National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma

Response to consultee and commentator comments on the draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Janssen	No comment	Response noted.
	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	This is an accurate summary of mantle cell lymphoma (MCL). We would however stress that this is a disease with a generally poor outcome and new and more effective treatments than those currently employed in the UK are urgently required	Comment noted. No action required.
	Napp Pharmaceuticals	In terms of standard 1st line treatments for mantle cell lymphoma, this depends on the fitness status of the patient. According to the latest national guidelines (attached –see page 9) fitter patients should receive high dose ara-C followed by stem cell transplantation. Therefore R-chemo is used in the less fit population. This will affect patients numbers calculated to be suitable for bendamustine–R.	Comment noted. Text has been added to the scope to highlight that stem cell transplantation may be an option for some patients.

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The technology/ intervention	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	We would like to add that bendamustine is generally well tolerated even in the older population and unlike R-CHOP, the drug does not cause total alopecia nor is it known to be cardiotoxic. This is important bearing in mind the high prevalence of cardiac co-morbidity in patients presenting with MCL	Comment noted. Adverse effects of treatment are an outcome measure included in the scope.
	Janssen	No comment	Response noted.
	Napp Pharmaceuticals	Yes, although it is important to clarify that BR has been studied in a clinical trial of patients with indolent NHL and mantle cell lymphoma, and not a separate mantle cell lymphoma trial. Therefore the trial was neither designed nor powered to compare efficacy of BR in mantle cell lymphoma specifically. The proposed licensed indication is: “First-line treatment of indolent non-Hodgkin’s lymphoma and mantle cell lymphoma in combination with rituximab” Mantle cell lymphoma will not be a separate licensed indication.	Comments noted.
Population	Roche	We would like to highlight that mantle cell lymphoma usually occurs in older adults, for whom fludarabine containing regimes may not be an option due to its high toxicity. This population therefore has a high mortality rate (particularly over the age of 70) and so any treatment option which negates the need for fludarabine use is likely to be welcomed.	Comment noted.

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	Lymphoma Association	The technology is likely to be of greatest benefit to older, frailer patients and those with co-morbidities, It will potentially allow some patients to receive effective treatment when other similarly effective regimens might not be suitable.	Comment noted.
	Janssen	No comment	Response noted.
	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	The first line setting is important although we would also like to see R-bendamustine assessed by NICE in the context of patients with recurrent disease previously treated with R-CHOP or other therapies	Comment noted. NICE is only able to appraise drugs within their marketing authorisation.

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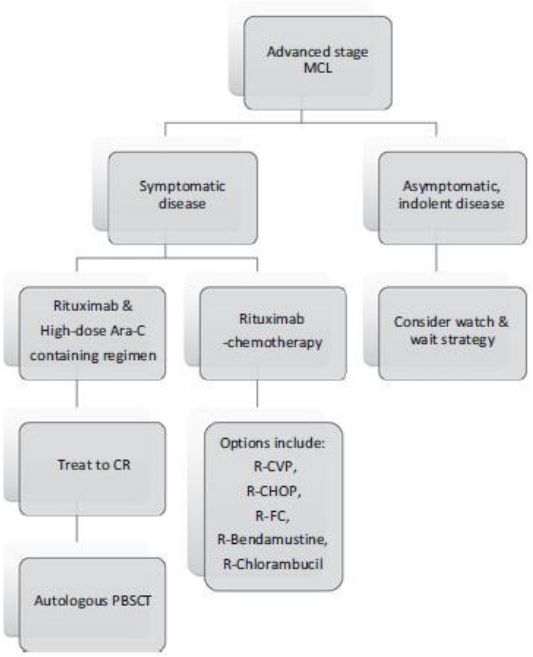
	Napp Pharmaceuticals	The population may be too broad as, according to the national mantle cell lymphoma guidelines, fitter patients should be treated with high dose ara-C plus rituximab followed by stem cell transplant (see diagram and guidelines attached).  Fig 1. Flow-chart of recommendations for first-line treatment of MCL (outside the context of a clinical trial). MCL, mantle cell lymphoma; Ara-C, cytarabine; R, rituximab; CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, vincristine, doxorubicin, prednisone; FC, fludarabine, cyclophosphamide; CR, complete response; PBSCT, peripheral blood stem cell transplantation.	Comments noted. It has now been highlighted within the scope that stem cell transplantation may be an option for some patients and that bendamustine would be considered when stem cell transplantation is unsuitable. Additional comparators have also been identified within the scope.

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Comparators	Lymphoma Association	R-bendamustine should be used in the first line treatment of older, less fit patients with MCL or younger patients who are unsuitable for transplant. R-CHOP and R-FC are appropriate comparators in this setting in addition to a number of other regimens eg R-chlorambucil and R-CVP. No single regimen can be described as 'best alternative care' because the choice of regimen depends on the age and fitness of the patients. R-FC is usually avoided in very elderly or frail patients. Hyper-CVAD is not routinely used in the UK and is not a suitable comparator. Other cytarabine-containing regimens are used in this country, but only for younger, fit patients who aim to proceed to autologous stem cell transplant.	Comments noted. The scope has been updated to include the comparators identified.
	Janssen	No comment	Response noted.
	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	R-CHOP is the appropriate comparator although it is true that fludarabine containing combinations are also employed in younger (but generally not older) patients	Comment noted. No action required.

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	Royal College of Pathologists and British Society for Haematology	The front line therapy for mantle cell lymphoma (MCL) depends on the age and fitness of the patient. In young fit patients the treatment of choice involves chemotherapy including cytarabine (Ara-C) followed by an autologous stem cell transplant. There are a number of cytarabine regimens, R-hyper CVAD is one of them. This is not widely used in the UK as it is more toxic and probably less efficacious then the Nordic protocol that is widely used. None of these regimens are appropriate comparators for bendamustine and rituximab (BR) which should be used for older patients where an autologous transplant approach is not applied. For these older patients, rituximab in addition to standard chemotherapy regimens are the treatments of choice and these form the comparators you should look at. These vary and depend on the age, fitness and co-morbidities of the patient. The most widely used combinations are R-CHOP and R-FC, but a number of other combinations are appropriate in older more frail patients such as R-CVP and R-chlorambucil. These various chemotherapy regimens are detailed in the recently published BCSH guidelines.[1] 1. Guidelines for the investigation and management of mantle cell lymphoma. McKay P, Leach M, Jackson R, Cook G, Rule S. Br J Haematol. 2012 Sep 21. doi: 10.1111/bjh.12046. [Epub ahead of print]	Comment noted. Comments noted. The scope has been updated to highlight that R-CHOP and R-FC are the most widely used combinations. Additional comparators have also been added.

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	Roche	"Fludarabine containing regimens" include several combinations of potential regimens. It would be helpful for NICE to specify which regimens will be used as a comparator, given differences in expected efficacy/safety across the different options and whether any of these regimens include rituximab.	Comments noted. The scope has been updated to identify the comparators in more detail.
	Napp Pharmaceuticals	The national mantle cell lymphoma guidelines state that recommended options in this patient population include R-CHOP, R-CVP, R-FC, R-bendamustine, R- chlorambucil. Our market research data suggest that the most commonly used regimen in the UK is R-CHOP. Also a recent published study by the European MCL network demonstrated superiority (in terms of overall survival and toxicity) of R-CHOP to R-FC in elderly patients (Kluin-Nelemans et al, N Engl J Med 2012, 367: 520-31	Comments noted. The scope has been updated to reflect the guidelines.
Outcomes	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	Yes but the following should also be considered: 1. The impact of R-CHOP on cardiac function 2. The relative side effects of R-bendamustine and its comparators with reference to quality of life during and after treatment	Comments noted. Adverse effects of treatment and health related quality of life are an outcome measure included in the scope.
	Lymphoma Association	The benefits of this technology in terms of likely reduced adverse events and consequently improved quality of life are very important to patients and must be fully taken into account.	Comments noted. Adverse effects of treatment and health related quality of life are an outcome measure included in the scope.
	Janssen	No comment	Response noted

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	Royal College of Pathologists and British Society for Haematology	*Are there subgroups where BR is likely to be more efficacious?* From an analysis perspective the short answer to this question is no, however BR is likely to be used in place of R-CHOP which is the most widely applied combination in the UK. The switch from R-CHOP to BR has been the international practice. BR is better tolerated than R-CHOP and as such can be used in more elderly patients where R-CHOP is contra-indicated. This would include patients with cardiac disease and generally frailer patients where avoidance of neutropenic sepsis is an advantage. In addition RB does not lead to alopecia, unlike R-CHOP. This can be a significant factor for some patients, especially elderly women. It will not be possible to look at these groups from the literature as most trials exclude these patients.	Comments noted. Adverse effects of treatment are an outcome measure included in the scope.
	Napp Pharmaceuticals	We suggest adding event free survival	Comment noted. It is unclear which additional events would be incorporated by adding this as an outcome measure.
Economic analysis	Janssen	No comment	Response noted
	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	We believe these to be appropriate	Comment noted

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Equality and Diversity	Janssen	No comment	Response noted
	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	R-bendamustine is suitable for older patients and those with co-morbidities for whom R-CHOP and fludarabine containing therapies may not be considered safe	Comment noted. Other comparators have now been added to the scope.
	Royal College of Pathologists and British Society for Haematology	No, but be aware that this is treatment for more elderly patients.	Comment noted. NICE is committed to promoting equality and eliminating unlawful discrimination on the grounds of race, disability, age, sex and gender, sexual orientation, and religion or belief, and to complying fully with our legal obligations on equality. Please see NICE's equality scheme www.nice.org.uk/aboutnice/howwework/NICEEqualitySchemee.jsp
Other considerations	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	The benefits of no known cardiotoxicity with bendamustine should also be considered	Comment noted. Adverse effects of treatment are an outcome measure included in the scope.

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	Royal College of Pathologists and British Society for Haematology	The most important papers in this area are discussed and highlighted in the BCSH guidance. The most important data is the randomised trial of RB v R-CHOP which is in press but as not yet published. However you have access to this data as it forms the companies submission for this appraisal.	Comment noted.
	Napp Pharmaceuticals	Our current regulatory submission is not for a separate MCL indication, because we do not have data from a pivotal MCL only trial. This is an important consideration which may have a bearing on whether this appraisal in isolation should proceed.	Comment noted

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Questions for consultation *Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?* *Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?* *Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.*	Lymphoma Association	The technology is likely to be more efficacious than R-CHOP and the other regimens suggested as comparators and it is better tolerated with fewer unpleasant side effects than the alternative regimens. With reduced haematotoxicity and therefore lower infection-risk, less cardiotoxicity than doxorubicin and no steroids included in the regimen, it is likely to be of particular benefit to those people with lymphoma who also have significant co-morbidities. *The relevant evidence is summarised in the recently published BCSH guidelines "Guidelines for the investigation and management of mantle cell lymphoma", McKay P, Leach M, Jackson R, Cook G and Rule S. Br J Haematol, 2012; 159: 405-426.* *Rummel MJ, et al. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent and mantle cell lymphomas (MCL): Updated results from the StiL NHL1 study. ASCO Meeting Abstracts, 2012; 30(18_suppl)): 3*	Comment noted.
	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	Probably not a step change in management of MCL but an important contribution nonetheless	Comment noted.

	Royal College of Pathologists and British Society for Haematology	RB is another immuno-chemotherapy regimen for use in MCL. It has two major advantages from a therapeutic perspective. Firstly, it is better tolerated and probably more efficacious than R-CHOP. This is based on the toxicity profile and the improvement in progression free survival observed in the Rummel data. The toxicity profile allows the most effective therapy to be delivered to older and more frail patients. The second major advantage is that BR is becoming the chemotherapy backbone of choice for incorporation of the newer oral therapies that are coming for the treatment of this disease. It is possible to combine BR with these agents without major additional toxicities. The approach of adding newer targeted therapies to BR as part of an up front strategy for elderly patients with MCL is currently at an advanced stage of development within the NCRI lymphoma studies group.	Comment noted. Adverse effects of treatment are an outcome measure included in the scope.
Questions for consultation *Have the most appropriate comparators for bendamustine in combination with rituximab for the first-line treatment of mantle cell lymphoma been included in the scope? Are the comparators listed routinely used in clinical practice? Is hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone (Hyper-CVAD) a relevant comparator? Is it used within the identified population?*	NCRI Clinical Studies Group / Royal College of Physicians / Royal College of Radiologists / Joint Collegiate Council on Oncology / Association of Cancer Physicians	R-CHOP and fludarabine containing combinations are the appropriate comparators for the MCL population. Hyper-CVAD is an intensive regimen that may be employed in the younger, fitter patient with blastoid MCL (a very aggressive variant) but this is a small sub-population. Most patients with MCL do not have the blastoid variant and are in an older age group	Comments noted. R-CHOP and fludarabine containing regimens will be taken forward as comparators.

Additional comments on the draft scope.	Napp Pharmaceuticals	Napp understood that this topic had been referred to the Minister and that a separate appraisal from ID434 was deemed appropriate. The rationale for this decision was that MCL follows a different clinical course from indolent NHL, and therefore NICE did not wish this subset of the proposed licensed population to be included in the submission for ID434. However we expected a separate scoping meeting to take place for this appraisal, as the draft scope is substantially different from the draft and final scope agreed for ID434, particularly with respect to the population and comparators. We are therefore surprised that NICE is planning to conduct the scoping for this appraisal as a 'paper exercise' as this seems to be inconsistent with the usual NICE process. As our supportive data for ID434 and this appraisal come from the same clinical trial, and we do not have data supporting a separate MCL indication, we believe there are substantial challenges with making a separate MCL submission. We therefore believe a face to face scoping meeting is imperative with respect to this particular appraisal so that we can discuss possible solutions along with other stakeholders.	It is not part of the NICE process to hold a scoping workshop after receiving a referral. MCL was discussed at the original workshop held in October 2010.

	Roche	We understand MCL to be a subset of NHL, and therefore it is unclear if two separate scoping exercises are required for essentially the same intervention/indication. It would be helpful for us if NICE could clarify why the MCL subgroup in particular has been chosen for appraisal.	The decision to appraise these conditions separately was made during the scoping stage. MCL has a different clinical course to indolent NHL Both conditions were discussed at the scoping workshop held in October 2010

The following consultees/commentators indicated that they had no comments on the draft scope

Department of Health
Royal College of Nursing
Pfizer