Brentuximab vedotin Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): Following autologous stem cell transplant (ASCT) or Following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option	C81	 00234a 00234b	 ODMS ODMS
Treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL).	C84	00234c	ODMS

If the reimbursement status is not defined, the indication has yet to be assessed through the formal reimbursement process.

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 is administered once every 21 days until disease progression or unacceptable toxicity develops.
Patients should be evaluated after 3 cycles and non-responders should not continue with brentuximab vedotin treatment.

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

Day	Drug	Dose	Route	Diluent and Rate	Cycle
1	Brentuximab vedotin	1.8mg/kg	IV infusion	150ml 0.9% NaCl over 30 minutes.	Repeat every 21 days
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.					
Dextrose 5% or Lactated Ringer's for Injection may also be used as diluent.					

ELIGIBILTY:

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

EXCLUSIONS:

- Hypersensitivity to brentuximab 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
- 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:

Table 1: Dose modification 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) 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 in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
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.

Table 3: Dose modification schedule 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: Minimal (**Refer to local policy).**

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)**
- Anti-fungal propylaxis **(Refer to local policy).**
- Anti-viral propylaxis **(Refer to local policy).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

This medicinal product 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.

- **Hepatitis B Reactivation**: All lymphoma patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, 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.
- **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.
- **Serious infections and opportunistic infections:** Patients should be carefully monitored during treatment for the emergence of possible serious and opportunistic infections.
- **Infusion-related reactions:** Immediate and delayed infusion-related reactions (IRR), as well as anaphylactic reactions, have been reported. 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.
- **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.
- **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.
- **Febrile neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- **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.

DRUG INTERACTIONS:

- Current drug interaction databases should be consulted for more information.

ATC CODE:

Brentuximab vedotin - L01XC12

REFERENCES:

1. Pro B, Advani R, Brice P et al. Brentuximab Vedotin (SGN-35) in Patients With Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma: Results of a Phase II Study. J Clin Oncol. (2012); 30 (18): 2190-2196.
2. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med. 2010; 363(19):1812-1821.
3. Younes A, Gopal A, Smith S et al. Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin's Lymphoma. J Clin Oncol (2012): 30 (18): 2183-2189.
4. ADCETRIS ® Summary of Product Characteristics. Accessed October 2018 Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002455/WC500135055.pdf

Version	Date	Amendment	Approved By
1	1/11/2014		Dr Deirdre O Mahony Dr Elisabeth Vandenberghe
2	23/06/2016	Updated Adverse Reactions to include pancreatitis, pulmonary toxicity and gastrointestinal complications	Dr Elisabeth Vandenberghe
3	18/10/2018	Updated with new NCCP regimen template. Updated other supportive care measures and Hepatitis B reactivation information to standardize across NCCP regimens for lymphoma	Dr Deirdre O Mahony Prof Elisabeth Vandenberghe

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/