

## R-CODOX-M Therapy (Patients greater than 65 years)

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of Burkitt Lymphoma in patients aged greater than 65 years	C83	00403a	

*\*If the reimbursement status is not defined<sup>1</sup>, the indication has yet to be assessed through the formal HSE reimbursement process.*

### 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  $\geq 10$  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 Protocol 00404)**

Treatment is administered as described in the treatment table below.

### Note:

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

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 <sup>2</sup>	IV infusion <sup>1</sup> Observe post infusion <sup>2</sup>	250ml -500ml 0.9% sodium chloride at a maximum rate of 400mg/hr <sup>1,3,4</sup>
1	Cyclophosphamide	800mg/m <sup>2</sup>	IV Bolus over 5-10min	Into the side arm of a fast running 0.9% NaCl infusion
1	<sup>5</sup> DOXOrubicin	40mg/m <sup>2</sup>	IV Bolus over 2-15 mins	Into the side arm of a fast running 0.9% NaCl infusion
1, 8	VinCRiStine	1.5mg/m <sup>2</sup> (max 2mg)	IV infusion	50ml minibag 0.9% NaCl over 5-15minutes <sup>6</sup>
2-5	Cyclophosphamide	200mg/m <sup>2</sup>	IV Bolus over 5-10min	Into the side arm of a fast running 0.9% NaCl infusion
10	Methotrexate	100mg/m <sup>2</sup>	IV infusion	500mls 0.9% NaCl over 1hour
10	Methotrexate	900mg/m <sup>2</sup>	IV infusion	1000mls 0.9% NaCl over 23 hours. Administer immediately after 1 <sup>st</sup> methotrexate infusion
11	Folinic Acid	15mg/m <sup>2</sup>	IV infusion	100ml 0.9% NaCl over 10minutes. Begin 36 hours from start of 1 <sup>st</sup> methotrexate and administer every 3 hours until 48 hours post. Then administer according to folinic acid rescue <b>Table 1</b> below.
13 onwards	G-CSF (Round to nearest whole syringe)	5mcg/kg	SC	Daily injection until ANC > 1 x 10 <sup>9</sup> /L for two consecutive days then discontinue

**See Note on Intrathecal Therapy Below**

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>RiTUXimab should be diluted to a final concentration of 1-4mg/ml.

<sup>4</sup> **Rapid rate infusion schedule<sup>ii</sup>** 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.

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<p><sup>5</sup>Lifetime cumulative dose of DOXOrubicin is 450mg/m<sup>2</sup>  <b>In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors below<sup>iii</sup> and to the age of the patient</b></p>
<p><sup>6</sup>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  <a href="https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf">https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/neurotoxicguidance.pdf</a></p>
<p><sup>7</sup><b>Methotrexate :</b>  Hydration and Alkalinisation regimens are required with methotrexate. See below for <b>suggested or</b> Refer to local policy</p> <p>GFR to be calculated prior to administration of methotrexate infusion</p> <p>Adequate hydration and urine output are essential for the rapid clearance of methotrexate.</p> <ul style="list-style-type: none"> <li>○ Commence pre-hydration with sodium bicarbonate containing infusions at 125mls/m<sup>2</sup>/hr at least 6 hours prior to methotrexate infusion.</li> <li>○ <b>Hydration</b> with at least 3L/m<sup>2</sup> /24 hours of <b>IV fluids</b> throughout treatment is essential until the methotrexate level is &lt;0. 1 micromol/L</li> <li>○ 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)</li> <li>○ <b>Alkalinisation</b> 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.) <ul style="list-style-type: none"> <li>➢ Check urine pH at regular intervals ( 6 hourly)</li> <li>➢ If the target pH is not reached adjust the sodium bicarbonate concentration to maintain the urinary pH ≥ 7.0</li> </ul> </li> <li>○ <b>Potassium</b> should be supplemented according to the local policy.</li> <li>○ Check <b>fluid balance</b> at regular intervals (4 hourly) through each day. (Furosemide may be administered if fluid output falls below 400mls/m<sup>2</sup> in a 4 hour period).</li> <li>○ <b>Methotrexate levels</b> 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).</li> </ul> <p>Continue alkalinisation, hydration and folinic acid rescue (Table 1) until methotrexate level is &lt;0. 1 micromol/L</p>

**Table1: 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
<b>48 hours</b>	No folinic Acid	15mg/m <sup>2</sup> every 6 hours	15mg/m <sup>2</sup> every 6 hours	10mg/m <sup>2</sup> every 3 hours	100mg/m <sup>2</sup> every 3 hours
<b>72 hours</b>	No folinic Acid	15mg/m <sup>2</sup> every 6 hours	10mg/m <sup>2</sup> every 3 hours	100mg/m <sup>2</sup> every 3 hours	1000mg/m <sup>2</sup> every 3 hours
<b>96 hours</b>	No folinic Acid	15mg/m <sup>2</sup> every 6 hours	10mg/m <sup>2</sup> every 3 hours	100mg/m <sup>2</sup> every 3 hours	1000mg/m <sup>2</sup> every 3 hours
<b>120 hours</b>	No folinic Acid	15mg/m <sup>2</sup> every 6 hours	10mg/m <sup>2</sup> every 3 hours	100mg/m <sup>2</sup> every 3 hours	1000mg/m <sup>2</sup> 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-IVAC .(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 <a href="https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/ITCguidance.pdf">https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/ITCguidance.pdf</a>			

**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 <a href="https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/ITCguidance.pdf">https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/safetyreview/ITCguidance.pdf</a>		

## 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<sup>2</sup> 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.

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## 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), Hepatitis C, HIV.  
\*Hepatitis B reactivation: See Adverse events/ Regimen specific complications

### Regular tests:

- FBC, renal and liver profile
- 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.

## 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	<b>GFR (ml/min)</b>	<b>Dose</b>	Not recommended in patients with a bilirubin >17micromol/L or serum transaminases or ALP more than 2-3 x upper limit of normal. Clinical Decision			
	>20	100%				
	10-20	75%				
	<10	50%				
DOXOrubicin	Dose reduce in severe renal impairment		<b>Bilirubin (micromol/L)</b>		<b>Dose</b>	
			20-51		50%	
			51-85		25%	
			>85		Omit	
			If AST 2-3 x normal, give 75% dose.			
*Methotrexate	<b>Cr Cl (ml/min)</b>	<b>Dose</b>	<b>Bilirubin (micromol/L)</b>		<b>AST</b>	<b>Dose</b>
	>80	100%	<50	and	<180	100%
	60	65%	51-85	or	>180	75%
	45	50%	>85			CI
	<30	CI	CI in severe hepatic impairment			
VinCRISTine	No dose reduction required		<b>Bilirubin (micromol/L)</b>		<b>AST/ALT</b>	<b>Dose</b>
			26-51	or	60-180	50%
			>51	and	Normal	50%
			>51	and	>180	Omit

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

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## 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 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:** High (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
Chlorpheniramine	10mg	IV bolus
Hydrocortisone	100mg	IV bolus ( 30-60minutes before riTUXimab)

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## 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:** *Where co-trimoxazole (Septrin®) is being used it should be omitted on 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<sup>9</sup>/L.*
- Anti-viral prophylaxis (**Refer to local policy**)
  - Anti-fungal prophylaxis (Avoid the concurrent use of azoles and vinCRISine (8)) (**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.

Please refer to NCCP Protocol 00208 RiTUXimab 375mg/m<sup>2</sup> Monotherapy-Follicular Lymphoma 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 evacuate 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:** VinCRISine 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 vinCRISine, 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 vinCRISine sulphate. Paralytic ileus may occur. The ileus will reverse itself upon temporary discontinuance of vinCRISine 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 vinCRISine cause pain and possible tissue necrosis if extravasated. (**Refer to local policy**).
- **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

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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.

## 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 eg. aminoglycosides and CISplatin can decrease clearance of methotrexate and lead to systemic toxicity.
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

Cyclophosphamide	L01AA01
DOXOrubicin	L01DB01
VinCRiStine	L01CA02
Cytarabine	L01BC01
Methotrexate	L01BA01
RiTUXimab	L01XC02

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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

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

<sup>i</sup> 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/>

<sup>ii</sup> 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.

<sup>iii</sup> 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

NCCP Regimen: R-CODOX-M Therapy(patients greater than 65 years)	Published: 17/11/2017 Review: 17/11/2019	Version number: 2
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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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