CPAG Summary Report for Clinical Panel – Policy 1629 Bortezomib for Relapsed/refractory Mantle Cell Lymphoma (MCL)

The Benefits of the Proposition			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	There is a survival benefit [C]	Overall Survival (OS) is a measure of how long following treatment patients are expected to live. It is not restricted to deaths that are disease-related; deaths of any cause are accounted for. Median OS was 23.5 months (95% CI20.3-27.9) as reported by Goy et al. These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
2.	Progression free survival	There is a survival benefit [C]	MCL is a disease of relapse and remission. Median Progression Free Survival (PFS) is a measure of how long following treatment patients can expect to remain both alive and free of disease progression. Patients may not be disease or symptom free during this period. PFS is preferred to Time to Progression (TTP) since it accounts for patients who have died. Median PFS was 6.5 months (95% CI 4.0 to 7.2), as reported by Goy et al (largest study, longest reported follow-up). These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.

3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Adverse events identified [B]	All trials reported on adverse events. Due to lack of any comparison with other treatments or standard care, it is not possible to determine what proportion of events are attributable to bortezomib treatment and what proportion are likely to be a direct consequence of the disease. Similarly, there is no evidence that bortezomib is more or less safe than other treatments. The PINNACLE trial reported that 98% of patients experienced at least 1 adverse event. The PINNACLE trial reported that 70% of patients experienced at least one toxicity of grade ≥3. Commonly reported grade ≥3 toxicities included fatigue and peripheral neuropathy.
11.	Delivery of intervention	Not measured	

Other health outcome measures determined by the evidence review			
	Outcome measure	Grade of evidence	Summary from evidence review
1.	Overall response rate (Complete Response (CR) + Complete Remission/unconfirmed	Grade B	Overall Response Rate (ORR) is a composite of all patients with any treatment response to bortezomib, whether partial or

	(Cru) + Partial Response (PR))		complete; all studies assessed this outcome. ORR was reported as 32% (95% CI 24-40) by Goy et al (largest study, with longest reported follow-up) and as 47% (95% CI 21.3-73.4) These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
2.	Complete response (CR + CRu)	Grade B	Complete Remission/unconfirmed (Cru) is intended to designate patients with curable histologies with a large mass prior to therapy, and for whom treatment eradicated all but the single persistent mass, which had shrunk by ≥75%. This acknowledges that in most cases the remaining mass represents scar tissue or fibrosis. It should not be applied to patients with multiple masses which have decreased by 75% in total; this is partial response. (Cheson, 2008). CRu is also intended to apply to patients with indeterminate bone marrow biopsy post-treatment, and should not be applied to patients who have not had repeated biopsy. Complete response was reported as 8% (95% CI 4-14) by Goy et al. These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.

3.	Complete response (CR only)	Grade B	Complete Response (CR) refers to resolution of detectable disease including resolution of symptoms, blood and biochemical markers, lymph node masses, any spleen enlargement, and bone marrow histology. CR was reported in 6% of patients (95% CI 3-12) by Fisher et al (largest study, longest reported follow-up). Goy et al did not report this outcome separately from CRu. These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
4.	Partial Response (PR)	Grade B	Partial response (PR) requires reduction in size of the spleen and liver nodules and the largest lymph node masses, no increase in other nodes and no increase in the size of liver or spleen, and no new sites of disease. PR was reported for 26% of patients by Fisher et al (largest study, longest reported follow-up). Goy et al did not report this outcome. These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
5.	Stable disease (SD)	Grade B	Stable disease (SD) refers to disease which has not responded to treatment, but has also not worsened during treatment.

			SD was reported for 33% (95% CI 26 to 42) of patients by Fisher et al. Results were similar (38-40%) in the remaining trials. These trials were not randomised or comparative, and there is therefore no evidence that bortezomib is any better or worse than other treatments for this outcome.
6.	Progressive disease (PD)	Grade B	Progressive disease (PD) refers to disease which has continued to worsen during treatment. PD was reported by Fisher et al for 25% of patients (95% CI 18 to 33). These trials were not randomised or comparative and there is therefore no evidence that bortezomib is any better or worse than other treatments for this outcome.
7.	Duration of response (DoR)	Grade B	MCL is a disease of relapse and remission. Median Duration of Response (DoR) is a measure of how long patients can expect their response to treatment to last. Median DoR was reported as 9.2 months (95% CI 4-7.3) by Goy et al (largest study, longest reported follow-up). These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
8.	Time to Progression (TTP)	Grade C	MCL is a disease of relapse and remission. Median Time To Progression (TTP) is a measure of how long following treatment patients can expect to remain free of disease progression.

			Patients may not be disease or symptom-free during this period. It is similar to PFS but does not capture data on patients who have died. Median TTP was 6.7 months (95% CI 4.0-7.3), as reported by Goy et al (largest study, longest reported follow-up). These results should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
9.	Time to First Response	Grade C	Median Time to First Response is a measure of how long after starting treatment patients may expect to first see a treatment response. Goy et al found the median to be 1.4 months. This result should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.
10.	Time to next therapy	Grade C	Time to next therapy is an indicator of how long following bortezomib treatment patients remain free of need to other drugs. This is an indicator of quality of life, and clinical benefit. Goy et al found median TTNT to be 7.4 months (95% CI 5.6-9.3). This result should be interpreted with caution; trial was not randomised or comparative. There is no evidence that bortezomib is any better or worse than other treatments for this outcome.