R-Gemcitabine (1000mg/m^2) Oxaliplatin Therapy[i] - 14 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Relapsed or refractory CD20 positive diffuse large B cell lymphoma in patients ineligible for stem cell transplant.	C83	00506a	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 is administered every **14 days** for up to **eight cycles** or until disease progression or unacceptable toxicity develops

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[2]	500ml 0.9% NaCl at a maximum rate of 400mg/hr[1,3,4]	Every 14 days
2	Gemcitabine	1000mg/m^2	IV infusion	250ml 0.9% NaCl over 100mins (i.e. rate of 10mg/m^2/min)	Every 14 days
2	Oxaliplatin[5]	100mg/m^2	IV infusion	500ml glucose 5% over 2 hours	Every 14 days

[1]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.

[2]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.

[3]Rituximab should be diluted to a final concentration of 1-4mg/ml.

[4] Rapid rate infusion schedule[ii] 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.

[5] Oxaliplatin is incompatible with 0.9% NaCl. Do not piggyback or flush lines with normal saline
For oxaliplatin doses ≤ 104mg use 250ml glucose 5%.
Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dysaesthesia reaction

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to riTUXimab, gemcitabine, oxaliplatin or any of the excipients
- Severe renal impairment (creatinine clearance < 30ml/min)
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- Cardiac function if clinically indicated
- Virology screen-Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation
- Creatinine clearance as clinically indicated

Regular tests:

- FBC, renal, liver profile and LDH prior to each cycle

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:

Prior to commencing a new treatment cycle (i.e. day 1), ANC must be >1 x 10^9/L and platelets > 100 x 10^9/L.

Table 1: Dose modifications for haematological toxicity

Day	ANC (x 10^9 /L)		Platelet count (x 10^9 /L)	Recommended dose of Gemcitabine
1	≥1	and	≥ 100	100 %
1	<1	or	<100	Delay 1 week, or until resolution. Consider the addition of G-CSF to subsequent cycles.
Febrile neutropenia				Consider the addition of G-CSF to subsequent cycles

Renal and Hepatic Impairment:

Table 2: Dose modifications in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
riTUXimab	No dose adjustment necessary		No dose adjustment necessary
Gemcitabine	**CrCl (ml/min**	**Dose**	AST elevations do not seem to cause dose limiting toxicities. If bilirubin > 27micromol/L, initiate treatment with dose of 800 mg/m^2.
	>30	100%	
	<30	Consider dose reduction. Clinical decision	
Oxaliplatin	**CrCl (ml/min)**	**Dose**	Little information available. Probably no dose reduction necessary Clinical decision
	>30	Treat at normal dose and monitor renal function	
	<30	Contraindicated	

Management of adverse events:

Table 3: 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
Oxaliplatin	
Neurotoxicity including peripheral neuropathy Grade 3 persisting for > 7 days Grade 4	Reduce oxaliplatin dose by 25%
Laryngo-pharyngeal dysesthesia	Increase infusion time from 2 to 6 hrs

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

RiTUXimab Minimal **(refer to local policy)**
Oxaliplatin Moderate **(refer to local policy)**
Gemcitabine Low **(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 2: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to riTUXimab infusion
Chlorphenamine	10mg	IV bolus 60minutes prior to riTUXimab infusion
Hydrocortisone	100mg	IV bolus 60 minutes prior to riTUXimab infusion

OTHER SUPPORTIVE CARE:

Tumour lysis syndrome prophylaxis **(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.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.

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**.**
- **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.
- **Cardiac Disorders**: Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely.
- **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 psy**chiatric symptoms). Patients should also be advise**d 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 that may further predispose patients to serious infections. Consideration should be given to the use of antimicrobial prophylaxis**.**

- **Hepatitis B Reactivation:** 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.
- **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.
- **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

Gemcitabine

- **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
- **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.
- **Renal Toxicity: Irreversible renal failure** associated with haemolytic uraemic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal impairment.

Oxaliplatin

- **Platinum Hypersensitivity**: Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations, the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated.
- **Laryngopharyngeal dysesthesia:** An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome
- **Extravasation:** Oxaliplatin causes irritation 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.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Gemcitabine	L01BC05
riTUXimab	L01XC02
Oxaliplatin	L01XA03

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Version	Date	Amendment	Approved By
1	13/08/2018		Dr Michael McCarthy
2	25/07/2019	Clarification of number of treatment cycles	Prof Maccon Keane
3	12/02/2020	Updated exclusions and drug interaction. Updated recommended dose modifications for oxaliplatin in renal impairment and emetogenic potential section. Updated adverse events and adverse effects/regimen specific complications.	Prof Maccon Keane
4	19/08/2020	Updated exclusion criteria Updated Baseline test Updated adverse event section	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This regimen is outside its licensed indication in Ireland. Patients should be informed of the unlicensed nature of this indication 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 aware of their responsibility in communicating any relevant information to the patient and also in 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.