

Dose Adjusted R-EPOCH Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Indicator
Treatment of patients with CD20 positive diffuse large B-cell Non Hodgkins lymphoma (NHL)	C83	00355a	

**If a reimbursement indicator (e.g. ODMS, CDS) is not defined, the drug and its detailed indication have not been assessed through the formal HSE reimbursement process.*

TREATMENT (Please see treatment table on next page):

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.

ELIGIBILITY:

- Previously untreated high or intermediate risk diffuse large B-cell NHL
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to cyclophosphamide, DOXOrubicin, etoposide, vinCRISTine, riTUXimab or any of the excipients
- A cumulative life-long dose of 450mg/m² of DOXOrubicin should only be exceeded with extreme caution as there is as risk of irreversible congestive heart failure
- Severe liver impairment (etoposide)
- Breast feeding
- Pregnancy

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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Drug	Dose Level								Administration	Day
	- 2	- 1	Dose Level 1 Initial dose	2	3	4	5	6		
RiTUXimab	375mg/m ²	375mg/m ²	375mg/m ²	375mg/m ²	375mg/m ²	375mg/m ²	375m ²	375mg/m ²	IV infusion in 250ml NaCl 0.9% ^{a,b}	1
^e Etoposide	50mg/m ²	50mg/m ²	50mg/m ²	60mg/m ²	72mg/m ²	86.4mg/m ²	103.7mg/m ²	124.4mg/m ²	Dilute in 1000ml NaCl 0.9% & infuse over 24 hours	1,2,3,4
^{c, e} DOXOrubicin	10mg/m ²	10mg/m ²	10mg/m ²	12mg/m ²	14.4mg/m ²	17.3mg/m ²	20mg/m ²	24.8mg/m ²	Concomitantly in 1000ml NaCl 0.9% & infuse IV over 24 hours	1,2,3,4
^{d, e} VinCRiStine	0.4mg/m ²	0.4mg/m ²	0.4mg/m ²	0.4mg/m ²	0.4mg/m ²	0.4mg/m ²	0.4mg/m ²	0.4mg/m ²		1,2,3,4
Cyclophosphamide	480mg/m ²	600mg/m ²	750mg/m ²	900mg/m ²	1080mg/m ²	1296mg/m ²	^f 1555mg/m ² (Requires mesna)	^f 1866mg/m ² (Requires mesna)	IV infusion in 250ml NaCl 0.9% over 30 minutes	5
^g G-CSF (Round to nearest whole syringe)	5µg/kg	5µg/kg	5µg/kg	5µg/kg	5µg/kg	5µg/kg	5µg/kg	5µg/kg	SC – No sooner than 24 hrs after the end of cyclophosphamide infusion	^h From day 6, until ANC ≥5 X10 ⁹ /L
Prednisolone	120mg/m ²	120mg/m ²	120mg/m ²	120mg/m ²	120mg/m ²	120mg/m ²	120mg/m ²	120mg/m ²	PO in two divided doses (i.e. 6am and 12noon)	1-5
^a The recommended initial rate for infusion of riTUXimab 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. Any deviation from the advised infusion rate should be noted in local policies. Please refer to NCCP Protocol 00208 RiTUXimab Therapy 375mg/m ² for detailed information on infusion schedule for riTUXimab.										
^b Recommended Observation period for riTUXimab : 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.										
^c 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 outlined below ⁱⁱ and to the age of the patient.										
^d 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										
^e There are various ways of administering DOXOrubicin, vinCRiStine and etoposide . See local hospital policy recommendations regarding preferred combinations to be administered concomitantly.										
^f At doses of cyclophosphamide above 1500mg/m ² pre-treatment is required with mesna. Give mesna dose equivalent to 20% of cyclophosphamide dose IV immediately before cyclophosphamide dose (T0) and 40% of the cyclophosphamide dose orally 2 and 6 hours (T2, T6) after the end of the cyclophosphamide infusion.										
Prophylactic Central Nervous System Intrathecal Methotrexate should be administered with this regimen as clinically indicated (Refer to local policy)										
^g A pegylated form of G-CSF may be substituted for standard G-CSF at an equivalent dose.										
^h Ensure GCSF is continued until beyond nadir even if WCC is raised (typically beyond Day 10)										

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TESTS:

Baseline tests:

- FBC, U&Es, LFTs, LDH, Uric acid, SPEP
- ECG
- Cardiac function using MUGA or ECHO (LVEF > 50% to administer doxorubicin) if >65 years or if clinically indicated (e.g. smoking history, hypertension).
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV.

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 stopping chemotherapy.

Regular tests:

- FBC (including ANC) twice weekly during treatment, three days apart
- U&Es, LFTs prior to each cycle
- Assessment of peripheral neuropathy status prior to each cycle
- 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
- Drug doses for subsequent cycles are based on previous cycle ANC nadir (Please see Table 1).
- Measurement of ANC nadir based on twice weekly FBC only which must be taken at least 3 days apart i.e. Low neutrophil count on 3 consecutive days does NOT require decreasing a level

Haematological:

Table 1: Dose adjustment of R-EPOCH based on previous cycle ANC nadir

FBC result	Action
If Nadir ANC $\geq 0.5 \times 10^9/L$ on all measurements	Increase 1 dose level above last cycle
If Nadir ANC $< 0.5 \times 10^9/L$ on 1 or 2 measurements	Dose at same level as last cycle
If the nadir ANC $< 0.5 \times 10^9/L$ on three separate measurements <u>OR</u> if the nadir platelet count is $< 25 \times 10^9/L$ on one measurement	Decrease to one level below the last cycle

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Renal and Hepatic Impairment:

Table 2: Dose modifications based on renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment												
RiTUXimab	Probably no dose reduction necessary	Probably no dose reduction necessary												
Etoposide	CrCl(ml/min)	Bilirubin 26-51 micromol/L or AST 60-180 give 50% dose Bilirubin >51 micromol/L or AST >180, clinical decision												
	>50		100%											
	15-50		75%											
	<15		50%											
	Subsequent doses should be based on clinical response													
Dialysis Start at reduced dose and increase according to clinical response.														
DOXOrubicin	No dose reduction required. Clinical decision in severe renal impairment	<table border="1"> <thead> <tr> <th>Bilirubin (micromol/L)</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>20-51</td> <td>50%</td> </tr> <tr> <td>51-85</td> <td>25%</td> </tr> <tr> <td>>85</td> <td>omit</td> </tr> </tbody> </table> If AST 2-3 x normal, give 75% dose. If AST >3x ULN, give 50% dose	Bilirubin (micromol/L)	Dose	20-51	50%	51-85	25%	>85	omit				
Bilirubin (micromol/L)	Dose													
20-51	50%													
51-85	25%													
>85	omit													
Cyclophosphamide	GFR (ml/min)	Consider SPC recommendations; however, exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision.												
	>20		100%											
	10-20		75%											
	<10		50%											
	Clinical decision – consider whether patient is being treated with high dose treatment. Dialysis Renal Drug Handbook -dose at 50-100% dose (CAPD, HD and HDF/High flux) Do not perform dialysis for 12 hours. Dose at 75-100% dose (CAV/VVHD). If anuric, mesna may not be required.													
VinCRiStine	No dose reduction required	<table border="1"> <thead> <tr> <th>Bilirubin (micromol/L)</th> <th>AST/ALT (Units)</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>26-51</td> <td>or 60-180</td> <td>50%</td> </tr> <tr> <td>>51</td> <td>and N</td> <td>50%</td> </tr> <tr> <td>>51</td> <td>and >180</td> <td>Omit</td> </tr> </tbody> </table>	Bilirubin (micromol/L)	AST/ALT (Units)	Dose	26-51	or 60-180	50%	>51	and N	50%	>51	and >180	Omit
Bilirubin (micromol/L)	AST/ALT (Units)	Dose												
26-51	or 60-180	50%												
>51	and N	50%												
>51	and >180	Omit												

Neurotoxicity:

Table 3: Dose modification of vinCRiStine based on neurotoxicity (CTCAE v 4.0)

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

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Table 4: 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:

Level -2, -1, 1, 2, 3, 4 - Moderate (Refer to local policy)
Level 5, 6 - 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.

Table 5: Suggested pre-medications prior to ritUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO
Chlorpheniramine	10mg	IV bolus
Hydrocortisone	100mg	IV bolus 30-60 minutes before ritUXimab

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**)
- Prophylactic regimen against vinCRistine induced constipation is recommended (**Refer to local policy**)
- Patients should have an increased fluid intake of 2-3 litres on day 5 to prevent haemorrhagic cystitis associated with cyclophosphamide.
- Consider mesna if high dose cyclophosphamide prescribed on dose escalation (>1.5g/m² at levels 5, 6)

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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 see NCCP Protocol 00208 RiTUXimab 375mg/m² Therapy for detailed information on the adverse effects/Regimen Specific Complications relating to RiTUXimab Therapy

- **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. Monitor infusion of etoposide for the first 15 minutes for signs of hypotension
- **Cardiac Toxicity:** 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.
- **Extravasation:** DOXOrubicin and vinCRiStine cause pain and possible tissue necrosis if extravasated (refer to local policy).

DRUG INTERACTIONS:

- Antihypertensives: Additive effect of hypotension during riTUXimab infusion. Consider withholding antihypertensives 12 hours before and during riTUXimab infusion.
- DOXOrubicin cardiotoxicity is enhanced by previous or concurrent use of other anthracyclines, or other potentially cardiotoxic drugs (e.g. 5-FU, cyclophosphamide or paclitaxel) or with products affecting cardiac function (e.g. calcium antagonists).
- Current drug interaction databases should be consulted for more information including potential for interactions with CYP3AR inhibitors/ inducers.

ATC CODE:

RiTUXimab	-	L01XC02
Cyclophosphamide	-	L01AA01
DOXOrubicin	-	L01DB01
Etoposide	-	L01CB01
VinCRiStine	-	L01CA02

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Version	Date	Amendment	Approved By
1	18/12/2017		Dr Cliona Grant, Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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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 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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