CPAG Summary Report for Clinical Panel – Bortezomib for relapsed/refractory Waldenstrom's macroglobulinaemia (WM)

The Benefits of the Proposition			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	B	Overall survival is the length of time from either diagnosis or start of treatment that the patient is still alive. Only 1 study presented outcome data for overall survival (Ghobrial, 2010). In this study, bortezomib was used in conjunction with rituximab. During the follow-up period (median 16 months), median overall survival was not reached. The authors estimate 12-month overall survival to be 94% (95% CI 86%-100%). The results of this study should be interpreted with caution: the trial was not randomised or comparative. A longer duration of follow-up would be required to capture data on overall survival in this population. None of the trials compared bortezomib to other drugs or treatments for WM so it is not clear whether any benefits are attributable directly to treatment with

			bortezomib in relapsed/refractory WM patients.
2.	Progression free survival (PFS)	B	Progression-free survival (PFS) is the length of time from either diagnosis or start of treatment to disease progression or patient death from any cause. One study which examined bortezomib monotherapy for WM (Chen et al, 2007) reported median PFS as being 16.3 months (95% CI 14.2-infinity). The very wide confidence interval is likely to reflect the study's small sample size. These results should be interpreted with caution as the study was not randomised or comparative. This study also included untreated WM patients so data for relapsed patients was subject to post-hoc subgroup analysis and should be considered with caution. Ghobrial et al (2010) reported on the use of bortezomib in conjunction with rituximab, with a median PFS of 15.6 months (95% CI 11.2- 21.1). The results of this study should be interpreted with caution: the trial was not randomised or comparative None of the trials compared bortezomib to other drugs or treatments for WM so it is not clear whether any benefits are attributable directly to treatment with

			bortezomib in relapsed/refractory WM patients.
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 5 included trials reported adverse events. The 2 studies which looked at bortezomib monotherapy reported grade III (moderated) or IV (severe) toxicities, including neuropathy, leukopenia, thrombocytopenia and fatigue. Because bortezomib was not compared to any other treatments, or to standard care, it is not possible to tell whether it is any more or less safe than other drugs for Waldenstrom's macroglobulinaemia.
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review			
No	Metric	Grade of evidence	Summary from evidence review

1	Complete response (CR)	B	Complete Response (CR) is where there is no detectable disease following a course of treatment. Neither study looking at bortezomib monotherapy reported CR in any study subjects, although small sample sizes in both studies mean the possibility of CR occurring in a small proportion of patients cannot be ruled out. Although data on complete response (CR) was reported by the included studies, the definitions of treatment response varied between studies or were not explicitly described. In conjunction with the varied nature of the included studies (use of bortezomib alone, in conjunction with rituximab and in differing regimens), it is not possible to produce a pooled estimate of the effect of bortezomib on achieving complete response in relapsed/refractory WM patients. In addition, studies were not randomised or comparative and there is therefore no evidence that bortezomib is any better or worse than other treatments for this outcome.
2	Partial response (PR)	B	Partial Response (PR) is where there is a decrease in tumour size or the amount of

			cancer detected in the body following treatment. In one of the studies looking at bortezomib monotherapy, 15% of patients achieved partial response. 46% of patients achieved partial response in a study of bortezomib plus rituximab and 1 patient was noted to have achieved partial remission following bortezomib and bendamustine, although the latter should be considered a case report only as only 1 patient in the study had a diagnosis of WM. Although data on partial response (CR) was reported by the included studies, the definitions of treatment response varied between studies or were not explicitly described. In conjunction with the varied nature of the included studies (use of bortezomib alone, in conjunction with rituximab and in differing regimens), it is not possible to produce a pooled estimate of the effect of bortezomib on achieving partial response in relapsed/refractory WM patients. In addition, studies were not randomised or comparative and there is therefore no evidence that bortezomib is any better or worse than other treatments for this

			outcome.
3	Stable disease	B/C	Stable disease is where a cancer is neither growing nor shrinking following a course of treatment. In the context of WM, this is generally related to the amount of a protein called immunoglobulin M (IgM) that is present in the blood. Results from included studies reported patients achieving stable disease as ranging from 0 to 70%. However, the definitions of stable disease varied between studies. In conjunction with the varied nature of the included studies (use of bortezomib alone, in conjunction with rituximab and in differing regimens), it is not possible to produce a pooled estimate of the effect of bortezomib on achieving stable disease in relapsed/refractory WM patients. In addition, studies were not randomised or comparative and there is therefore no evidence that bortezomib is any better or worse than other treatments for this outcome.
4	Progressive disease	B	Progressive disease is where the disease is progressing and worsening. In the context of WM, this generally relates to the amount of IgM present in the blood.

			Progressive disease was reported by two of the included studies. 1 patient was reported to have progressive disease in a study of bortezomib monotherapy and 1 patient in the study of bortezomib plus rituximab. The varied nature of the included studies (use of bortezomib alone, in conjunction with rituximab and in differing regimens) means it is not possible to produce a pooled estimate of the effect of bortezomib on achieving stable disease in relapsed/refractory WM patients. In addition, studies were not randomised or comparative and there is therefore no evidence that bortezomib is any better or worse than other treatments for this outcome.
5	Time to progression	B/C	Time to progression is a similar measure to progression free survival but does not account for deaths occurring before progression (PFS is, hence, the preferred outcome). One of the two studies examining the use of bortezomib monotherapy reported median time to progression of 6.6 months with a range of 2.9 to 21.4+ months. This wide range in results increases the uncertainty about the validity of the outcome in this study, with a larger

			sample size required to provide greater certainty around this measure. Median time to progression was 16.4 months in the study of bortezomib and rituximab. The varied nature of the included studies reporting this outcome (use of bortezomib alone, in conjunction with rituximab and in differing regimens) means it is not possible to produce a pooled estimate of the effect of bortezomib on achieving stable disease in relapsed/refractory WM patients. In addition, studies were not randomised or comparative and there is therefore no evidence that bortezomib is any better or worse than other treatments for this outcome.