Brentuximab vedotin and ESHAP therapy[i] (BRESHAP)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with relapsed/refractory CD30+ Hodgkin's lymphoma	C81	00530a	Brentuximab vedotin – ODMS Etoposide, CISplatin and cytarabine – 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 BRESHAP can be repeated at 21 day intervals depending on myelosuppression for up to three cycles in responding patients as a bridge to transplant unless disease progression or unacceptable toxicity develops

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate	Cycle
1	Brentuximab vedotin	[1,2]1.8mg/kg	IV infusion[3]	150ml 0.9% NaCl over 30 minutes.[4]	1-3
1-4	Methylprednisolone	250mg	IV infusion	100ml 0.9% NaCl over 15 minutes	1-3
1-4	Etoposide	40mg/m^2	IV infusion	500ml 0.9% NaCl over 1 hour	1-3
1-4	[5]CISplatin	25mg/m^2	IV infusion	1000ml 0.9% NaCl over 24 hours	1-3
5	Cytarabine	2000mg/m^2	IV infusion	1000mls 0.9% NaCl over 2 hours	1-3
6 onwards (starting at least 24 hours post cytarabine infusion)	[6]G-CSF	[7]5mcg/kg	SC (Round to nearest whole syringe)	Daily injection until ANC >1x10^9/L for 2 consecutive days	
[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]**Pre 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					
[6]G-CSF support is required with this regimen (**Refer to local policy or see Suggested support above**)					
[7]For stem cell mobilisation dose at 10mcg/kg and continue until stem cell harvest is complete (**Refer to local policy)**					

ELIGIBILTY:

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

EXCLUSIONS:

- Hypersensitivity to brentuximab vedotin, CISplatin, etoposide, cytarabine or to any of the excipients.

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, blood glucose
- Assessment of pre-existing neuropathy
- LDH, Uric acid
- Audiology and creatinine clearance if clinically indicated
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), Hepatitis, HIV.

*Hepatitis B reactivation: See adverse events/ Regimen specific complications

Regular tests:

- FBC, renal and liver profile, blood glucose prior to each cycle
- Clinical assessment to exclude neuropathy
- LDH prior to each cycle
- Regular glucose monitoring while receiving steroid therapy-urinalysis 2-4 times/day 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 schedule of brentuximab vedotin based on haematological adverse reactions.

ANC (x10^9/L)	Dose
≥1.0	100% Dose
<1.0	Withhold dose until toxicity returns to ≤ Grade 2 or baseline then resume treatment at the same dose and schedule*. Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles. For the second occurrence of Grade 4 toxicity (if neutropenia , while receiving growth factor support), withhold dose until toxicity is ≤ Grade 2, then reduce the dose to 1.2 mg/kg and resume treatment*

*Patients who develop Grade 3 or Grade 4 lymphopenia may continue treatment without interruption.

Renal and Hepatic Impairment:

Table 2: Recommended dose modification in renal and hepatic impairment

Drug	Renal impairment		Hepatic impairment			
Brentuximab vedotin	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. Patients with renal impairment should be closely monitored for adverse events.		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. Patients with hepatic impairment should be closely monitored for adverse events.			
CISplatin	**CrCl (ml/min)**	**Dose**	No dose modification required			
	>60	100%				
	45-60	75%				
	<45	Clinical decision				
Etoposide	**CrCl(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					
Cytarabine	**CrCl (ml/min)**	**Dose**	If bilirubin >34micromol/L, give 50% dose. Escalate doses in subsequent cycles in the absence of toxicity.			
	>60	100%				
	45-60	60%				
	30-45	50%				
	<30	Avoid				

Adverse events

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

Adverse reactions	Recommended dose modification
Peripheral neuropathy • Grade 2 or 3 • Grade 4	• Withhold dose until toxicity returns to ≤ Grade 1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks. • Discontinue
PML	Discontinue
Stevens-Johnson syndrome	Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (**Refer to local policy).**

PREMEDICATIONS:

- Hydration prior to CISplatin administration **(Refer to local policy or see recommendations above)**
- Patients who have experienced a prior infusion-related reaction with brentuximab vedotin should be premedicated with analgesics, antihistamines and corticosteroids for subsequent infusions.
- To prevent a chemical induced conjunctivitis developing with cytarabine, Prednisolone eye drops (e.g. Pred Mild) 1-2 drops per eye 4 hourly during waking hours prior to cytarabine and continued 5 days post treatment should be considered

OTHER SUPPORTIVE CARE:

- Patients receiving brentuximab vedotin who are eligible for allogeneic transplantation should receive irradiated blood products.
- 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)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

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

- **Hepatitis B Reactivation**: All 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 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.
- **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 vedotin

- **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.
- **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. Patient evaluation may include physical examination, laboratory evaluation for serum amylase and serum lipase, and abdominal imaging, such as ultrasound and other appropriate diagnostic measures. 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.
- **Peripheral neuropathy:** Brentuximab vedotin treatment may cause a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. Brentuximab vedotin-induced peripheral neuropathy is typically an effect of cumulative exposure to this medicinal product 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.
- **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, neutropenic 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.

CISplatin

- **Renal toxicity:** Renal toxicity is common with CISplatin. Encourage oral hydration.
- **Ototoxicity and sensory neural damage** should be assessed by history prior to each cycle of CISplatin

Cytarabine

- **Neurotoxicity:** This may occur in patients treated with high dose cytarabine. Assess cerebellar function prior to each cytarabine dose. The risk of neurotoxicity is enhanced in the presence of renal impairment. Ensure that dose of cytarabine is adjusted in renal impairment (Ref Table 2).
- **Cytarabine syndrome:** Treatment with cytarabine may cause a 'Cytarabine Syndrome' characterised by flu-like symptoms, skin rash and occasionally chest pain.
- **Myelosuppression:** Cytarabine is a potent bone marrow suppressant. Patients receiving this drug must be under close medical supervision and should have leucocyte and platelet counts performed daily

DRUG INTERACTIONS:

- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Brentuximab vedotin	L01XC12
CISplatin	L01XA01
Etoposide	L01CB01
Cytarabine	L01BC01

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3. Garcia-Sanz, R et al. Brentuximab vedotin and ESHAP is highly effective as second-line therapy for Hodgkin lymphoma patients (long-term results of a trial by the Spanish GELTAMO Group) Annals of Oncology 30: 612–620, 2019

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Version	Date	Amendment	Approved By
1	30/09/2019		Dr Amjad Hayat

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i]This is an unlicensed indication for the use of brentuximab vedotin in combination with ESHAP 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.