(R**)-DHAP Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of relapsed Non Hodgkin Lymphoma**	C85	00395a	Hospital
Treatment of relapsed Hodgkins Lymphoma	C81	00395b	Hospital

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

** RiTUXimab to be included in all CD20 positive patients

TREATMENT:

CISplatin is administered on Day 1 and cytarabine is administered twice daily on day 2. Treatment is repeated at 21 day intervals for up to 6 cycles.
If DHAP is being used prior to autologous SCT, peripheral blood stem cell harvesting is usually performed on cycle 2 or 3.

Facilities to treat anaphylaxis MUST be present when therapy is administered

Note: Specific Hydration therapy is required for the safe administration of [a]CISplatin (see table below)

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1-4	Dexamethasone	40mg	PO/IV infusion	
1	RiTUXimab	375mg/m^2	IV infusion[1] Observe post infusion[2]	250 to 500ml 0.9% NaCl at a maximum rate of 400mg/hr[1,3,4]
1	[a]CISplatin	100mg/m^2	IV infusion	1000ml 0.9% NaCl over 24 hours
2	Cytarabine	2000mg/m^2 **AM**	IV infusion	1000ml 0.9% NaCl over 2 hours
2	Cytarabine	2000mg/m^2 **PM** (12 hours after start of first cytarabine infusion)	IV infusion	1000ml 0.9% NaCl over 2 hours
6 onwards	G-CSF	5mcg/kg (round to nearest whole syringe)	SC	Continued until ANC >1x10$^{9/}$L for 2 consecutive days
G-CSF support is required with this regimen (Refer to local policy or see Suggested support above)				

[a]**Pre and post hydration therapy required for CISplatin** See local hospital policy recommendations. Suggested prehydration for CISplatin therapy: 1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 20mmol/L if indicated) in 1000 mL sodium chloride 0.9% over 60 minutes. Administer CISplatin as described above Post hydration: Administer 1000 ml 0.9% NaCl over 60mins Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (4,5).
Maintain strict fluid balance during therapy, by (1) monitoring fluid balance and (2) daily weights. If fluid balance becomes positive by >1000mls or weight increases by >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide
[1]**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.
[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[ii] 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.

The starting dose of the drugs detailed above may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

ELIGIBILTY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to CISplatin, cytarabine or any of the excipients.
- Moderate/severe renal impairment (creatinine clearance < 60 mL/mi)
- Significant hearing impairment/tinnitus

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, U&Es, LFTs, LDH, Urate
- Audiology and creatinine clearance if clinically indicated.

- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV.
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, U&Es, LFTs, LDH prior to each cycle
- Regular glucose monitoring while receiving steroid therapy-urinalysis daily
  If glucose detected in urinalysis, monitor blood glucose daily.

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

Haematological:

Table 1 : Dose modification for haematological toxicity

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
<1	and/or	<100	Discuss with Consultant

Renal and Hepatic Impairment:

Table 2: Dose modifications based on renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment
CISplatin	**GFR (ml/min)**	**Dose**	No dose modification required
	>60	100%	
	45-59	75%	
	<45	consider carboplatin	
Cytarabine	**GFR (ml/min)**	**Dose**	If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.
	>60	100%	
	45-60	60%	
	30-45	50%	
	<30	Avoid	

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.

Table 3: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO
Chlorpheniramine	10mg	IV bolus
Ensure dexamethasone is given at least 30 minutes prior to riTUXimab infusion		

- Hydration prior and post CISplatin administration **(Refer to local policy or see recommendations above).**
- To prevent a chemical induced conjunctivitis developing with cytarabine, Prednisolone eye drops (e.g. Pred Mild) 1-2 drops per eye 4 hourly during waking hours prior to cytarabine and continued 5 days post treatment should be considered.

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)**
- Mouthcare **(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.

- **Myelosuppression:** DHAP causes severe bone marrow suppression and patients require daily blood monitoring during treatment and at least twice weekly until marrow recovery post therapy.
- **Renal toxicity:** Renal toxicity is common with CISplatin.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle of CISplatin
- **Neurotoxicity:** This may occur in patients treated with high dose cytarabine. Assess cerebellar function prior to each cytarabine dose. The risk of neurotoxicity is enhanced in the presence of renal impairment. Ensure that dose of cytarabine is adjusted in renal impairment (Ref Table 2).
- **Cytarabine syndrome:** Treatment with cytarabine may cause a 'Cytarabine Syndrome' characterised by flu-like symptoms, skin rash and occasionally chest pain.
- **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.

Please Refer to NCCP Protocol 00208 RiTUXimab Monotherapy for detailed information on adverse reactions/Regimen Specific Complications associated with RiTUXimab Therapy

DRUG INTERACTIONS:

- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, NSAIDS) due to additive nephrotoxicity. Monitor renal function closely.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

CISplatin	L01XA01
Cytarabine	L01BC01

REFERENCES:

1. Velasquez WS. Et al. Effective Salvage Therapy for Lymphoma with CISplatin in combination with High Dose Ara_C and Dexamethasone (DHAP). Blood; 1988;71:117-122
2. Josting A, Rudolph C, et al. Time-intensified dexamethasone/cisplatin/cytarabine: an effective salvage therapy with low toxicity in patients with relapsed and refractory Hodgkin's disease. Ann Oncol. 2002;13(10):1628
3. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-4190.
4. Nephrotoxicity Associated with CISplatin EviQ ID: 184 v.3 https://www.eviq.org.au/clinical-resources/side-effect-and-toxicity-management/prophylaxis-and-prevention/184-nephrotoxicity-associated-with-CISplatin
5. Portilla D et al. CISplatin nephrotoxicity. UptoDate Accessed Oct 2017 https://www.uptodate.com/contents/CISplatin-nephrotoxicity?source=search_result&search=CISplatin%20hydration&selectedTitle=1~150
6. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-cytotoxics.pdf
7. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network. Available at http://londoncancer.org/media/65594/hepatic-impairment-dosage-adjustment-for-cytotoxics.pdf
8. Cisplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed May 2017. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0749-119-002_06062013115044.pdf
9. Cytarabine 100mg/ml Solution for Injection or Infusion. Accessed May 2017 Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1390-091-001_09122014091042.pdf

Version	Date	Amendment	Approved By
1	08/07/2017 27/06/2017		Prof Elizabeth Vandenberghe Prof Maccon Keane
2	17/10/2018	Updated CISplatin hydration protocol.	Prof Maccon Keane

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.