# Brentuximab vedotin and ICE Therapy[i]

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|---|---|---|---|
| Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL) | C81 | 00528a | Brentuximab– ODMS[ii]<br>CARBOplatin – Hospital<br>Etoposide – Hospital<br>Ifosfamide – Hospital |

## 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 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 | Brentuximab vedotin | 1.8mg/kg [1,2] | IV infusion[3,4] | 150ml 0.9% NaCl over 30 minutes. | 1-3 |
| **22, (cycle 3 Only)** | Brentuximab vedotin | 1.8mg/kg [1,2] | IV infusion[3,4] | 150ml 0.9% NaCl over 30 minutes. | **3 ONLY** |
| 1, 2 , 3 | Etoposide | 100mg/m$^2$ | IV infusion | 1000mls 0.9% NaCl over 60 minutes. | 1-3 |
| 2 | CARBOplatin | AUC 5 | IV infusion | 500ml glucose 5% over 60 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[5] | 5000mg/ m$^2$ | IV infusion | In 1000ml 0.9% NaCl over 24 hours[6] | 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[7] | 5mcg/kg[8] | SC (Round to nearest whole syringe) | Continued until ANC >1x10$^{9}$/L for 2 consecutive days | 1-3 |

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

[2]Final concentration of brentuximab should be 0.4-1.2mg/ml

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

[4]Dextrose 5% or Lactated Ringer's for Injection may also be used as diluent.

**[5]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

**[6]** 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.

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

[8]For stem cell mobilisation dose of 5mcg/kg or 10mcg/kg may be used and continue until stem cell harvest is complete (**Refer to local policy )**

**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 Cockroft and Gault formula to measure creatinine clearance
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese and anorexic patients the formulae may not give accurate results and measured GFR is recommended. 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 (6).

**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
- Confirmation of lymphomatous CD30 expression using a validated test method.

## EXCLUSIONS:

- Hypersensitivity to brentuximab, 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, blood glucose
- Clinical assessment to exclude neuropathy for brentuximab therapy
- 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 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**

<table>
<tr><th>Drug</th><th colspan="3">Renal impairment</th><th colspan="4">Hepatic impairment</th></tr>
<tr><td>Brentuximab</td><td colspan="3">The recommended starting dose in patients with severe renal impairment is 1.2 mg/kg administered as an IV infusion over 30 minutes every 3 weeks.<br>Patients with renal impairment should be closely monitored for adverse events.</td><td colspan="4">The recommended starting dose in patients with hepatic impairment is 1.2 mg/kg administered as an IV infusion over 30 minutes every 3 weeks.<br>Patients with hepatic impairment should be closely monitored for adverse events.</td></tr>
<tr><td>CARBOplatin</td><td colspan="3">• Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.<br>• In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.<br>• 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.<br>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 remeasuring the GFR or to recalculating using Cockroft & Gault or Wright formulae taking care this does result in a dose reduction</td><td colspan="4">No dose modification required</td></tr>
<tr><td rowspan="5">Etoposide</td><td>Cr Cl (ml/min)</td><td colspan="2">Dose</td><td>Total Bilirubin (micromol/L)</td><td>AST</td><td colspan="2">Dose</td></tr>
<tr><td>>50</td><td colspan="2">100%</td><td>26-51</td><td>or 60-180</td><td colspan="2">50%</td></tr>
<tr><td>15-50</td><td colspan="2">75%</td><td>>51</td><td>or >180</td><td colspan="2">Clinical decision</td></tr>
<tr><td><15</td><td colspan="2">50%</td><td colspan="4" rowspan="2"></td></tr>
<tr><td colspan="3">Subsequent doses should be based on clinical response</td></tr>
<tr><td rowspan="4">Ifosfamide</td><td>CrCL (ml/min)</td><td colspan="2">Dose</td><td colspan="3">Total Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td>>60</td><td colspan="2">100%</td><td colspan="4" rowspan="3">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 (7)<br>The SPC states that it is not recommended in patients with a bilirubin >17 micromol/L or transaminases ≥ 2.5 xULN</td></tr>
<tr><td>40-59</td><td colspan="2">70%</td></tr>
<tr><td><40</td><td colspan="2">Clinical decision</td></tr>
</table>

## Management of adverse events:

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

| Adverse reactions* | Recommended dose modification |
|---|---|
| Sensory neuropathy<br>• Grade 2<br>• Grade 3<br>• Grade 4 | <br>Continue treatment at same dose level<br>Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks.<br>Discontinue |
| Motor neuropathy<br>• Grade 2<br>• Grade ≥3 | <br>Reduce dose to 1.2 mg/kg up to a maximum of 120 mg every 3 weeks<br>Discontinue |
| PML** | Discontinue |
| Stevens-Johnson syndrome | Discontinue |

*Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03
** PML= Progressive multifocal leukoencephalopathy

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

Brentuximab vedotin: Low risk **(Refer to local policy).**
CARBOplatin: High risk **(Refer to local policy).**
Etoposide: Low risk **(Refer to local policy).**
Ifosfamide*: High risk **(Refer to local policy).**
**Consider increased risk of ifosfamide-induced neurotoxicity due to inhibition of CYP3A4 by aprepitant*.

### PREMEDICATIONS:

Patients who have experienced a prior infusion-related reaction with brentuximab should be pre medicated 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)**
- 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.*

- **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.
- **Serious infections and opportunistic infections:** Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections
- **Tumour lysis syndrome:** Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome. These patients should be monitored closely and managed according to best medical practice.
- **Febrile neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.

**Brentuximab:**

**The medicinal product brentuximab vedotin is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.**

- **Hepatotoxicity** in the form of elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) has been reported with brentuximab vedotin. Serious cases of hepatotoxicity, including fatal outcomes, have also occurred. Pre-existing liver disease, comorbidities, and concomitant medications may also increase the risk.
- **Peripheral neuropathy:** Brentuximab vedotin treatment may cause a peripheral neuropathy which is related to cumulative exposure and is reversible in most cases. Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of brentuximab vedotin or discontinuation of treatment.
- **Progressive multifocal leukoencephalopathy(PML):** John Cunningham virus (JCV) reactivation resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in brentuximab vedotin-treated patients. Patients should be closely monitored for new or worsening neurological, cognitive, or behavioural signs or symptoms, which may be suggestive of PML. Brentuximab vedotin dosing should be held for any suspected case of PML. If a diagnosis of PML is confirmed treatment with brentuximab vedotin should be permanently discontinued.
- **Pancreatitis:** Acute pancreatitis has been observed in patients treated with brentuximab vedotin. Fatal outcomes have been reported. Patients should be closely monitored for new or worsening abdominal pain, which may be suggestive of acute pancreatitis. Brentuximab vedotin should be held for any suspected case of acute pancreatitis. Brentuximab vedotin should be discontinued if a diagnosis of acute pancreatitis is confirmed.
- **Pulmonary Toxicity:** Cases of pulmonary toxicity, including pneumonitis, interstitial lung disease, and acute respiratory distress syndrome (ARDS), some with fatal outcomes, have been reported in patients receiving brentuximab vedotin. Although a causal association with brentuximab vedotin has not been established, the risk of pulmonary toxicity cannot be ruled out. In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Consider holding brentuximab vedotin dosing during evaluation and until symptomatic improvement.
- **Infusion-related reactions:** Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported with brentuximab. Patients should be carefully monitored during and after infusion. If an anaphylactic reaction occurs, administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy should be

administered.

- **Stevens-Johnson syndrome:** If this occurs, treatment with brentuximab vedotin should be discontinued and appropriate medical therapy administered**.**
- **Gastrointestinal Complications:** Gastrointestinal (GI) complications including intestinal obstruction, ileus, enterocolitis, neutropaenic colitis, erosion, ulcer, perforation and haemorrhage, some with fatal outcomes, have been reported in patients treated with brentuximab vedotin. In the event of new or worsening GI symptoms, perform a prompt diagnostic evaluation and treat appropriately.
- **Hyperglycaemia:** Hyperglycaemia has been reported during clinical trials in patients with an elevated Body Mass Index (BMI) with or without a history of diabetes mellitus. Any patient who experiences hyperglycaemia should have their serum glucose closely monitored. Anti-diabetic treatment should be administered as appropriate**.**
- **Sodium content in excipients:** This medicinal product contains a maximum of 2.1mmol of sodium per dose, which needs to be taken into consideration for patients on a controlled sodium diet.

**CARBOplatin**

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with CISplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years

**Ifosfamide**

- **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

## 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 e.g. interaction potential with CYP3A4 inhibitors/ inducers.
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

| | |
|---|---|
| Brentuximab vedotin | L01XC12 |
| CARBOplatin | L01XA02 |
| Etoposide | L01CB01 |
| Ifosfamide | L01AA06 |

## REFERENCES:


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6. Floyd J and Kerr TA. Chemotherapy hepatotoxicity and dose modification in patients with liver disease UptoDate https://www.uptodate.com/contents/chemotherapy-hepatotoxicity-and-dose-modification-in-patients-with-liver-disease#H14
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| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 12/11/2020 | | 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.

[ii] ODMS – Oncology Drug Management System
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/