(*riTUXimab)-Gemcitabine, cycloPHOSphamide, vinCRIStine and prednisoLONE (*R)-GCVP) Therapy–21 days[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved 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	N/A

*riTUXimab to be included in CD20 positive patients
** This is for post 2012 indications only

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 systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	riTUXimab **(CD20+ patients only)**	375mg/m^2	IV infusion Observe post infusion	500mL 0.9% NaCl at a maximum rate of 400mg/hour[a]	Every 21 days for 6 cycles
1	cycloPHOSphamide	750mg/m^2	IV infusion[b]	250mL 0.9% NaCl over 30 minutes	Every 21 days for 6 cycles
1	vinCRIStine[c]	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[d]	750mg/m^2	IV infusion	250mL 0.9% NaCl over 30 minutes	Cycle 1
1, 8	Gemcitabine	875mg/m^2	IV infusion	250mL 0.9% NaCl over 30 minutes	Cycle 2
1, 8	Gemcitabine	1000mg/m^2	IV infusion	250mL 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[e]	5mcg/kg	SC (Round to nearest whole syringe)	Daily injection until ANC >1x10^9/L for 7 consecutive days	
[a] See Table 1: Guidance for administration of riTUXimab					
[b] cycloPHOSphamide may also be administered as an IV bolus over 5-10 minutes					

[c] 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 Available on the NCCP website
[d] 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.
[e] 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.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Table 1: Guidance for administration of riTUXimab

The recommended initial rate for infusion is 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions can be infused at an initial rate of 100 mg/hour, and increased by 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour. 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 Available on the NCCP website 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.

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 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%	Delay until recovery, then 75%

	dose in subsequent courses.	dose in subsequent courses.

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment
riTUXimab [a]	Renal impairment: no need for dose adjustment is expected Haemodialysis: no dose adjustment is needed		No need for dose adjustment is expected
cycloPHOSphamide [b]	**CrCl (mL/min)**	**Dose**	Mild and moderate: no need for dose adjustment is expected Severe: not recommended, due to risk of reduced efficacy
	≥ 30	No dose adjustment is needed	
	10-29	Consider 75% of the original dose	
	< 10	Not recommended, if unavoidable consider 50% of the original dose	
	Haemodialysis	Not recommended, if unavoidable consider 50% of the original dose.	
vinCRIStine [c]	Renal impairment: no need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		Bilirubin > 51 micromol/L: 50% of original dose
Gemcitabine [d]	**CrCl (mL/min)**	**Dose**	If total bilirubin <27 µmol/L: no dose adjustment is needed If total bilirubin ≥27 µmol/L, either start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring.
	≥ 30	No dose adjustment is needed	
	< 30	No need for dose adjustment is expected	
	Haemodialysis	No need for dose adjustment is expected. Start haemodialysis 6-12 hours after administration.	

[a] riTUXimab (renal and hepatic from Giraud et al (2023))
[b] cycloPHOSphamide (renal and hepatic from Giraud et al (2023))
[c] vinCRIStine (renal and hepatic from Giraud et al (2023))
[d] Gemcitabine (renal from Giraud et al (2023); hepatic (based on Giraud et al (2023) and as agreed with clinical reviewer)

Management of adverse events:

Table 4: Dose Modification for Adverse Events

Adverse reactions		Recommended dose modification
Grade 3 (except nausea & vomiting, alopecia)		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.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website :

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

cycloPHOSphamide: Moderate **(Refer to local policy)**

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

Gemcitabine: Low **(Refer to local policy)**

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) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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.

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS

- **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.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

COMPANY RESOURCES/Useful Links:

riTUXimab:

- Please refer to the HPRA website (www.hpra.ie) for the individual product for list of relevant support resources.

REFERENCES:

1. Fields P et al. First Analysis of a Phase II Study of Rituximab-Gemcitabine, Cyclophosphamide, Vincristine and Prednisolone (RGCVP) for Diffuse Large B Cell Lymphoma (DLBCL) Patients Considered Unsuitable

for Anthracycline Containing ChemoImmunotherapy. An NCRI Lymphoma Clinical Studies Group Trial. Blood (2011) 118 (21): 1634. http://doi.org/10.1182/blood.V118.21.1634.1634
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
3. 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
4. Vinca alkaloids + Azoles. Stockley's Drug Interactions 11th Edition
5. riTUXimab Summary of Product Characteristics. Last updated 29/11/2023. Accessed 14/02/2024. Available at: https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf
6. cycloPHOSphamide Summary of Product Characteristics. Last updated 21/12/2018. Accessed 15/02/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-002_21122018112109.pdf
7. vinCRIStine Summary of Product Characteristics. Last updated 09/10/2023. Accessed 15/02/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-232-001_09102023163547.pdf
8. Gemcitabine Summary of Product Characteristics. Last updated 18/04/2019. Accessed 15/02/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-039-002_18042019163628.pdf

Version	Date	Amendment	Approved By
1	12/09/2022		NCCP Lymphoid Clinical Advisory Group
2	06/06/2024	Regimen reviewed.Aligned Table 3: Dose modification in renal and hepatic impairment to Giraud et al (2023).Updated ADVERSE EFFECTS and DRUG INTERACTIONS sections to align with NCCP Standardisation. Separated REGIMEN SPECIFIC COMPLICATIONS section.Added COMPANY RESOURCES/Useful Links section.	Prof Ezzat Elhassadi
2a	27/11/2024	Updated emetogenic potential section with standard wording.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of riTUXimab and gemcitabine in Ireland. Patients 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" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy

[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.