Brentuximab vedotin, Etoposide, methylPREDNISolone, Cytarabine and CISplatin, (ESHAP) therapy[i] (BRESHAP)

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adult patients with relapsed/refractory CD30+ Hodgkin's lymphoma	C81	00530a	Brentuximab vedotin – ODMS 30/09/2021 Etoposide, CISplatin and cytarabine – 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 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 systemic anticancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	Brentuximab vedotin	1.8mg/kg[a]	IV infusion[b]	150mL 0.9% NaCl over 30 minutes[c, d]	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	CISplatin[e]	25mg/m^2	IV infusion	1000mL 0.9% NaCl over 24 hours	1-3
5	Cytarabine	2000mg/m^2	IV infusion	1000mL 0.9% NaCl over 2 hours	1-3
6 onwards (starting at least 24 hours post cytarabine infusion)	G-CSF[f]	5mcg/kg[g]	SC (Round to nearest whole syringe)	Daily injection until ANC >1x10^9/L for 2 consecutive days	

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

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

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

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

[e]**Pre hydration therapy** required for CISplatin
See local hospital policy recommendations.
Suggested prehydration for CISplatin therapy:

1. Administer 10mmol magnesium sulphate ($MgSO_4$) ((+/-KCl 10-20mmol/L if indicated) in 1000mL NaCl 0.9% over 60-120 minutes. (Refer to relevant local hospital policy for advice on administration of electrolyte infusions).

Administer CISplatin as described above.

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

[g]For stem cell mobilisation dose at 10mcg/kg and continue until stem cell harvest is complete (**Refer to local policy)**

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

ELIGIBILITY:

- Indications as above

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

EXCLUSIONS:

- Hypersensitivity to brentuximab vedotin, methylPREDNISolone, 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 C and HIV

*Hepatitis B reactivation: See 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[a]	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 should be avoided in patients with severe renal impairment- Discuss 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.
CISplatin[b]	**CrCl (mL/minute)**	**Dose**	No need for dose adjustment is expected.	
	>60	100%		
	50-59	75% of the original dose		
	40-49	50% of the original dose		
	<40	Not recommended		
	Haemodialysis	50% of the original dose may be considered		
Etoposide[c]	**CrCl (mL/minute)**	**Dose**	Bilirubin <50 micromol/L and normal albumin and normal renal function	No need for dose adjustment is expected.
	>50	No dose adjustment is needed		
	10-50	75% of the original dose, increase if tolerated	Bilirubin >50 micromol/L or decreased albumin levels	Consider 50% of the dose, increase if tolerated
	Haemodialysis	Not dialysed, consider 75% of the original dose.		
Cytarabine[d]	**CrCl (mL/minute)**	**Dose**	Mild and moderate	No need for dose adjustment is expected.
	≥60	No dose adjustment is needed	Severe	Consider 25-50% of the original dose and increase if tolerated

	<31-59	50% of the original dose		
	<30	Not recommended		
	Haemodialysis	50% of the original dose, start haemodialysis 4-5 hours after administration		

[a] Brentuximab vedotin: renal and hepatic dose modifications from SmPC,
[b] CISplatin: renal and hepatic dose modifications from Giraud et al (2023),
[c] Etoposide: renal and hepatic dose modifications from Giraud et al (2023),
[d] Cytarabine: renal and hepatic dose modifications from Giraud et al (2023).

Adverse events

Table 3: Dosing recommendations for new or worsening peripheral sensory or motor neuropathy during combination therapy

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 linked here:

Brentuximab Vedotin: Low **(Refer to local policy)**
Etoposide: Low **(Refer to local policy)**
CISplatin: High **(Refer to local policy)**
Cytarabine: Moderate **(Refer to local policy)**

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) - link here
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - link here

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

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:

1. NCCP SACT clinical Advisory lymphoid group: Brentuximab vedotin in combination with chemotherapy in patients with relapsed or primary refractory Hodgkin lymphoma. Evidence into practice –rapid review June 2018
2. 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
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
4. Irish Medication Safety Network: Best Practice Guidelines For the Safe Use of Intravenous Potassium in Irish Hospitals Available here
5. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or

hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023 Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
7. 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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10. Cytarabine 100mg/mL Solution for Injection or Infusion. Last updated 26/11/2020. Accessed 28/05/2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-082-001_26112020144445.pdf

Version	Date	Amendment	Approved By
1	30/09/2019		Dr Amjad Hayat
2	22/08/2024	Regimen reviewed. Updated treatment table to align with new regimen template. Updated Table 2 recommendations for dosing in renal and hepatic impairment. Updated Table 3 dose modifications for adverse events. Updated Supportive Care (including emetogenic potiential). Updated Adverse Effects, Regimen Specific Complications and Drug Interaction sections. ATC codes removed. Updated in line with NCCP Standardisation.	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.