CPAG Summary Report for Clinical Panel – 1608 Bendamustine for relapsed multiple myeloma

The Benefits of the Proposition (Grade of Evidence to be left blank)			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Choose an item.	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. The best quality study for this outcome measure (Stohr et al 2015) found a median OS of 17 months (n=58). No evidence was found for an association between the dose of bendamustine used (above or below 120mg/m^2) and median overall survival (15 months vs 16.7 months) (p=0.58). There was also no significant difference observed in median OS when bendamustine was used alone (OS 17 months) compared to its use in conjunction with steroids (OS 13.5 months) (p=0.85). This result suggests that on average patients with relapsed or refractory multiple myeloma survived 17 months following commencement of bendamustine therapy. Because the study had no comparator group of patients receiving best supportive care without bendamustine, we do not know whether bendamustine is more or less effective in terms of overall survival than best supportive care. Additionally, the study had a relatively small sample size and was retrospective, with the possibility of bias in relation to which patients were and were not included.
2.	Progression free survival	Choose an item.	Progression free survival is the time between the first treatment and one of the following: progressive disease, relapse after response or death from any cause. Progression free survival

			(PFS) and event free survival (EFS) were both defined in the studies reviewed as the time from first bendamustine treatment to disease progression or death or relapse. The best quality study for this outcome measure (Stohr et al 2015) found a median EFS to be 7 months (n=58), and found no difference in EFS when bendamustine was used alone compared to its use in combination with steroids (EFS 7 months for both, p=0.6). Although reporting was unclear, Cox regression analysis suggested an association between EFS and calcium level (p=0.02, hazard ratio (HR) 1.6) and prior Autologous Stem Cell Transplantation (p=0.03, HR 3.9). This suggests that on average patients with relapsed or refractory multiple myeloma survive for 7 months following first bendamustine treatment before progression of disease, relapse or death, and that factors such as calcium level and prior treatment may affect survival. The implications of the results of the study are not entirely clear as there is no comparison made with patients who did not have the bendamustine treatment, and we do not know how long the latter group might survive without measurable disease progression. This is an uncontrolled retrospective study. The design of the study, i.e. looking back at case notes, introduces the possibility of selection bias in the selection of patients for the study and in the study population outcome information obtained, as it is possible that not all the relevant patients or information are included in the study.
3.	Mobility	Choose an item.	Not directly assessed
4.	Self-care	Choose an item.	Not directly assessed
5.	Usual activities	Choose an item.	Not directly assessed

6.	Pain	Choose an item.	Not directly assessed
7.	Anxiety / Depression	Choose an item.	Not directly assessed
8.	Replacement of more toxic treatment	Choose an item.	Not directly assessed
9.	Dependency on care giver / supporting independence	Choose an item.	Not directly assessed
10.	Safety	Choose an item.	An adverse event (AE) is any untoward medical occurrence in a patient who has been given a treatment which does not necessarily have a causal relationship with this treatment. In the studies reviewed, adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, in which Grade 1 refers to mild AE, Grade 2 moderate AE, Grade 3 severe AE, Grade 4 life-threatening or disabling AE and Grade 5 refers to death related to AE. The best quality study for this outcome measure, Stohr et al (2015), found 71% of patients (n=41) experienced severe (grade 3 or 4) anaemia, 16% (n=9) severe leucopenia and 21% (n=12) severe thrombocytopenia. However, it is reported that of the 30 patients with grade 4 anaemia, this only developed during or after bendamustine treatment in 6 patients (ie 24 had grade 4 anaemia prior to bendamustine treatment). Bendamustine dosage and whether patients had concomitant steroids did not influence the severity of the anaemia (p values not provided). A small number of patients suffered a mild allergy to bendamustine. Other side effects included mild fatigue, nausea, and vomiting. This suggests that severe (grade 3) and life-threatening (grade 4) levels of haematological toxicity are not uncommon in patients who have had bendamustine treatment for late stage multiple myeloma. This is an uncontrolled retrospective study. The lack of comparator in the study limits

			the strength of conclusions that can be drawn because, for example, many of the reported side effects may have been due to the illness itself and without a comparator group, we do not know how many were due to the bendamustine treatment. This is indicated, for example, by the relatively large proportion of patients that had grade 4 anaemia prior to bendamustine treatment. Additionally, the retrospective design of the study introduces the possibility of bias in the selection of patients for the study and in the outcome information obtained, as it is possible that not all the relevant patients or information were included.
11.	Delivery of intervention	Choose an item.	Not directly assessed

Other health outcome measures determined by the evidence review (Grade of Evidence to be left blank)			
No	Outcome measure	*Grade of evidence*	Summary from evidence review
1.	Overall Response rate (ORR)	Choose an item.	The overall response rate (ORR) to bendamustine is the proportion of patients with either a complete response (CR) or partial response (PR) following treatment. CR is when there is no detectable disease following a course of treatment. It does not always mean the disease has been cured but is the best result that can be reported and means that there is no evidence of disease. PR is a decrease in tumour size or the amount of cancer detected in the body following treatment. The best quality study for this outcome measure, Stohr et al (2015), found an ORR of 59% among 58 patients with relapsed or refractory multiple myeloma, of whom 44 could be evaluated for response. No complete remission was observed. 20% (9 patients) had a partial response and a further 39% (17 patients) had a minimal response. No significant difference was found in ORR when groups who received bendamustine with and

			without a steroid were compared (59% in both groups), nor when a dose of bendamustine above and below 120mg/m^2 were compared (53% vs 64%) (p=1). This suggests that 59% of patients had some response to bendamustine treatment. However the response may have been small and short-lived. This is an uncontrolled retrospective study of a relatively small sample size (n=58). The lack of comparator in the study limits the strength of conclusions that can be drawn. Additionally, the impact, if any, of a minimal response on patients' quality of life or overall survival is not known. The retrospective design of the study introduces the possibility of bias in the selection of patients for the study and in the outcome information obtained, as it is possible that not all the relevant patients or information were included.
2.		Choose an item.	
3.		Choose an item.	
4.		Choose an item.	
5.		Choose an item.	