CPAG Summary Report for Clinical Panel – Policy 1630 Bendamustine-based chemotherapy for first-line treatment of Mantle cell lymphoma (MCL) in adults

The Benefits of the Proposition – *Use of bendamustine plus rituximab (BR) Vs. CHOP plus rituximab or CVP plus rituximab as a first line treatment to treat mantle cell lymphoma*			
No	*Outcome measures*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	There is a survival benefit [B]	A study of 261 previously untreated patients with Stage III or IV disease due to indolent or mantle cell lymphomas (MCL) were randomised to receive bendamustine with rituximab (of whom 46 had MCL) and 253 randomised to receive rituximab with cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) (of whom 48 had MCL). At a median follow up of 45 months median progression free survival was longer in the subgroup of patients with MCL that received bendamustine with rituximab vs. R-CHOP (35.4 months vs. 22.1 months) equating to a difference of 13.3 months. Progression free survival was defined as the time between first treatment and one of the following events: progressive disease, relapse after

			response or death from any cause. This is a subgroup analysis and therefore could be viewed as being hypothesis generating. Overall the trial was designed to demonstrate that bendamustine with rituximab was non-inferior to R-CHOP. The trial was conducted before the use of maintenance rituximab became standard clinical practice and therefore this may limit the generalisability of the results described.
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]	A study of 224 previously untreated patients with Stage III or IV disease due to indolent or mantle cell lymphomas (MCL) randomised to receive bendamustine with rituximab (of whom 36 had MCL) and 223 randomised to receive R-CHOP or

			rituximab with cyclophosphamide, vincristine and prednisolone (R-CVP) (of whom 38 had MCL). Bendamustine with rituximab has a different side effect profile to R-CHOP/R-CVP greatly reducing the incidence of alopecia and peripheral neuropathy. It caused less leukopenia and neutropenia but more lymphocytopenia. Bendamustine with rituximab has a higher risk of drug hypersensitivity and skin rash. The risk of secondary malignancies for bendamustine with rituximab and R-CHOP/R-CVP does not appear to be different.
11.	Delivery of intervention	Not measured	

Other health outcome measures determined by the evidence review - *Use of bendamustine plus rituximab (BR) Vs. CHOP plus rituximab or CVP plus rituximab as a first line treatment to treat mantle cell lymphoma*			
No	Outcome measure	Grade of evidence	Summary from evidence review
1	Overall response rate (ORR)	Grade B	A study of 224 previously untreated patients with Stage III or IV disease due to indolent or mantle cell lymphomas (MCL) randomised to receive bendamustine with

			rituximab (BR) (of whom 36 had MCL) and 223 randomised to receive R-CHOP or R-CVP (of whom 38 had MCL). For the subgroup of patients with MCL the recorded overall response rates were 94% vs. 85% for BR vs. R-CHOP or R-CVP respectively. Response rates were defined as being based on standard WHO criteria. This is a subgroup analysis and therefore could be viewed as being hypothesis generating. Overall the trial was designed to demonstrate that BR was non-inferior to R-CHOP.
2	Impact on quality of life	Grade B	In a study 224 previously untreated patients with Stage III or IV disease due to indolent or mantle cell lymphomas (MCL) randomised to receive bendamustine with rituximab (BR) (of who 36 had MCL) and 223 randomised to receive R-CHOP or R-CVP (of who 38 had MCL). Patients treated with BR reported improvements in cognitive functioning, physical functioning, social functioning, emotional

			functioning and global health status and a reduction in dyspnoea, constipation and fatigue at some but not all time points compared with standard treatment. Patients treated with standard treatment reported less nausea and vomiting and appetite loss at several time points. BR showed some advantages in quality of life (QoL) compared to R-CHOP/R-CVP but the clinical significance of the benefits was small, and the differences between the groups were not statistically significant at all points in time.

The Benefits of the Proposition - *Use of bendamustine-based regimens compare with other regimens in the treatment of patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant*

No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
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	Not measured	

	on care giver / supporting independence		
10.	Safety	Not measured	
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review - *Use of bendamustine-based regimens compare with other regimens in the treatment of patients receiving intensive first-line treatment prior to consolidation with high-dose chemotherapy and autologous stem cell transplant*			
No	Metric	Grade of evidence	Summary from evidence review
1.	Rate of confirmed and unconfirmed Complete response	Grade C	In a study, 23 patients received three cycles of rituximab/ cytarabine/bendamustine followed by three cycles of rituximab/ high-dose cytarabine provided there was evidence of stable disease or improvement. 22 patients achieved a complete response equating to a response rate of 96% (90% CI: 81-100%). This is a very small open-label single arm study and as such is limited by the fact there is no control arm and can only be regarded as hypothesis generating. There are no follow up data available as yet to enable any assessment of PFS or longer term adverse events.