R-CODOX-M Therapy
(Patients less than or equal to 65 years)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Treatment of Burkitt Lymphoma in patients less than or equal to 65 years	C83	00398a	Hospital

TREATMENT:

The starting dose of the drugs detailed may be adjusted downward by the prescribing clinician, using their medical judgement, to consider a patient's specific clinical circumstances.

Low Risk Disease defined as Stage I/ II disease, ECOG 0-2, No tumour mass ≥10 cm, Normal LDH level (4): Patients receive **three cycles of R-CODOX-M**

High Risk Disease defined as all other patients (4) are treated with **four cycles of chemotherapy consisting of alternating R-CODOX-M and R-IVAC (Ref NCCP regimen 00399)**

Treatment is administered as described in the treatment table below.

Note:

- **Hydration, alkalinisation and folinic acid therapy required with high dose methotrexate (See Table Below)**
- **Commence next cycle on the day that the unsupported absolute neutrophil count (ANC) is >1x 10^9/L and platelet count is >75 x 10^9/L**

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

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Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
0	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]
1	Cyclophosphamide	800mg/m^2	IV Bolus over 5-10min	Into the side arm of a fast running 0.9% NaCl infusion
1	[5]DOXOrubicin	40mg/m^2	IV Bolus over 2-15 min	Into the side arm of a fast running 0.9% NaCl infusion
1, 8	vinCRIStine	1.5mg/m^2 (max 2mg)	IV infusion	50ml minibag 0.9% NaCl over 15min[6]
2-5	Cyclophosphamide	200mg/m^2	IV Bolus over 5-10min	Into the side arm of a fast running 0.9% NaCl infusion
10	Methotrexate	300mg/m^2	IV infusion	500ml 0.9% NaCl over 1hour
10	Methotrexate	2700mg/m^2	IV infusion	1000ml 0.9% NaCl over 23 hours. Administer immediately after 1st methotrexate infusion
11	Folinic Acid	15mg/m^2	IV infusion	100ml 0.9% NaCl over 10mintes. Begin 36 hours from start of 1st methotrexate and administer every 3 hours until 48 hours post. Then administer according to folinic acid rescue **Table 1** below.
13 onwards	G-CSF (round to nearest whole syringe)	5microgram /kg	SC	Daily injection until ANC >1x10^9/L for two consecutive days then discontinue

See Note on Intrathecal Therapy Below

[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] 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.

[5]Lifetime cumulative dose of DOXOrubicin is 450mg/m^2
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors below[ii] and to the age of the patient

[6]vinCRIStine is a neurotoxic chemotherapeutic agent.
Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer available here

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[7]**Methotrexate :**
Hydration and Alkalinisation regimens are required with methotrexate. See below for **suggested or** Refer to local policy

GFR to be calculated prior to administration of methotrexate infusion

Adequate hydration and urine output are essential for the rapid clearance of methotrexate.

- Commence pre-hydration with sodium bicarbonate containing infusions at 125mls/m^2/hr at least 6 hours prior to methotrexate infusion.
- **Hydration** with at least 3L/m^2 /24 hours of **IV fluids** throughout treatment is essential until the methotrexate level is <0. 1 micromol/L
- Urine pH should be ≥ 7.0 prior to commencement and during the methotrexate and folinic acid rescue. Check urine pH at regular intervals (6 hourly)
- **Alkalinisation** can be achieved with 50mmol of sodium bicarbonate over 8 hours in 1000ml sodium chloride 0.9%.
  (This volume administered for alkalinisation is included in the total volume of hydration.)
  - Check urine pH at regular intervals (6 hourly)
  - If the target pH is not reached adjust the sodium bicarbonate concentration to maintain the urinary pH ≥ 7.0
- **Potassium** should be supplemented according to the local policy.
- Check **fluid balance** at regular intervals (4 hourly) through each day. (Furosemide may be administered if fluid output falls below 400mls/m^2 in a 4 hour period).
- **Methotrexate levels** must be taken 48 hours, 72 hours, 96 hours and 120 hours as appropriate after commencement of the initial methotrexate infusion (book levels in advance with lab).

Continue alkalinisation, hydration and folinic acid rescue (Table 1) until methotrexate level is <0. 1 micromol/L

Table 1: Table for the Calculation of Folinic Acid Rescue on the basis of Methotrexate Levels

Time after starting Methotrexate infusion	Methotrexate Plasma Concentration micromol/L				
	<0.1	**0.1-2**	**2-20**	**20-100**	**>100**
48 hours	No folinic Acid	15mg/m^2 every 6 hours	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours
72 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
96 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
120 hours	No folinic Acid	15mg/m^2 every 6 hours	10mg/m^2 every 3 hours	100mg/m^2 every 3 hours	1000mg/m^2 every 3 hours
If serum creatinine increases by more than 50% above baseline at 24 hours increase folinic acid rescue.					
At time points over 120 hours continue folinic acid as recommended for 120 hours					

Intrathecal (IT) Therapy

- Patients without CNS involvement should receive standard intrathecal therapy (**see Table 2 below**)
- Patients with proven or suspected CNS disease should receive intensified intrathecal treatment during the first cycle of R-CODOX-M / R-IVA C (**see Table 3 below**).
- If CNS disease has cleared after the first cycles of chemotherapy, patients should receive standard IT therapy with subsequent cycles of R-CODOX-M or R-IVAC.

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Table 2: Standard Intrathecal therapy for patients without CNS disease

Day	Drug	Dose	Route and Method of Administration
-1,6*	Cytarabine	70mg	Intrathecal injection
15	Methotrexate	12.5mg	Intrathecal injection
16	Folinic Acid	15mg	PO To be taken 24 hours after Intrathecal methotrexate
*Timing of Intrathecal therapy can be moved +/- 3 days as per local policy. Refer to NCCP Guidance on the Safe Use of Intrathecal Chemotherapy in the Treatment of Cancer https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/ITCguidance.pdf			

Table 3: Intensified Intrathecal therapy for patients with proven or suspected CNS disease

Day	Drug	Intrathecal Dose
1,3, 5	Cytarabine	70mg
15, 17	Methotrexate	12.5mg
16, 18	Folinic Acid	15mg PO to be taken 24 hours after methotrexate
Timing of Intrathecal therapy can be moved +/- 3 days as per local policy. Refer to NCCP Guidance on the Safe Use of Intrathecal Chemotherapy in the Treatment of Cancer https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/ITCguidance.pdf		

ELIGIBILITY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to cytarabine, DOXOrubicin, vinCRIStine, cyclophosphamide, methotrexate, riTUXimab or any of the excipients
- A cumulative life-long dose of 450mg/m^2 of DOXOrubicin should only be exceeded with extreme caution as there is as risk of irreversible congestive heart failure

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, renal and liver profile
- LDH, Uric acid
- ECG
- MUGA or ECHO should be considered prior to the administration of DOXOrubicin in high-risk patients
- Virology screen -Hepatitis B* (HBsAg, HBcoreAb), HepatitisC, HIV.
  ***Hepatitis B reactivation: See Adverse events/ Regimen specific complications**

Regular tests:

- FBC, renal and liver profile
- LDH
- Cardiac function if clinically indicated

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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.

Renal and Hepatic Impairment:

Table 4: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Cyclophosphamide	**CrCl (ml/min)**	**Dose**	Severe impairment: Clinical decision			
	>20	100%				
	10-20	75%				
	<10	50%				
DOXOrubicin	Dose reduce in severe renal impairment		**Bilirubin (micromol/L)**	**Dose**		
			20-51	50%		
			51-85	25%		
			>85	Omit		
			If AST 2-3 x normal, give 75% dose.			
			If AST >3x ULN, give 50% dose			
***Methotrexate**	**CrCl (ml/min)**	**Dose**	**Bilirubin (micromol/L)**		**AST**	**Dose**
	>80	100%	<50	and	<180	100%
	60-80	65%	51-85	or	>180	75%
	45-60	50%	>85			Contraindicated
	30-45	Clinical decision	Contraindicated in severe hepatic impairment			
	<30	Contraindicated				
vinCRIStine	**No dose reduction required**		**Bilirubin (micromol/L)**		**AST/ALT**	**Dose**
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit

*CrCl > 50ml/min recommended before administration of high-dose methotrexate (2, 3).

Other Toxicity:

Table 5: Dose modification of vinCRIStine based on neurotoxicity (CTCAE v4.0)

Symptom	Dose of vinCRIStine
Grade 1	100%
Grade 2	Hold until recovery then reduce dose by 50%
Grade 3,4	Omit

Table 6: 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

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		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:

Cyclophosphamide DOXOrubicin combination	High	**(Refer to local policy).**
vinCRIStine	Minimal	**(Refer to local policy)..**
Methotrexate	Moderate	**(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. Consider the inclusion of a glucocorticoid in patients not receiving glucocorticoid containing chemotherapy.

Table 7: 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)**
- Proton pump Inhibitor**(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
  Note: ***Omit co-trimoxazole (Septrin®) from days 1-21 of each R-CODOX-M cycle. Restart on day 22 and continue prophylaxis throughout the R-IVAC cycles, until chemotherapy is complete and neutrophils > 1x10^9/L.***
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRIStine (8) **(Refer to local policy)**

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ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Please refer to NCCP regimen 00542 riTUXimab 375mg/m^2 Combination Therapy-21 day for detailed information on adverse effects/regimen specific complications for riTUXimab

- **High dose methotrexate**: Monitoring of methotrexate levels is essential as delayed methotrexate excretion is potentially an emergency situation. Renal function must be evaluated prior to treatment and patients with creatinine clearance less than 50 mL/min should not receive high dose methotrexate. Methotrexate exits slowly from third space compartments (e.g. pleural effusions or ascites), resulting in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to remove the fluid before treatment and to monitor plasma methotrexate levels.
- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely while on riTUXimab. DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with cardiac dysfunction**.**
- **Neuropathy:** vinCRIStine may cause peripheral neuropathy which is dose related and cumulative, requiring monitoring before each dose is administered. The presence of pre-existing neuropathies or previous treatment with other neurotoxic drugs may increase risk of peripheral neuropathy. Patients with mild peripheral neuropathy can usually continue to receive full doses of vinCRIStine, but when symptoms increase in severity and interfere with neurologic function, dose reduction or discontinuation of the drug may be necessary. The natural history following discontinuation of treatment is gradual improvement, which may take up to several months. A routine prophylactic regimen against constipation is recommended for all patients receiving vinCRIStine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRIStine and with symptomatic care.
- **Precautions for Intrathecal Administration:** Refer to NCCP Guidance on the Safe Use of Intrathecal Chemotherapy in the Treatment of Cancer **https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/ITCguidance.pdf**
- **Extravasation**: DOXOrubicin and vinCRIStine cause pain and possible tissue necrosis if extravasated**. (Refer to local policy).**
- **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:

- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- Drugs which compromise renal function e.g. aminoglycosides and CISplatin can decrease clearance of methotrexate and lead to systemic toxicity.
- Concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) and penicillins reduces renal clearance of methotrexate and these drugs should be avoided when using high dose methotrexate.
- Avoid concurrent use of Cotrimoxazole when using high dose methotrexate ***Refer to other supportive care above.**
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	15/11/2017		Prof E Vandenberghe Prof M Keane
2	04/06/2019	Clarification of methotrexate monitoring levels	Prof E Vandenberghe Prof M Keane
3	12/11/2020	Regimen review Standardisation of treatment and premedications tables. Updated recommended dose modification of cyclophosphamide and methotrexate in hepatic impairment. Updated recommended dose modification of methotrexate in renal impairment. Updated supportive care with regard to PJP prophylaxis. Updated emetogenic potential Update of adverse events with regard to management of hepatitis B reactivationUpdated drug interactions section.	Prof E Vandenberghe
4	11/08/2022	Updated emetogenic potential	Prof E Vandenberghe

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.

[ii] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.

Risk factors for developing anthracycline-induced cardiotoxicity include:
- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- prior or concomitant radiotherapy to the mediastinal/pericardial area
- pre-existing heart disease
- concomitant use of other potentially cardiotoxic drugs

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient.

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