AL Amyloidosis: cycloPHOSphamide, Bortezomib and dexAMETHasone (CVD) 28-Day Therapy[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of newly diagnosed systemic AL amyloidosis	E85	00652a	Hospital
Treatment of relapsed/refractory systemic AL amyloidosis	E85	00652b	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.

Treatment consists of four 4-week cycles as described in the treatment table below.

Twice weekly dosing of bortezomib is reserved for patients with renal dysfunction where the intention is to salvage the kidney, and usually reserved for one cycle in total. Patients with cardiac disease should only be treated with once weekly bortezomib regimen.

All patients should receive a minimum of three cycles of treatment unless unacceptable toxicity occurs. Response should be assessed at the end of each cycle:

- Patients who achieve a complete response or VGPR will continue for one more cycle after achieving response (e.g. if patient has achieved CR or VGPR at cycle 1 or 2, they will finish three cycles and stop. If they achieve CR or plateau after cycle 3, they will receive one more cycle after achieving CR or plateau).
- Patients with ongoing reduction in dFLC should continue until they achieve VGPR or complete response or to a maximum of 8 cycles.
- Patients who have not responded to treatment by end of cycle 2 will need regime modification after discussion with the complex care centre (Currently, NHS National Amyloidosis Centre, UK) or as per local practice.

Day	Drug	Dose	Route
1 , 8, 15, 22	[a]Bortezomib	1.3mg/m^2	[b, c] SC (abdomen or thigh)
1, 8, 15	cycloPHOSphamide	[d]350mg/m^2 (Max 500mg)	PO
1, 8, 15, 22	dexAMETHasone	[e]10mg	PO, Take in the morning with food
[a]Bortezomib is a proteasome inhibitor and is neurotoxic. Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer			
[b] In individual cases with marked abdominal oedema due to uncertainty with absorption, where approved by Consultant, bortezomib may be administered as IV bolus over 3-5 seconds through a peripheral or central intravenous catheter followed by a flush with 0.9% NaCl. Note the concentration of bortezomib solution should be 1mg/ml when administered via the IV route			
[c]The solution should be injected subcutaneously, at a 45-90^o angle. Injection sites should be rotated for successive injections. If local injection site reactions occur, either a less concentrated solution may be administered SC or a switch to IV injection is recommended.			
[d] cycloPHOSphamide is available as 50mg tablets. They should be swallowed with sufficient fluid without chewing. The tablets should not be divided before use.			
[e] Dose may be increased to 20mg once daily if tolerated			

ELIGIBILITY:

- Indications as above
- ECOG 0-2
- Patients with pre-existing severe neuropathy should be treated with bortezomib only after careful risk/benefit assessment. Caution should be exercised as further treatment may result in severe prolonged neuropathy

EXCLUSIONS:

- Hypersensitivity to cycloPHOSphamide, bortezomib, boron, dexAMETHasone or any of the excipients
- Acute diffuse infiltrative pulmonary and pericardial disease
- Pregnancy
- Lactation

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- FBC, Renal, Liver and Bone profile.
- Blood pressure.
- Blood glucose* if being treated with oral hypoglycaemics **(*See Drug Interactions).**
- Assessment of peripheral neuropathy status.
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), hepatitis C, HIV, CMV *(**Reference Adverse Events/Regimen Specific Complications for information on Hepatitis B reactivation**)

Regular tests:

- FBC to be done minimum of day 1 and day 8 of each cycle
- Renal, Liver and bone profile
- Blood pressure weekly.
- Assessment of peripheral neuropathy status
- Blood glucose* if being treated with oral hypoglycaemics **(*See Drug Interactions)**

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 toxicities

Table 1: Dose Modification of Bortezomib and cycloPHOSphamide for Haematological Toxicity

Prior to Starting a new cycle			
ANC (x10^9/L)		**Platelets(x10^9/L)**	**Dose of Bortezomib and cycloPHOSphamide**
≥ 0.5	and	≥ 30	100% Dose
<0.5	or	<30	Consider delay until recovery checking FBC weekly; reduce dose of bortezomib to 1mg/m^2 If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.
During a cycle			
ANC (x10^9/L)		**Platelets(x10^9/L)**	**Dose of Bortezomib and cycloPHOSphamide**
<0.5	or	<30	Omit cycloPHOSphamide day 15 Withhold treatment with bortezomib until recovery of toxicity. Reinitiate treatment at a reduced dose of bortezomib (1.3 to 1mg/m^2 or 1mg/m^2 to 0.7mg/m^2) and consider dose reduction of cycloPHOSphamide If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.

Renal and hepatic impairment:

Table 2: Dose Modification of Bortezomib and cycloPHOSphamide in Renal or hepatic Impairment

Drug	**Renal impairment**	**Hepatic impairment**			
Bortezomib	No dose adjustment is needed Haemodialysis: no dose adjustment is needed	**Grade of Hepatic Impairment***	**Bilirubin Level**	**(AST) levels**	**Modification of starting dose**
		Mild	≤1 x ULN	> ULN	None
			>1-1.5xULN	Any	None
		Moderate	>1.5-3xULN	Any	Reduce dose to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent

<table>
<tr><td></td><td colspan="2"></td><td></td><td></td><td></td><td>cycles based on patient tolerability.</td></tr>
<tr><td rowspan="5">cycloPHOSphamide</td><td>Creatinine Clearance ml/min</td><td>Dose modification</td><td colspan="4" rowspan="5">Mild/moderate: no need for dose adjustment expected

Severe: Not recommended, due to risk of reduced efficacy</td></tr>
<tr><td>≥30</td><td>No dose adjustment needed</td></tr>
<tr><td>10-29</td><td>Consider 75% of original dose</td></tr>
<tr><td>< 10</td><td>Not recommended. If unavoidable, consider 50% of original dose</td></tr>
<tr><td>Haemodialysis</td><td>Not recommended. If unavoidable, consider 50% of original dose</td></tr>
</table>

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe)

Neuropathic pain and/or peripheral neuropathy:

Table 3: Dose modifications for Bortezomib Related Neuropathy

Severity of neuropathy	Dose Modification
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2	Reduce dose to 1 mg/m^2
Grade 2 with pain or Grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment and reduce dose to 0.7mg/m^2 once every week
Grade 4 and/or severe autonomic neuropathy	Discontinue treatment
Grade 1: Asymptomatic; clinical or diagnostic observations only Grade 2: Moderate symptoms; limiting instrumental Activities of Daily Living (ADL) Grade 3: Severe symptoms; limiting self-care ADL Grade 4: Life-threatening consequences; urgent intervention indicated *Grading based on NCI Common Toxicity Criteria CTCAE v 4*	

Dose reductions for other toxicities:

Table 4: Dose Modification of Bortezomib for Adverse Events

Adverse reactions	Recommended dose modification
Grade 3 Non-haematological toxicity	Withhold treatment until symptoms of the toxicity have resolved. Treatment may be reinitiated at a 25% reduced dose (1.3mg/m^2 reduced to 1mg/m^2; 1mg/m^2 reduced to 0.7mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.
New or worsening pulmonary symptoms (e.g. cough, dyspnoea)	Withhold treatment. Prompt diagnostic evaluation required and benefit/risk ratio should be considered prior to continuing bortezomib therapy.
Posterior Reversible Encephalopathy Syndrome (PRES)	Discontinue treatment.

SUPPORTIVE CARE:

Bortezomib: Low (**Refer to local policy).**
cycloPHOSphamide: Moderate to high **(refer to local policy)**

PREMEDICATIONS: Not usually required. Ensure patient remains well hydrated during treatment.

OTHER SUPPORTIVE CARE:

- **Patients with cardiac involvement of their AL amyloidosis or have > Mayo Clinic Stage II disease should be admitted for 48 hours after the first two doses of bortezomib therapy**
- **Patients with cardiac involvement of their AL amyloidosis or have > Mayo Clinic Stage II disease should be commence the following**
    - **Doxycycline 100 mg BD PO; Continue throughout treatment and until organ regression**
    - **Prior to starting bortezomib treatment the patient should be euvolaemic**
    - **Amiodarone 200 mg TDS x 1 week, then reduced as follows: 200 mg BD x 1 week, then 100 mg OD for 2 weeks.**
- H_2-antagonist or PPI in patients receiving dexamethasone therapy (**Refer to local policy**).
- Low dose antiviral prophylaxis (**Refer to local policy**).
- Consider PJP prophylaxis (**Refer to local policy**).
- Tumour Lysis Syndrome prophylaxis (**Refer to local policy**)
- Bisphosphonates should be considered in all patients with myeloma related bone disease**.**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

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

- **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

Bortezomib

- **Peripheral Neuropathy:** Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.
- **Hypotension**: Treatment is commonly associated with orthostatic/postural hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Caution is advised when treating patients with a history of syncope receiving medicinal products known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting.
- **Hepatic Impairment;** Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with bortezomib at reduced doses and closely monitored for toxicities.
- **Gastrointestinal toxicity:** Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment
- **Haematological toxicity:** Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. Therefore platelet counts should be monitored prior to each dose of bortezomib and bortezomib should be withheld when the platelet count is $<25 \times 10^9$/L. Potential benefit of treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding. Complete blood counts with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. Platelet transfusion should be considered when clinically appropriate.
- **Seizures:** Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.
- **Posterior Reversible Encephalopathy Syndrome (PRES):** In patients developing PRES, treatment with bortezomib should be discontinued.
- **Heart Failure**: Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Patients with risk factors for or existing heart disease should be closely monitored.
- **Renal Impairment:** Patients with renal impairment should be monitored closely.

cycloPHOSphamide

- **Haemorrhagic cystitis**: Ensure patient is well hydrated.

dexAMETHasone

- **Steroid use:** Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).

DRUG INTERACTIONS:

- Additive hypotensive effect with anti-hypertensives and bortezomib. Blood pressure should be monitored and ensure patient is well hydrated prior to bortezomib dose. Adjustment of anti-hypertensives may be required.
- During clinical trials, hypoglycemia was uncommonly reported and hyperglycemia commonly reported in diabetic patients receiving oral hypoglycemics. Patients on oral anti-diabetic agents receiving bortezomib treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their anti-diabetic medications.
- Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates. Current drug interaction databases should be consulted for more information.
- CYP3A-inhibitors also decrease the conversion of cycloPHOShamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A-inducers increase the conversion of cycloPHOSphamide to both its active and inactive metabolites.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	26/03/2024		Dr Mark Coyne
1a	12/4/2024	Amended footnote error in treatment table	NCCP

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[i] This regimen is outside of its licensed indication and this is an unlicensed posology for the use of Velcade® in Ireland. Patients should be informed of the unlicensed nature of this indication 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 aware of their responsibility in communicating any relevant information to the patient and also in 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