEP
- ECG
- MUGA or ECHO should be considered prior to the administration of DOXOrubicin
- 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 neurotoxicity prior to dosing with vinCRIStine
- Cardiac function if 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

Renal and Hepatic Impairment:

Table 2: Recommended dose modifications in renal and hepatic Impairment:

Drug	Renal Impairment		Hepatic Impairment	
riTUXimab	No dose modification required		No dose modification required	
cycloPHOSphamide	**CrCl (ml/min)**	**Dose**	Mild and moderate: no need for dose adjustment expected Severe: not recommended, due to risk of reduced efficacy	
	≥30	No dose adjustment needed		
	10-29	Consider 75% of original dose		
	<10	Not recommended, if unavoidable consider 50% of original dose		
	Haemodialysis	Not recommended, if unavoidable consider 50% of original dose		
DOXOrubicin	**CrCl (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**	**Dose**
			20-50	50% of original dose
	>10	No dose adjustment needed	51-86	25% of original dose
	<10	No dose adjustment expected	>86 or Child-Pugh C	Not recommended
	Haemodialysis	75% of original dose may be considered		
vinCRIStine	No dose modification expected Haemodialysis: No need for dose adjustment expected		**Total Bilirubin (micromol/L)**	**Dose**
			>51	50%
Cytarabine	**CrCl (ml/min)**	**Dose**	Mild and moderate: no need for dose adjustment is expected Severe: consider 25-50% of the original dose and increase if tolerated	
	≥60	No dose adjustment needed		
	31-59	50% of original dose		
	≤30	Not recommended		
	Haemodialysis	50% of original dose, start haemodialysis 4 to 5 hours after administration		

Management of adverse events:

Neurotoxicity:

Table 3: 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 4: Dose modification schedule of riTUXimab based on adverse events

Adverse reactions	Recommended dose modification
Severe infusion related reaction (e.g. dyspnoea, bronchospasm, hypotension or hypoxia) First occurrence Second 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 discontinuing treatment. Consider coverage with steroids for those who are not already receiving steroids.
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/DOXOrubicin: High **(Refer to local policy)**
vinCRIStine: Minimal **(Refer to local policy)**
Cytarabine: Moderate **(Refer to local policy)**

- Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.

PREMEDICATIONS:

R-CHOP: Cycles 1, 3, 5:

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 in Cycles 1,3,5.

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		

riTUXimab and High Dose Cytarabine: Cycles 2, 4, 6.
Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of riTUXimab. Consider the inclusion of a glucocorticoid in patients not receiving glucocorticoid containing chemotherapy.

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
Hydrocortisone	100mg	IV bolus 60 minutes prior to riTUXimab infusion

- To prevent a chemical induced conjunctivitis developing with **cytarabine**, prednisoLONE eye drops (e.g. Pred Mild®) 1-2 drops per eye 4 hourly during waking hours prior to cytarabine and continued 5 days post treatment should be considered.

OTHER SUPPORTIVE CARE:

- Prophylactic regimen against vinCRIStine induced constipation is recommended **(Refer to local policy)**.
- Proton pump inhibitor while on prednisoLONE **(Refer to local policy).**
- Tumour lysis syndrome prophylaxis **(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 (6) **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Please refer to:
NCCP regimen 00307 (riTUXimab) cycloPHOSphamide, DOXOrubicin, vinCRIStine and prednisoLONE (R)-CHOP) Therapy– 21 days
NCCP regimen 00365 High Dose Cytarabine Therapy and
NCCP 00542 riTUXimab 375mg/m^2 Combination Therapy – 21 day

For detailed information on adverse effects/regimen specific complications for these regimens.

DRUG INTERACTIONS:

- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- There is a diminished response to vaccines and increased risk of infection with live vaccines. Vaccination with live virus vaccines is not recommended for patients on riTUXimab therapy.
- 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).

- Consider increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4 by aprepitant.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. 3rd Nordic Mantle cell lymphoma phase II protocol version February 2007, Amendment 1, 2 and 2 included]
3. 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
4. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: 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	08/03/2017		Prof E Vandenberghe Prof Maccon Keane
2	27/03/2019	Updated to new NCCP regimen template. Standardisation of treatment table and baseline tests Updated dosing modifications in hepatic impairment	Prof E Vandenberghe Prof Maccon Keane
3	04/10/2021	Reviewed. Treatment table: Amended cyclophosphamide route of administration and added footnote. Added to exclusions (hypersensitivity). Updated recommendations for cyclophosphamide hepatic impairment. Amended emetogenic potential.	Prof Maccon Keane
4	20/12/2023	Updated treatment table admin order. Updated emetogenic section. Updated drug interactions section. Updated renal and hepatic dose modifications to Krens recommendations.	Prof E Vandenberghe 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.