Fludarabine, cyclophosphamide and riTUXimab (FC IV+R) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of B-cell chronic lymphocytic leukaemia (CLL)	C91	00241a	Hospital

**If the reimbursement status is not defined [1], the indication has yet to be assessed through the formal HSE reimbursement process.*

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.

RiTUXimab is administered at a dose of 375 mg/m^2 body surface area on day 1 of the first treatment cycle followed by 500 mg/m^2 body surface area administered on day 1 of each subsequent cycle.

Chemotherapy should be given after the riTUXumab infusion.
This consists of fludarabine and cyclophosphamide administered on days 1, 2 and 3.

A treatment cycle lasts 28 days and treatment is administered for a maximum of 6 cycles or until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when riTUXimab and chemotherapy are administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	riTUXimab*	375mg/m^2	IV infusion[1] Observe post infusion[1]	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[1]	1
1	riTUXimab	500mg/m^2	IV infusion[1] Observe post infusion[1]	500ml 0.9% sodium chloride at a maximum rate of 400mg/hr[1]	2-6
1-3	Fludarabine[2]	25mg/m^2	IV infusion	100ml 0.9%sodium chloride over -30 min	1-6
1-3	Cyclophosphamide	250mg/m^2	IV infusion[3]	100ml 0.9% sodium chloride over 30min	1-6
* The risk of cytokine release syndrome is low but is increased when the peripheral blood lymphocyte count >20 x 10 9/L. There is no requirement to withhold riTUXimab based on the lymphocyte count, clinicians may wish to pre-medicate patients with high tumour burden with steroids prior to riTUXimab infusion, fractionate the RiTUXimab for the first cycle or omit the riTUXimab from the first cycle of treatment.					
[1] See **table 1**:Guidance for administration of riTUXimab					
[2] All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation).					
[3] Cyclophosphamide may also be administered as an IV bolus over 5-10mins					

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 [ii] 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.

ELIGIBILTY:

- Indications as above
- ECOG status 0-1

EXCLUSIONS:

- Hypersensitivity to fludarabine, cyclophosphamide, riTUXimab or any of the excipients or to murine proteins.
- Active, severe infections (e.g. tuberculosis, sepsis and opportunistic infections)
- Lactation
- Haemolytic anaemia

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

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

Regular tests:

- FBC weekly for first cycle only and then prior to each cycle
- Renal and liver profile prior to each cycle
- 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.
- No dose reductions of riTUXimab are recommended. The dose of riTUXimab should remain 100% throughout treatment, regardless of dose reductions on the fludarabine and cyclophosphamide.

Haematological:

Table 1: Recommended dose modification in haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
< 1.0	or	<100	Delay until recovery *
*Consider decreasing fludarabine and cyclophosphamide by 25% each for subsequent cycles, after delay following count recovery. No dose reduction required if decreased counts are due to disease.			

Renal and Hepatic Impairment:

Table 2: Recommended dose modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment
riTUXimab	**No dose reduction necessary**		**No dose reduction necessary**
Fludarabine	**CrCL (ml/min)**	**Dose**	No data available. Use with caution
	>70	**100%**	
	30-70	**50%**	
	<30	**CI**	
Cyclophosphamide	**CrCL (ml/min)**	**Dose**	Dose reduction may need to be considered in severe hepatic impairment. Clinical decision
	>20	**100%**	
	10-20	**75%**	
	<10	**50%**	

Management of adverse events:

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

Adverse reactions	Recommended dose modification
Severe infusion related reaction (e.g dyspnoea, bronchospasm, hypotension or hypoxia) First occurrence Second 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. 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: Moderate (**Refer to local policy).**

PREMEDICATIONS: Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each infusion of riTUXimab.
Premedication with glucocorticoids should be considered if riTUXimab is not given in combination with glucocorticoid containing chemotherapy for treatment of CLL.

Table 4: 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:

- All patients receiving fludarabine should receive irradiated blood products **(Refer to local hospital policy).**
- Tumour lysis syndrome prophylaxis – consider use of allopurinol 300mg daily for the first cycle **(Refer to local hospital policy)**
- PJP prophylaxis is required for all patients until lymphopenia resolved**(Refer to local hospital policy).**
- Anti-viral prophylaxis is required for all patients until lymphopenia resolved **(Refer to local hospital policy)**
- Consider G-CSF therapy for all patients on FCR therapy (**Refer to local hospital 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.
- **Infections:** Due to the highly immunosuppressive nature of this regimen, PJP prophylaxis and anti-viral prophylaxis is recommended for all patients until T cell recovery. Caution is required in pre-treated patients, those with pre-existing cytopenias, those with a history of opportunistic infections and patients > 65 years of age.
- **Renal Impairment:** Fludarabine must be administered cautiously in patients with renal insufficiency (see Table Renal and Hepatic Dysfunction above). Patients with reduced renal function have demonstrated an increased total body exposure
- **Hypersensitivity/Infusion Reactions:** Close monitoring is required throughout the first infusion of riTUXimab. 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 of riTUXimab. 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.
- **Hepatitis B Reactivation:** The immunosuppression associated with fludarabine may increase the risk of re-activation of hepatitis B. Although the risk of this is probably small, fludarabine should be avoided in patients with known prior hepatitis B (HBsAg positive or anti-hepatitis B antibody positive) unless the clinical situation justifies this increased risk and this has been explained to the

patient. All 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 regular 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 stopping chemotherapy. Hepatitis B reactivation has been reported in patients receiving riTUXimab including fulminant hepatitis with fatal outcome

- **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.
- **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.

DRUG INTERACTIONS:

- 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 FCR therapy.
- Current drug interaction databases should be consulted for more information

ATC CODE:

Fludarabine	-	L01BB05
Cyclophosphamide	-	L01AA01
riTUXimab	-	L01XC02

REFERENCES:

1. Badoux, X. C., M. J. Keating, X. Wang, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood 2011;117(11):3016-3024.
2. Hallek, M., K. Fischer, G. Fingerle-Rowson, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet 2010;376 (9747):1164-1174.
3. Robak, T., A. Dmoszynska, P. Solal-Celigny, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol 2010;28(10):1756-1765.
4. Tam, C. S., S. O'Brien, W. Wierda, et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukemia. Blood 2008;112(4):975-980.
5. Mabthera® Summary of Product characteristics accessed 29/1/19 Available at https://www.ema.europa.eu/documents/product-information/mabthera-epar-product-information_en.pdf
6. Fludara summary of product characteristics accessed January 2019 available at

https://www.medicines.org.uk/emc/product/1125/smpc
7. cyclophosphamide 500mg powder for solution or injection Summary of product characteristics Assessed January 2019 – Available at https://www.medicines.org.uk/emc/product/3526/smpc
8. NCCP | RiTUXimab Rapid Infusion Rate Guidance | V1 2017 available at https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/guidance%20on%20rituximab%20rapid%20infusion%20rate.pdf

Version	Date	Amendment	Approved By
1	08/03/2017		Prof Elizabeth Vandenberghe
2	27/03/2019	Updated to new NCCP template, Standardisation of treatment table and adverse effects/regimen specific complications Updated dosing modifications in hepatic impairment	Prof Elizabeth Vandenberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/

[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.