riTUXimab** Gemcitabine, Dexamethasone and CISplatin ((R**)-GDP) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of relapsed Non Hodgkin Lymphoma**	C85	00441a	Hospital
Treatment of relapsed Hodgkin's Lymphoma	C81	00441b	Hospital

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

** riTUXimab to be included in all CD20 positive patients

TREATMENT:

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.

Treatment is repeated at 21 day intervals for up to 6 cycles or until disease progression or unacceptable toxicity develops.
If GDP 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 CISplatin (see table below)

Order of admin	Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1	1-4	Dexamethasone	40mg	PO/IV infusion	
2	1	riTUXimab	375mg/m^2	IV infusion[1] Observe post infusion	500ml 0.9% NaCl at a maximum rate of 400mg/hr[1]
3	1, 8	Gemcitabine	1000mg/m^2	IV infusion	250mls 0.9% NaCl over 30minutes
4	1	[2, 3]CISplatin	75mg/m^2	IV infusion	1000ml 0.9% NaCl over 1hour
Use of G_CSF when used for stem cell harvest					
	9-15	G-CSF (round to nearest whole syringe)	5mcg/kg	SC	[4]Continue until mobilisation completed.
Use of G-CSF when not for stem cell harvest, in high risk patients					
	9-15	G-CSF (round to nearest whole syringe	5mcg/kg	SC	Continue until neutrophil recovery (Refer to local policy)

[1] See table 1:Guidance for administration of riTUXimab

[2]**CISplatin Hydration**
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 (3, 4).
[3]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 diuresis with furosemide
[4]G-CSF should be discontinued after completion of stem cell harvesting. Pegfilgrastim must NOT be used

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

EXCLUSIONS:

- Hypersensitivity to CISplatin, gemcitabine, riTUXimab or any of the excipients.
- Significant hearing impairment/tinnitus
- Pre existing neuropathies > Grade 2

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
- 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, renal and liver profile prior to each cycle and as clinically indicated
- LDH prior to each cycle and FBC on day 8
- 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

Day	ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
1	≥1	and	>50	100% Dose
1	<1.0	or	<50	Delay treatment by one week
8	0.5-0.9			Administer full dose of gemcitabine and consider G-CSF therapy
8	<0.5	or	<50	Omit gemcitabine and consider dose reduction for next cycle

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/Clinical decision	
Gemcitabine	**GFR (ml/min)**	**Dose**	AST elevations do not seem to cause dose limiting toxicities. If bilirubin > 27 micromol/L, initiate treatment with dose of 800 mg/m^2 .
	<30	Consider dose reduction/Clinical decision	

Other toxicity:

Table 3: Dose modification for adverse events

Adverse event	Dose Modification
Grade 3 Non-haematologic toxicity (except nausea, vomiting or alopecia)	25% dose reduction of gemcitabine and CISplatin
Serum creatinine between 140 and 199micromol/L	Reduce dose of CISplatin by 25%
Grade 4 non-haematologic toxicity	Discontinue treatment
Serum creatinine ≥200 micromol/L	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Day 1 - High **(Refer to local policy)**
Day 8 - Low **(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 glucocorticoid component of the treatment regimen (Dexamethasone 40mg) is given at least 30 minutes prior to riTUXimab infusion		

- Hydration prior and post CISplatin administration **(Refer to local policy or see recommendations above).**

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:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Support with platelet transfusion may be required.
- **Renal toxicity:** Renal toxicity is common with CISplatin.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle of CISplatin
- **Pulmonary toxicity:** Acute shortness of breath may occur with gemcitabine. Discontinue treatment if drug-induced pneumonitis is suspected**.**
- **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 00542 RiTUXimab 375 mg/m^2 Combination Therapy-21 day 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:

CilSplatin L01XA01
Gemcitabine L01BC05

REFERENCES:

1. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and CISplatin versus dexamethasone, cytarabine, and CISplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014 Nov 1;32(31):3490-6.
2. Baetz T, Belch A, Couban S. et al. Gemcitabine, dexamethasone and CISplatin is an active and non-toxic chemotherapy regimen in relapsed or refractory Hodgkin's disease: a phase II study by the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 2003;14(12):1762-1767.
3. 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
4. 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
5. CISplatin 1mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics Accessed Sept 2018. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0749-119-002_06062013115044.pdf
6. Gemcitabine 40 mg/ml Concentrate for Solution for Infusion Summary of Product Characteristics Accessed Sept 2018. Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA1380-015-003_16042013100051.pdf

Version	Date	Amendment	Approved By
1	24/01/2019		Dr Anne Fortune

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.