Bendamustine Monotherapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	*Reimbursement Status
Treatment of patients with relapsed or refractory Chronic Lymphocytic Leukaemia (CLL)	C91	00527a	Hospital

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

Bendamustine is administered on day 1 and day 2 of a 28 day cycle for up to 6 cycles or until disease progression or unacceptable toxicity develops.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1 and 2	Bendamustine	*70 mg/m²	IV infusion	500ml NaCl 0.9% over 60 minutes	Every 28 days
*Dose may be escalated up to 100mg/m2 at the discretion of the clinician					

ELIGIBILTY:

- Indications as above
- ECOG status 0-2

EXCLUSIONS:

- Hypersensitivity to bendamustine, or any of the excipients
- 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 Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), Hepatitis, HIV.

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

Regular tests:

- FBC, renal and liver profile prior to each cycle

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 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:

Table 2; Dose modification in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
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

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:
Bendamustine - Moderate **(Refer to local policy)**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- Tumour lysis syndrome prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- Proton pump Inhibitor**(Refer to local policy)**

Note: <u>All patient who receive bendamustine should receive irradiated blood products throughout their chemotherapy and for life</u>

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately.

- **Cardiac Disorders:** Patients with a history of cardiac disease and/or cardiotoxic chemotherapy should be monitored closely. During treatment with bendamustine hydrochloride the concentration of potassium in the blood must be closely monitored and potassium supplement 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.
- **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. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. 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.
- **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 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.
- **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.
- **Tumour lysis syndrome:** Tumour lysis syndrome associated with bendamustine treatment has been reported. The onset tends to be within 48 hours of the first dose of bendamustine. Standard preventive measures should be put in place. The use of allopurinol during the first one to two weeks of bendamustine therapy can be considered but is not given as standard. There have been a few cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis reported when bendamustine and allopurinol were administered concomitantly.
- **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/µl) and low CD4-positive T-cell (T-helper cell) counts (< 200/µl) 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, acyclovir and cimetidine exists.
- Combination of bendamustine with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

Bendamustine- LA01AA09

REFERENCES:

1. Bergmann MA, Goebeler ME, Herold M, et al. Efficacy of bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase I/II study of the German CLL Study Group. Haematologica 2005; 90: 1357-64.
2. Cheson BD, Wendtner CM, Pieper A, et al. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel. Clin Lymphoma Myeloma Leuk 2010;10:21-7.
3. HPRA summary of product characteristics bendamustine accessed Sept 2018 - https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0405-072-001_16052018153049.pdf

Version	Date	Amendment	Approved By
1	29/01/2019		Dr Derville O'Shea

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/