RiTUXimab 375mg/m^2 Therapy-Follicular Lymphoma

INDICATIONS FOR USE:

INDICATION	ICD10	Protocol Code
Maintenance therapy for the treatment of follicular CD20 positive, B-cell NHL patients responding to induction therapy.	C82	00208a
Monotherapy for treatment of patients with stage III-IV follicular CD20 positive, B-cell NHL who are chemoresistant or are in the second or subsequent relapse after chemotherapy.	C82	00208b

ELIGIBILTY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to riTUXimab 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

TESTS:

Baseline tests: FBC, U&Es, LFTs, Uric acid, SPEP, DAT
Cardiac function if clinically indicated, *
Virology screen -Hepatitis B (HBsAg, HBcoreAb)
Hepatitis B Reactivation: All lymphoma patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
*See Adverse Effects/Regimen Specific Complications

Regular tests:
FBC, U&Es, LFTs, LDH.
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.

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.

Maintenance Therapy

- Previously untreated follicular NHL: RiTUXimab is administered **once every 2 months** (starting 2 months after the last dose of induction therapy) for a **maximum period of two years** (12 doses) or until disease progression or unacceptable toxicity occurs.
- Relapsed/refractory follicular lymphoma: In patients who have responded in induction therapy, riTUXimab is administered **once every 3 months** (starting 3 months after the last dose of induction therapy) for a **maximum period of two years** (8 doses) or until disease progression or unacceptable toxicity occurs.

Monotherapy

- First Line: RiTUXimab monotherapy is administered once weekly for four weeks (4 doses).
- Relapsed/refractory: RiTUXimab monotherapy is administered **once weekly for four weeks (4 doses)** or until disease progression or unacceptable toxicity occurs as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
- For retreatment in patients who have responded to previous treatment with riTUXimab monotherapy for relapsed/refractory follicular lymphoma, riTUXimab is administered **once weekly for four weeks** or until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when riTUXimab therapy is administered.

Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
RiTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[2]	250ml -500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[1,3]	1
[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[i] 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.				

DOSE MODIFICATIONS:

Any dose modification should be discussed with a Consultant

No dose reductions of riTUXimab are recommended.

Table 1: Dose modification schedule 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.
Mild or moderate infusion-related reaction		Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: 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.
Suggested pre-medications:
Chlorpheniramine 10mg IV + paracetamol 1gram PO.
Consider hydrocortisone 100mg-200mg IV 30 minutes prior to therapy in patients not receiving glucocorticoid containing chemotherapy.

TAKE HOME MEDICATIONS: Not usually required**.**

OTHER SUPPORTIVE CARE: No specific recommendations

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **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.
- **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.
- **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 psychiatric symptoms). Patients should also be advised 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:** This has been reported in patients receiving riTUXimab including fulminant hepatitis with fatal outcome.
- **Vaccines:** Physicians should review the patient's vaccination status and follow current immunisation guidelines prior to riTUXimab therapy. Vaccination should be completed at least 4 weeks prior to first administration of riTUXimab.

- 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 or whilst peripherally B cell depleted.
- Patients treated with riTUXimab may receive non-live vaccinations

DRUG INTERACTIONS:

- Currently, there is limited data on possible drug interactions with riTUXimab.
- 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.
- 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.
- Current drug interaction databases should be consulted for more information

ATC CODE:

RiTUXimab L01XC02

REIMBURSEMENT CATEGORY:

RiTUXimab is funded through local hospital budgets (Jan 2016).

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.

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Version	Date	Amendment	Approved By
1	20/12/2016		Dr Amjad Hayat Dr Derville O'Shea Dr Maccon Keane

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.