Brentuximab vedotin and Bendamustine Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL)	C81	00529a	Brentuximab- ODMS Bendamustine -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.

Brentuximab is administered on day one and bendamustine on day one and two 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 the chemotherapy is administered.

Order of admin	Day	Drug	Dose	Route	Diluent and Rate	Cycle
1	1	Brentuximab vedotin	[a]1.8mg/kg	IV infusion	150ml 0.9% NaCl[b] over 30 minutes.	Repeat every 21 days
2	1 and 2	Bendamustine	[c]90 mg/m²	IV infusion	500ml NaCl 0.9% over 60 minutes	Repeat every 21 days
[a]For patient weight > 100kg, the dose calculation should use 100kg. Final concentration of brentuximab should be 0.4-1.2mg/ml.						
Patient should be carefully monitored during and after infusion in case of infusion related reactions.						
[b]Dextrose 5% or Lactated Ringer's for Injection may also be used as diluent.						
[c] Dose of bendamustine may be reduced to 70mg/m^2 at clinicians discretion						
G-CSF support is recommended with this regimen (**Refer to local policy**)						

ELIGIBILTY:

- Indications as above
- Confirmation of lymphomatous CD30 expression using a validated test method.
- ECOG 0-2
- Life expectancy > 3 months

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.
- Creatinine clearance (CrCl) < 40 mL/min
- AST or ALT >2.5 x upper limit of normal and total bilirubin > 1.5 x upper limit of normal

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, 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

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 it should be managed by dose delays

Table 1: Recommended dose modifications in haematological toxicity

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) in subsequent cycles for patients who develop Grade 3 or 4 neutropenia*

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

Renal and Hepatic Impairment:

Table 2: Dose modification of brentuximab vedotin and bendamustine 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.	
Bendamustine	**Cr Cl (ml/min)**	**Dose**	**Serum bilirubin (micromol/L)**	**Dose**
	>10	No dose adjustment necessary	< 21	No dose adjustment necessary
	Experience in patients with severe renal impairment is limited.		21-51	30% Dose reduction
			>51	No data available

Management of adverse events

Table 3: Recommended dose modification schedule based on adverse events

Adverse reactions	Dose
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:

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

PREMEDICATIONS:

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

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

- Patients who experience a prior infusion related reaction with brentuximab should also be pre-medicated 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 propylaxis **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Brentuximab vedotin is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions. *The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details*.

- **Febrile neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Serious infections and opportunistic infections:** Patients should be carefully monitored during treatment with bendamustine and brentuximab therapy 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
- **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.

Brentuximab

- **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.

Bendamustine

- **Anaphylaxis:** Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions. Patients who experienced Grade 3 or worse allergic-type reactions were typically not re-challenged.
- **Tumour lysis syndrome:** Tumour lysis syndrome associated with bendamustine treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of bendamustine. Standard preventive measures should be considered. The use of allopurinol during the first one to two weeks of bendamustine therapy can be considered but is not considered as standard. There have been reports of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis when bendamustine and allopurinol were administered concomitantly.
- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely. During treatment with bendamustine hydrochloride monitor potassium. Supplements must be given when K+ <3.5 mEq/l, and ECG measurement must be performed. Fatal cases of myocardial infarction and cardiac failure have been reported with bendamustine hydrochloride treatment. Patients with concurrent or history of cardiac disease should be observed closely.

- **Skin reactions:** A number of skin reactions have been reported with bendamustine therapy. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when bendamustine hydrochloride was given in combination with other anticancer agents, so the precise relationship is uncertain. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, bendamustine should be withheld or discontinued. For severe skin reactions where a relationship to bendamustine hydrochloride is suspected, treatment should be discontinued.
- **Fertility:** Women of childbearing potential must use effective methods of contraception both before and during bendamustine therapy. Men being treated with bendamustine are advised not to father a child during and for up to 6 months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with bendamustine.
- **Infections:** Serious and fatal infections have occurred with bendamustine hydrochloride, including bacterial (sepsis, pneumonia and opportunistic infections such as Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV). Treatment with bendamustine hydrochloride may cause prolonged lymphocytopenia (< 600/microlitre) and low CD4-positive T-cell (T-helper cell) counts (< 200/microlitre) for at least 7–9 months after the completion of treatment. Lymphocytopenia and CD4-positive T-cell depletion are more pronounced when bendamustine is combined with rituximab. Patients with lymphopenia and low CD4-positive T-cell count following treatment with bendamustine hydrochloride are more susceptible to (opportunistic) infections. In case of low CD4-positive T-cell counts (< 200/microlitre) Pneumocystis jirovecii pneumonia (PJP) prophylaxis should be considered. All patients should be monitored for respiratory signs and symptoms throughout treatment. Patients should be advised to report new signs of infection, including fever or respiratory symptoms promptly. Discontinuation of bendamustine hydrochloride should be considered if there are signs of (opportunistic) infections.

DRUG INTERACTIONS:

- Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme, Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, and acyclovir exists.
- Combination of bendamustine with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.
- There have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol were administered concomitantly.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Brentuximab vedotin	-	L01XC12
Bendamustine	-	LA01AA09

REFERENCES:

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6. HPRA summary of product characteristics bendamustine accessed September 2019 - https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0405-072-001_16052018153049.pdf

Version	Date	Amendment	Approved By
1	18/10/2019		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.