*riTUXimab, dexAMETHasone, Cytarabine and Oxaliplatin ((*R)-DHAOx) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status**
Treatment of relapsed Non Hodgkin's Lymphoma*	C85	00834a	N/A
Treatment of relapsed Hodgkin's Lymphoma	C81	00834b	N/A
First line treatment of mantle cell lymphoma	C83	00834c	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 with riTUXimab and oxaliplatin are administered on day 1, and cytarabine is administered twice daily on day 2 of a 21 day cycle for up to 6 cycles.

If regimen is being used prior to autologous SCT, peripheral blood stem cell harvesting is usually performed:

- on cycle 2 or 3 when used in relapsed/refractory lymphoma
- on cycle 3 or 4 when used for first line therapy in MCL.

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

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1-4	dexAMETHasone	40mg	PO	n/a	Every 21 days
1	riTUXimab	375mg/m^2	IV infusion[a] Observe post infusion[a]	500mL 0.9% sodium chloride at a maximum rate of 400mg/hour[a]	Every 21 days
1	Oxaliplatin	130mg/m^2	IV infusion	500mL glucose 5%[b] over 2 hours[c]	Every 21 days
2	Cytarabine	2000mg/m^2 **AM**	IV infusion	1000mL 0.9% NaCl over 2 hours	Every 21 days
2	Cytarabine	2000mg/m^2 **PM** (12 hours after start of first cytarabine infusion)	IV infusion	1000mL 0.9% NaCl over 2 hours	Every 21 days
6 onwards	G-CSF[d]	5mcg/kg[e] (round to nearest whole syringe)	SC	Continued until ANC >1x10^{9}/L for 2 consecutive days	n/a
[a]See Table 1: Guidance for administration of riTUXimab.					
[b]Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with normal saline. For oxaliplatin doses ≤ 104mg use 250ml glucose 5%.					
[c] Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction.					
[d] G-CSF support is required with this regimen **(Refer to local policy or see suggested support above).**					
[e] Standard mobilisation dose of g-CSF post R-DHAOx mobilisation is 5 mcg/Kg; however this must be verified on an individual basis with local harvesting centre (**Refer to local policy).**					

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/hr. 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[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

EXCLUSIONS:

- Hypersensitivity to riTUXimab, cytarabine, oxaliplatin or any of the excipients
- Pregnancy
- Breastfeeding

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:

- FBC, U&Es, LFTs, LDH, Urate
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV
  *See Regimen Specific Complications re hepatitis B reactivation

Regular tests:

- FBC, U&Es, LFTs, LDH prior to each cycle
- Regular glucose monitoring while receiving steroid therapy - urinalysis daily. If glucose detected in urinalysis, monitor blood glucose daily

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.

Haematological:

Table 2: Dose modification for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
<1	and/or	<100	Discuss with Consultant

Renal and Hepatic Impairment:

Table 3: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment	
riTUXimab	No need for dose adjustment is expected Haemodialysis: No dose adjustment is needed		No need for dose adjustment is expected	
Oxaliplatin	**CrCl (ml/min)**	**Dose**	No dose adjustment is needed	
	≥30	No dose adjustment is needed		
	<30	Consider 50% of the original dose		
	Haemodialysis	Consider 50% of the original dose, haemodialysis within 90 minutes after administration.		
Cytarabine	**CrCl (ml/min)**	**Dose**	Mild and moderate	No need for dose adjustment is expected
	≥60	No dose adjustment is needed	Severe	Consider 25-50% of the original dose and increase if tolerated
	31-59	50% of the original dose		
	<30	Not recommended		
	Haemodialysis	50% of the original dose, start haemodialysis 4-5 hours after administration		
riTUXimab (renal and hepatic - Giraud et al 2023) Oxaliplatin (renal and hepatic - Giraud et al 2023) Cytarabine (renal and hepatic - Giraud et al 2023)				

Management of adverse events:

Table 4: Dose Modification of oxaliplatin due to oxaliplatin induced peripheral neuropathy

Toxicity Grade	Dose Modification of oxaliplatin
Grade 1	100%
Grade 2 paraesthesia persisting until next cycle	Reduce dose to 100mg/m^2
Grade 3 paraesthesia > 7 days but resolved before next cycle	Reduce dose to 100mg/m^2
Grade 3 paraesthesia persisting until next cycle	Discontinue oxaliplatin
Grade 4 of any duration	Discontinue oxaliplatin

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting available on the NCCP website

riTUXimab: Minimal (**Refer to local policy)**
Oxaliplatin: Moderate (**Refer to local policy)**
Cytarabine: Moderate (**Refer to local policy)**

For information:
Within NCIS regimens, anti-emetics have been standardised by the 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:

- 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.
- 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 (dexAMETHasone 40mg) is given at least 30 minutes prior to riTUXimab infusion		

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Mouthcare **(Refer to local policy)**

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

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3. Chau, I., et al. An oxaliplatin-based chemotherapy in patients with relapsed or refractory intermediate and high-grade non-Hodgkin's lymphoma. Br J Haematol 2001. 115(4):786-792.
4. Lignon J, et al. Rituximab, Dexamethasone, Cytarabine and Oxaliplatin (R-DHAX) is an Effective and Safe Salvage Regimen in Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma. Clin Lymphoma Myeloma Leuk, 2010 10(4):262-269
5. Witzig TE, et al. Long-term follow-up of chemoimmunotherapy with rituximab, oxaliplatin, cytosine arabinoside, dexamethasone (ROAD) in patients with relapsed CD20+ B-cell non-Hodgkin lymphoma: Results of a study of the Mayo Clinic Cancer Center Research Consortium (MCCRC) MC0485 now known as academic and community cancer research united (ACCRU). Am J Hematol, 2017 92(10):1004-1010
6. Rigacci, L., et al. Oxaliplatin-based chemotherapy (dexamethasone, high-dose cytarabine, and oxaliplatin) +/-rituximab is an effective salvage regimen in patients with relapsed or refractory lymphoma. Cancer 2010. 116(19):4573-4579.
7. 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/
8. 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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10. Oxaliplatin 5mg/ml concentrate for solution for infusion Summary of Product Characteristics. Last updated: 11/10/2022. Accessed Nov 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-049-001_11102022125814.pdf
11. Cytarabine 100mg/ml Solution for Injection Summary of Product Characteristics. Last updated: 18/08/2021. Accessed Nov 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-200-002_18082021114137.pdf

Version	Date	Amendment	Approved By
1	24/01/2025		NCCP Lymphoid CAG

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The rapid infusion is an unlicensed means of administration of riTUXimab for the indication 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.