Dexamethasone, riTUXimab and Cyclophosphamide (DRC)Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of symptomatic treatment naive or relapsed/refractory Waldenstrom's macroglobulinaemia	C88	00532a	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 21 days for up to 6 cycles or until disease progression or unacceptable toxicity develops.

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

Order of admin	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	1	Dexamethasone	20mg	PO/ IV infusion	PO or 100 ml NaCl 0.9% over 15 minutes	Every 21 days
2	1	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[1]	500ml NaCl 0.9% sodium chloride at a maximum rate of 400mg/hr[1,]	Every 21 days
3	1,2,3,4,5	Cyclophosphamide[2]	[3,4]100 mg/m^2 **TWICE DAILY (Total daily dose 200mg/m^2)**	PO	n/a	Every 21 days
[1] See table 1:Guidance for administration of RiTUXimab						
[2] Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cyclophosphamide.						
[3]Cyclophosphamide is available as 50mg tablets. They should be swallowed with sufficient fluid without chewing. The tablets should not be divided before use.						
[4] Total dose over 5 days -1000 mg/m^2						

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[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
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to riTUXimab, cyclophosphamide, dexamethasone or any of the excipients or to murine proteins.
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Patients in a severely immunocompromised state

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
- Calcium, glucose, serum protein electrophoresis and paraprotein quantitation, CRP, immunoglobulin levels, serum free light chains (plasma viscosity, β2-microglobulin,)
- Cardiac function if clinically indicated
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Serum protein electrophoresis and paraprotein quantitation
- 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: Dose modification of cyclophosphamide and riTUXimab in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment
Cyclophosphamide	**CrCl (ml/min)**	**Cyclophosphamide Dose**	Severe impairment: Clinical decision
	>20	100%	
	10-20	75%	
	<10	50%	
	Clinical decision – consider whether patient is being treated with high dose treatment.		
riTUXimab	No dose reduction necessary		No dose reduction necessary

Management of adverse events:

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

Adverse reactions	Discontinue	Recommended dose modification
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 discontinuing treatment	Consider coverage with steroids for those who are not already receiving steroids as pre-medication.
Mild or moderate infusion-related reaction		Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Cyclophosphamide: Moderate to High (**Refer to local policy).**
riTUXimab: Minimal (**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 4: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to riTUXimab infusion
Chlorpheniramine	10mg	IV bolus 60minutes prior to riTUXimab infusion
Ensure glucocorticoid component of the treatment regimen (Dexamethasone) 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)**

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.

Cyclophosphamide

- **Haemorrhagic cystitis:** Ensure patient is well hydrated.

RiTUXimab

- **Hypersensitivity/Infusion Reactions:** Close monitoring is required throughout the first infusion of riTUXimab. **(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.
- **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:** This has been reported in patients receiving riTUXimab including fulminant hepatitis with fatal outcome. 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 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. If a patient develops PML, the dosing of riTUXimab must be permanently discontinued.
- **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.

DRUG INTERACTIONS:

- Antihypertensive: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensive 12 hours before and during riTUXimab infusion.
- Patients with human anti-mouse antibody or human anti-chimeric antibody (HAMA/HACA) titres may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.
- CYP3A inhibitors decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers may also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Dimopoulos, M. A., A. Anagnostopoulos, M. C. Kyrtsonis, et al. Primary treatment of Waldenstrom macroglobulinemia with dexamethasone, riTUXimab, and cyclophosphamide. J Clin Oncol 2007;25(22):3344-3349.
2. Dimopoulos, M. A., M. A. Gertz, E. Kastritis, et al.Update on treatment recommendations from the Fourth International Workshop on Waldenstrom's Macroglobulinemia. J Clin Oncol 2009;27(1):120-126
3. LeBlond V, Kastritis, E, Advani R et al. Treatment recommendations from the Eighth International Workshop on Waldenstrom's Macroglobulinemia. Blood 2016;128(10):1321-1328.
4. Kastritis, E., Gavriatopoulou, M., Kyrtsonis M, et al. Dexamethasone, riTUXimab, and cyclophosphamide as primary treatment of Waldenstrom macroglobulinaemia: final analysis of a phase 2 study. Blood 2015;126(11): 1392-1394

5. Dexamethasone Phosphate 4mg/ml solution for injection Summary of Product Characteristics. Accessed April 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-201-001_18022021141502.pdf
6. Cyclophosphamide (Endoxana®) Summary of Product Characteristics. Accessed April 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-003_21122018112109.pdf
7. RiTUXimab (MabThera®) Summary of Product Characteristics. Accessed April 2021. Available at https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf
8. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
9. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
10. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. 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

Version	Date	Amendment	Approved By
1	24/01/2019		Dr Anne Fortune
2	27/04/2021	Updated recommendation for hepatic impairment (cyclophosphamide), emetogenic potential and adverse effects (hepatitis B reactivation)	Dr Anne Fortune

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] 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.