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

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status**
Treatment of relapsed/refractory Non Hodgkin's Lymphoma (NHL)*	C85	00751a	N/A
Treatment of relapsed/refractory Hodgkin's Lymphoma (HL)	C81	00751b	N/A

* riTUXimab to be included in CD20 positive patients
** This is for post 2012 indications only

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 Days 1-3 as described in the treatment table every 21 days.
Standard salvage treatment for HL or DLBCL patients eligible for consolidation autologous or allogeneic stem cell transplantation or CAR-T therapy is 3 cycles of R-ICE.
Salvage treatment for patients ineligible for standard consolidation autologous or allogeneic stem cell transplantation or CAR-T therapy is 4 cycles of R-ICE.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Note: Specific Hydration therapy is required for the safe administration of ifosfamide (See Table below).

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	riTUXimab	375mg/m^2	IV infusion[a, b] Observe post infusion[a]	500mL 0.9% NaCl at a maximum rate of 400mg/hour[a]	All
1, 2, 3	Etoposide	100mg/m^2	IV infusion	1000mL 0.9% NaCl over 60 minutes	All
1	CARBOplatin	AUC 5	IV infusion	500mL glucose 5% over 30 minutes	All
1, 2, 3	Mesna	500mg/m^2	IV Bolus	Into the side arm of a fast-flowing 0.9% NaCl drip, 15 minutes before ifosfamide infusion starts.	All
1, 2, 3	Ifosfamide[c]	1667mg/m^2	IV infusion	In 1000mL 0.9% NaCl over 2 hours	All
1, 2, 3	Mesna	500mg/m^2	IV Bolus	Into the side arm of a fast-flowing 0.9% NaCl drip, 4 hours post start of ifosfamide infusion.	All
1, 2, 3	Mesna	1000mg/m^2	PO	To be taken 8 hours post start of ifosfamide infusion.	All
From day 4	G-CSF	5mcg/kg	Subcutaneous (SC) injection (Round to nearest whole syringe)	Continued until ANC >1x10^{9}/L for 2 consecutive days	All

[a]See Table 1: Guidance for administration of riTUXimab.
[b]from Cycle 2 onwards, riTUXimab SC (fixed dose of 1,400mg) may be considered.
[c]**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 >1000mL or weight increases by >1Kg, the patient should be reviewed and consideration given to diuresing with furosemide.

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Table 1: Guidance for administration of IV riTUXimab

The recommended initial rate for infusion is 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions can be infused at an initial rate of 100 mg/hour, and increased by 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour. Development of an allergic reaction may require a slower infusion rate. 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 [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)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- **Estimation of GFR (eGFR)** can be done by using the Wright formula or using the Cockcroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125mL/min.
- For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, the formulae may not give accurate results and measured GFR is recommended.
  - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available, the use of the adjusted ideal body weight for Cockcroft and Gault may be considered.
  - Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered.

- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (mL/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (mL/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above

CAUTION:

- Patients with abnormal renal function or at increased risk of ifosfamide encephalopathy would not be deemed suitable for outpatient ICE.

EXCLUSIONS:

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

*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- LDH, Uric acid
- Isotope GFR measurement (preferred) or GFR / Cr Clearance estimation
- Virology screen - Hepatitis B (HBsAg, HBcoreAb) & C, HIV
  *See 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 2: Dose modification in 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 3: Dose modifications in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment	
riTUXimab[a]	No need for dose adjustment is expected Haemodialysis: no dose adjustment is needed		No need for dose adjustment is expected	
Etoposide[b]	**CrCl (mL/min)**	**Dose**	**Total Bilirubin (micromol/L)**	**Dose**
	>50	No dose adjustment is needed	< 50 and normal albumin and normal renal function	No need for dose adjustment is expected
	10-50	75% of the original dose, increase if tolerated	≥ 50 or decreased albumin levels	Consider 50% of the dose, increase if tolerated
	Haemodialysis	Not dialysed, consider 75% of the original dose		
CARBOplatin	See note below*		No dose modification required	
Ifosfamide[c]	**CrCl (mL/min)**	**Dose**		
	≥50	No dose adjustment is needed	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy. 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 > 300units/L or bilirubin > 51.3 micromol/L. The SPC states that it is not recommended in patients with a bilirubin >17 umol/L or transaminases >2-3xULN. Clinical decision.	
	< 50	Not recommended		
	Haemodialysis	Not recommended		

[a] riTUXimab (renal and hepatic - Giraud et al);
[b]Etoposide (renal and hepatic - Giraud et al);
[c]Ifosfamide (renal - Giraud et al, hepatic -based on Giraud et al 2023 and as agreed with clinical reviewer)

***Renal dysfunction and CARBOplatin:**

- Patients with creatinine clearance values of <60mL/min are at greater risk of developing myelosuppression.
- If GFR between 20 to ≤ 30mL/min, CARBOplatin should be administered with extreme caution
- If GFR ≤ 20mL/min, CARBOplatin should not be administered at all
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required on each cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases,

consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 4: 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 • Second 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. 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:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting Available on the NCCP website

riTUXimab: Minimal **(Refer to local policy).**
Etoposide: Low **(Refer to local policy).**
CARBOplatin: High **(Refer to local policy).**
Ifosfamide: High **(Refer to local policy).**

Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant.

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists Haemato-oncologists and information is available in the following document:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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 5: Suggested pre-medications prior to riTUXimab infusion

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

OTHER SUPPORTIVE CARE:

- Proton pump inhibitor **(Refer to local policy)**
- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
    - **Note: When this regimen is being used for stem cell mobilisation, do not give co-trimoxazole for 2 weeks prior to collection. Recommence when collection completed**
- Mouth care **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**

ADVERSE EFFECTS:

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS:

- **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 **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

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12. Etoposide Summary of Product Characteristics. Last updated 28/09/2023. Accessed December 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-201-001_28092023132640.pdf
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14. Ifosfamide (Mitoxana®) Summary of Product Characteristics. Last updated 11/09/2023. Accessed December 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-028-001_11092023124600.pdf

Version	Date	Amendment	Approved By
1	02/11/2022		NCCP Lymphoid Clinical Advisory Group
2	03/09/2024	Reviewed. Updated exclusions and tests sections in line with NCCP standardisation. Updated renal and hepatic dose modifications in line with Giraud recommendations 2023 (except ifosfamide hepatic dose modification) Updated other Supportive Care for PJP prophylaxis. Regimen updated in line with NCCP standardisation.	Dr Anne Fortune

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.