Brentuximab vedotin and Ifosfamide, CARBOplatin and Etoposide (ICE) Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL)	C81	00528a	Brentuximab– ODMS 12/11/2021 Ifosfamide, CARBOplatin and Etoposide – N/A

* This applies to post 2012 indications

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 with ICE is administered on Day 1-3 as described in the treatment table below every 21 days depending on myelosuppression for up to three cycles in responding patients as a bridge to transplant unless disease progression or unacceptable toxicity develops
- Brentuximab vedotin is administered on day 1 of each cycle 1-3 and a fourth dose is administered on day 22 of cycle 3.

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	Brentuximab vedotin	1.8mg/kg [a]	IV infusion[b]	150mL 0.9% NaCl[c, d] over 30 minutes.	1-3
22, (cycle 3 Only)	Brentuximab vedotin	1.8mg/kg [a]	IV infusion[b]	150mL 0.9% NaCl[c, d] over 30 minutes.	**3 ONLY**
1, 2 , 3	Etoposide	100mg/m^2	IV infusion	1000mL 0.9% NaCl over 60 minutes.	1-3
2	CARBOplatin	AUC 5	IV infusion	500mL glucose 5% over 30 minutes.	1-3
2	Mesna	1000mg/m^2	IV Bolus	Into the side arm of a fast-flowing 0.9% NaCl drip immediately before ifosfamide infusion starts.	1-3
2	Ifosfamide[e]	5000mg/m^2	IV infusion	In 1000mL 0.9% NaCl over 24 hours[f]	1-3
2	Mesna	5000mg/m^2	IV infusion	In 1000mL 0.9% NaCl over 24 hours. Y-sited with the ifosfamide	1-3
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.	1-3
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.	1-3
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.	1-3
From day 6	G-CSF[g]	5mcg/kg[h]	SC	Continued until ANC >1x10^9/L for 2	1-3

			(Round to nearest whole syringe)	consecutive days.	

[a]For patient weight > 100kg, the dose calculation should use 100kg.

[b]Patient should be carefully monitored during and after infusion in case of infusion related reactions.

[c]Final concentration of brentuximab should be 0.4-1.2mg/mL

[d]Glucose 5% or Compound Sodium Lactate (Hartmann's Solution) may also be used as diluent.

[e]**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 >1 Kg, the patient should be reviewed and consideration given to diuresing with furosemide.

[f]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.

[g]G-CSF support is required with this regimen (**Refer to local policy or see Suggested support above**).

[h] Standard mobilisation dose of g-CSF post Bv-ICE mobilisation is 5 mcg/Kg; however this must be verified on an individual basis with local harvesting centre (**Refer to local policy).**

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

CARBOPLATIN DOSE:

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

Dose (mg) = target AUC (mg/mL x minute) x (GFR mL/minute +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/minute
- For obese patients and those with a low serum creatinine due to low body weight or postoperative 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

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

S= 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- Confirmation of lymphomatous CD30 expression using a validated test method.

EXCLUSIONS:

- Hypersensitivity to brentuximab, 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 Oncologist or Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal and liver profile, blood glucose
- Isotope GFR measurement or GFR/CrCl estimation
- Clinical assessment to exclude neuropathy for brentuximab therapy
- Virology screen - Hepatitis B* (HBsAg, HBcoreAb), Hepatitis C and HIV

***See Regimen Specific Complications re Hepatitis B reactivation**

Regular tests:

- FBC, renal and liver profile daily during therapy and twice weekly until count recovery
- Blood glucose prior to each cycle
- 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		
Brentuximab	There is no clinical trial experience in patients with renal impairment, where CrCl is ≤40 mL/minute. Use of brentuximab vedotin in combination with chemotherapy in patients with severe renal impairment should be reviewed with consultant.		**Mild:** The recommended starting dose is 1.2 mg/kg every 3 weeks. **Moderate to Severe:** There is no clinical trial experience, therefore this combination with chemotherapy should be avoided. Discuss with consultant.		
CARBOplatin	*See note below		No dose modification required		
Etoposide	**Cr Cl (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 dose.			
Ifosfamide	**CrCL (ml/min)**	**Dose**	**Total Bilirubin (micromol/L)**		**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 > 300IU/L or bilirubin > 51.3 micromol/L. Clinical decision.		
	<50 or haemodialysis	Not recommended			

[a] Brentuximab vedotin: renal – SmPc and as per clinician feedback, hepatic - SmPC
[b] CARBOplatin: NCCP Standardisation
[c] Etoposide: renal and hepatic dose modifications from Giraud et al (2023)
[d] Ifosfamide: renal and hepatic dose modifications from Giraud et al (2023) and clinician feedback

***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 per 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 3: Dose modification of brentuximab vedotin based on adverse events

Adverse reactions		Dose
Peripheral sensory or motor neuropathy*	Grade 1	Continue with the same dose and schedule.
	Grade 2	Sensory neuropathy: Continue treatment at same dose level. Motor neuropathy: Reduce dose to 1.2 mg/kg, up to a maximum of 120 mg every 3 weeks.
	Grade 3	Sensory neuropathy: Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks. Motor neuropathy: Discontinue treatment.
	Grade 4	Discontinue treatment.
Progressive Multifocal Leukoencephalopathy (PML)		Discontinue treatment.
Severe Cutaneous Adverse Reactions (SCARs)		Discontinue treatment.
*Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

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

Brentuximab vedotin: Low **(Refer to local policy).**
CARBOplatin: High **(Refer to local policy).**
Etoposide: Low **(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 and Haemato-oncologists and information is available in the following documents:

- 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:

Patients who have experienced a prior infusion-related reaction with brentuximab vedotin should be premedicated with analgesics, antihistamines and corticosteroids for subsequent infusions.

OTHER SUPPORTIVE CARE:

- Patients receiving brentuximab vedotin who are eligible for allogeneic transplantation should receive irradiated blood products
- 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:** 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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3. Garcia-Sanz, R et al. Brentuximab Vedotin Plus ESHAP (BRESHAP) Is a Highly Effective Combination for Inducing Remission in Refractory and Relapsed Hodgkin Lymphoma Patients Prior to Autologous Stem Cell Transplant: A Trial of the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO) Blood 2016 128:1109
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12. Brentuximab (ADCETRIS®) Summary of Product Characteristics. Last updated 01/12/2023. Accessed 27/05/2024. Available at https://www.ema.europa.eu/en/documents/product-information/adcetris-epar-product-information_en.pdf

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Version	Date	Amendment	Approved By
1	12/11/2020		NCCP Lymphoid CAG
2	18/11/2024	Regimen reviewed. Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing and creatinine value. Updated exclusion criteria Updated testing section. Updated recommendations for dosing in renal and hepatic impairment (Table 2). Updated Table 3 to align with SmPC. Updated PJP Prophylaxis in Other Supportive Care. Regimen updated in line with NCCP standardisation	NCCP Lymphoid CAG

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of brentuximab vedotin 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" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.