Brentuximab vedotin and Bendamustine 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	00529a	Brentuximab vedotin - ODMS 18/10/2021 Bendamustine: 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.

Brentuximab vedotin is administered on day 1 and bendamustine on day 1 and 2 of a 21 day cycle for up to 6 cycles as a bridge to transplant unless disease progression or unacceptable toxicity develops.

Note:
Patients should be evaluated after a minimum of 2 cycles for suitability for ASCT. If further cycles are administered patients should be evaluated after cycle 4.

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

Admin. Order	Day	Drug	Dose	Route	Diluent and Rate	Cycle
1	1	Brentuximab vedotin	1.8mg/kg[a]	IV infusion[b]	150mL 0.9% NaCl[c,d] over 30 minutes.	Repeat every 21 days
2	1 and 2	Bendamustine	90[e] mg/m²	IV infusion	500mL NaCl 0.9% over 60 minutes[f]	Repeat every 21 days
1	3 onwards (starting at least 24 hours post bendamustine infusion)	G-CSF[g]	5 mcg/kg	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]Patient 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) may also be used as diluent.
[e]Dose of bendamustine may be reduced to 70mg/m² at clinicians discretion
[f]A shorter administration time of 30 minutes may be used at the discretion of the prescribing consultant
[g]G-CSF support is recommended with this regimen (**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.
- ECOG 0-2

CAUTION:

- Bendamustine should be avoided as part of a salvage regimen for patients where CAR-T cell therapy is anticipated.

EXCLUSIONS:

- Hypersensitivity to brentuximab vedotin, bendamustine or to any of the excipients.
- Combined use of bleomycin and brentuximab vedotin is contraindicated due to pulmonary toxicity.

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, uric acid
- Assessment of pre-existing neuropathy
- 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

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:

- If neutropenia develops during treatment, see Table 1 for appropriate dosing recommendations for combination therapy.

Table 1: Dose modification of bendamustine in haematological toxicity

ANC (x 10^9/L)		Platelets(x 10^9/L)	Dose of Bendamustine
≥1	and	≥75	100%
<1	or	<75	Delay until recovery

Renal and Hepatic Impairment:

- Patients with renal and hepatic impairment should be closely monitored for adverse effects during treatment with brentuximab vedotin

Table 2: Dose modification of brentuximab vedotin and bendamustine 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.
Bendamustine [b]	No dose adjustment is needed	**Mild: (bilirubin <20 micromol/L)**	No dose adjustment is needed
	Haemodialysis: No dose adjustment is needed	**Moderate: (bilirubin 20-51 micromol/L)**	70% of the original dose
		Severe: (bilirubin >51micromol/L)	Not recommended

[a] Brentuximab vedotin: renal and hepatic dose modifications from SmPC
[b] Bendamustine: renal and hepatic dose modifications from Giraud et al (2023)

Management of 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 1.2mg/kg, up to a maximum of 120mg every 3 weeks.
	Grade 3	Sensory neuropathy: Reduce dose to 1.2mg/kg, up to a maximum of 120mg 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:

Bendamustine: Moderate **(Refer to local policy)**
Brentuximab vedotin: Low (**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:

Table 4: Suggested premedications prior to brentuximab vedotin administration when used in combination with bendamustine (required pre-brentuximab vedotin on day 1 only)

Drug	Dose	Route
methylPREDNISolone	100mg	IV 60 minutes prior to brentuximab vedotin administration
Chlorphenamine	10mg	IV 60 minutes prior to brentuximab vedotin administration

- Patients who experience a prior infusion related reaction with brentuximab vedotin should also be premedicated with analgesics for subsequent infusions in addition to the recommended antihistamines and corticosteroids

OTHER SUPPORTIVE CARE:

- Patients receiving brentuximab vedotin and bendamustine 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).** *See Drug Interactions below
- PJP prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Anti-viral 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. LaCasce A S, Bociek R G et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood 2015 126(23)3982.
3. O'Connor et al. Brentuximab vedotin plus bendamustine in relapsed or refractory Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1–2 trial. Lancet Oncol 2018:19;257-66.
4. 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/
5. 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
6. Brentuximab vedotin (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
7. Bendamustine Summary of Product Characteristics. Last updated 20.07.2023. Accessed 29.05.2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1986-121-002_20072023160713.pdf

Version	Date	Amendment	Approved By
1	18/10/2019		Dr Anne Fortune
2	29/07/2024	Regimen Reviewed. Amended infusion time for Bendamustine. Updated eligibility criteria. Updated recommendations for dosing in renal and hepatic impairment (Table 2). Updated Table 3. Updated adverse events and drug interaction sections.	Dr Anne Fortune

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

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