(R*)-ICE ((RiTUXimab), Ifosfamide, CARBOplatin and Etoposide) Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of relapsed/refractory Non Hodgkin's Lymphoma*	C85	00397a	Hospital
Treatment of relapsed/refractory Hodgkin's Lymphoma	C81	00397b	Hospital

* RiTUXimab to be included in all CD20 positive patients

TREATMENT:

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 on Day 1-3 as described in table every 21 days until remission induction or up to a maximum of 6 cycles.

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

Note: **Specific Hydration therapy is required for the safe administration of [a]ifosfamide (See Table below)**

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	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]	1-6
1, 2 , 3	Etoposide	100mg/m^2	IV infusion	1000mls 0.9% NaCl over 60minutes	1-6
2	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 60 min	1-6
2	Mesna	1000mg/m^2	IV Bolus	Into the side arm of a fast-flowing 0.9% NaCl drip immediately before ifosfamide infusion starts	1-6
2	[a]Ifosfamide	5000mg/ m^2	IV infusion	In 1000ml 0.9% NaCl over 24 hours[b]	1-6
2	Mesna	5000mg/ m^2	IV infusion	In 1000ml 0.9% NaCl over 24 hours. Y-sited with the ifosfamide	1-6
3	Mesna	1000mg/m^2	IV bolus	Into the side arm of a fast-flowing 0.9% NaCl drip 3 hours post end ifosfamide infusion	1-6
3	Mesna	1000mg/m^2	IV bolus	Into the side arm of a fast-flowing 0.9% NaCl drip 6 hours post end ifosfamide infusion	1-6
3	Mesna	1000mg/m^2	IV bolus	Into the side arm of a fast-flowing 0.9% NaCl drip 9 hours post end ifosfamide infusion	1-6
From day 6	G-CSF	5mcg/kg	SC (Round to nearest whole syringe)	Continued until ANC >1x10$^{9/}$L for 2 consecutive days	1-6
[a]Ifosfamide Hydration: (Refer to local policy or see suggested hydration below).					

Ensure IV hydration (1L NaCL 0.9% IV every 6 hours) is given, commencing prior to first dose of ifosfamide and continuing for 24 hours after completion. Furosemide should also be administered if required to ensure a urinary output of at least 100ml/hour 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
[b] In order to facilitate the infusion of ifosfamide over 24 hours consideration may be given to splitting the dose of ifosfamide over multiple infusion bags for stability reasons.
[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[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.

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Estimation of GFR (eGFR)** can be done by using the Wright formula or using the Cockroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- **Measured GFR** (e.g. nuclear renogram) may be preferable:
  - Where renal function is borderline.
  - For obese and anorexic patients as the formulae may not give accurate results. Where obesity or overweight is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight for Cockroft and Gault may be considered (4).
- Modification of dose based on renal function
  - If Cockroft & Gault or Wright formula are used, the dose should be adjusted per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
  - If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to re-measuring the GFR or to recalculating using Cockroft & Gault or Wright formulae taking care this does result in a dose reduction

ELIGIBILTY:

- Indications as above

EXCLUSIONS:

- Hypersensitivity to CARBOplatin, etoposide, ifosfamide or any of the excipients.

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Oncologist or Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- Virology screen -Hepatitis B (HBsAg, HBcoreAb) & C, HIV.
  *See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation

Regular tests:

- FBC, renal profile and LDH daily during therapy and twice weekly until count recovery
- Assess neurological function daily while on ifosfamide
- Check urinalysis for haematuria prior to ifosfamide and daily during treatment with ifosfamide

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. Recommended dose modification for haematological toxicity

ANC (x 10^9/L)		Platelets(x 10^9/L)	Dose
<1	and/or	<50	Discuss with consultant before proceeding

Renal and Hepatic Impairment:

Table 2. Recommended dose modifications in patients with renal or hepatic impairment

Drug	Renal impairment		Hepatic impairment			
CARBOplatin	**Cr Cl (ml/min)**	**Dose**	No dose modification required			
	<60	Greater risk of developing myelosuppression				
	<20	Contra-indicated				
Etoposide	**Cr Cl (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**		**AST**	**Dose**
	>50	100%	26-51	or	60-180	50%
	15-50	75%	>51	or	>180	Clinical decision
	<15	50%				
	Subsequent doses should be based on clinical response					
Ifosfamide	**CrCl (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**			**Dose**
	>60	100%	Dose reductions are probably not necessary for patients with altered liver function. However ifosfamide is extensively hepatically metabolised and some clinicians recommend a 25% dose reduction for patients with significant hepatic dysfunction (serum AST > 300IU/L or bilirubin > 51.3 micromol/L (4) The SPC states that it is not recommended in patients with a bilirubin >17 umol/L or transaminases >2-3xULN			
	40-59	70%				
	<40	Clinical decision				
riTUXimab	No dose adjustment necessary		No dose adjustment necessary			

Management of adverse events:

Table 3: Dose Modification of riTUXimab based on Adverse Events

Adverse reactions	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 coverage with steroids for those who are not already receiving steroids. Consider discontinuing treatment
Mild or moderate infusion-related reaction	Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Day 1 Low **(Refer to local policy).**
Day 2 High **(Refer to local policy).**
Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.

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 3: Suggested pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to riTUXimab infusion
Chlorpheniramine	10mg	IV bolus 60minutes prior to riTUXimab infusion
Hydrocortisone	100mg	IV bolus (60minutes prior to riTUXimab)

OTHER SUPPORTIVE CARE:

Proton pump inhibitor **(Refer to local policy)**
Tumour lysis syndrome prophylaxis **(Refer to local policy)**
PJP prophylaxis **(Refer to local policy)**
Mouth care **(Refer to local policy)**
Anti-viral prophylaxis **(Refer to local policy)**
Anti-fungal prophylaxis **(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.

- **Ifosfamide-induced encephalopathy:** This may occur in patients treated with high doses of ifosfamide.
    - Consider risk factors for ifosfamide induced encephalopathy (renal insufficiency, low serum albumin, large pelvic mass).
    - Methylene blue, dexmedetomidine (a sympathetic blocker) or thiamine may be a treatment option for the prevention and management of ifosfamide-associated encephalopathy **(Refer to local policy)**
- **Renal and urothelial toxicity:** Ifosfamide is both nephrotoxic and urotoxic. For prophylaxis of hemorrhagic cystitis, ifosfamide should be used in combination with mesna. Ifosfamide should be used with caution, if at all, in patients with active urinary tract infections.
- **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 anti-viral therapy, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with regular 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 Regimen 00542 RiTUXimab 375mg/m2 Combination Therapy -21 day** and **Regimen 00261 CARBOplatin (AUC 4-6) Monotherapy-21 days** for detailed information on adverse reactions/Regimen Specific Complications associated with RiTUXimab and CARBOplatin Therapy

DRUG INTERACTIONS:

- Avoid concurrent use of CARBOplatin and ifosfamide with nephrotoxic drugs (e.g. aminoglycosides, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.
- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, NSAIDS). When necessary perform regular audiometric testing
- Current drug interaction databases should be consulted for more information eg interaction potential with CYP3A4 inhibitors/ inducers.

ATC CODE:

CARBOplatin	L01XA02
Etoposide	L01CB01
Ifosfamide	L01AA06
RiTUXimab	L01XC02

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2. Hertzberg, MS. Crombie C, Benson W. et al. Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non Hodgkin's and Hodgkin's lymphoma. Ann Oncol 2006;17 (4):iv25-30.
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Version	Date	Amendment	Approved By
1	08/07/2017 27/06/2017		Prof Elizabeth Vandenberghe, Prof Maccon Keane
2	26/07/2019	Standardisation of treatment table Updated Emetogenic Potential Amended recommendation for Hep B reactivation	Prof Elizabeth 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.