National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Bortezomib for previously untreated mantle cell lymphoma

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	Janssen-Cilag	We believe it is appropriate that this topic is referred to NICE for appraisal.	Comment noted. No changes to the scope are required.
	Lymphoma Association	This is one of a number of possible treatments for mantle cell lymphoma that it may be appropriate for NICE to assess in future.	Comment noted. No changes to the scope are required.
	Napp Pharmaceuticals Limited	No comment	Noted.
	Royal College of Pathologists, British Society for Haematology (RCPath, BSH)	*[Would it be appropriate to refer this topic to NICE for appraisal?]* Yes	Comment noted. No changes to the scope are required.
Wording	Janssen-Cilag	No comment.	Noted.
	Lymphoma Association	The licence does not yet include this indication, therefore it is difficult at present to comment on the stated remit.	Comment noted.

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	Napp Pharmaceuticals Limited	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?]* Yes	Comment noted. No changes to the scope are required.
	RCPath, BSH	*[Does the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology or technologies that NICE should consider?]* Yes	Comment noted. No changes to the scope are required.
Timing Issues	Janssen-Cilag	No comment.	Noted.
	Lymphoma Association	The relevant trial results have recently been presented.	Comment noted. No changes to the scope are required.
	Napp Pharmaceuticals Limited	No comment	Noted.
	RCPath, BSH	Data was presented a couple of weeks ago at ASCO and EHA showing the PFS advantage of the addition of Velcade to R-CHP over R-CHOP. This will form the basis of a licensing submission so the timing is good for this appraisal.	Comment noted. No changes to the scope are required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments	Action

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Background information	Janssen-Cilag	No comment.	Noted.
	Lymphoma Association	Treatment options include the list of drugs given, which may be used in a variety of regimens; however, not all of these would be suitable for those who are older/less fit. The current wording suggests these drugs might all be used together, eg, that chlorambucil (note correct spelling) would be used with bendamustine. A small proportion of people with a more indolent form of MCL are managed with the watch-and-wait approach. Some form of gentle therapy would probably be offered to most previously untreated patients who required treatment.	Comments noted. The background section of the scope intends to provide a brief overview of the condition and treatment pathway. No changes to the scope are required.
	Napp Pharmaceuticals Limited	The information is accurate	Comment noted. No changes to the scope are required.
	RCPath, BSH	Fine	Comment noted. No changes to the scope are required.
The technology/ intervention	Janssen-Cilag	The anticipated licensed indication for bortezomib is: “VELCADE in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma”.	Comment noted. No changes to the scope are required.
	Lymphoma Association	In myeloma, bortezomib can now be administered subcutaneously. Will this also be the case for people with lymphoma?	Attendees at the scoping workshop considered that it was likely that bortezomib would be administered subcutaneously for

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			mantle cell lymphoma. The scope has been updated to include this mode of administration
	Napp Pharmaceuticals Limited	*[Is the description of the technology or technologies accurate?]* Yes	Comment noted. No changes to the scope are required.
	RCPath, BSH	*[Is the description of the technology or technologies accurate?]* Yes	Comment noted. No changes to the scope are required.
Population	Janssen-Cilag	As stated above, the target indication has been broadened beyond that described in the draft scope to also include stem cell eligible patients (i.e., inclusion of all MCL first line patients).	Comment noted. Since the scoping workshop, bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone received an marketing authorisation for "*the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation*". The scope has been updated accordingly.

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	Lymphoma Association	Population seems appropriate, as per the trial.	Comment noted. No changes to the scope are required.
	Napp Pharmaceuticals Limited	Yes. The population should be defined as per the licensing regulatory trial.	Comment noted. Since the scoping workshop, bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone received an marketing authorisation for "*the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation*". The scope has been updated accordingly.
	RCPath, BSH	This is applicable to those patients who are NOT candidates for an up front autologous transplant. Almost every patient is at an advanced stage at presentation so this applies to virtually all patients.	Comment noted. Since the scoping workshop, bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone received an marketing authorisation

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			for "*the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation*". The scope has been updated accordingly.
Comparators	Janssen-Cilag	No comment.	Noted.
	Lymphoma Association	In the trial published by Kluin-Nelemans et al. (NEJM 2012; 367: 520-531), in a similar population of patients, R-CHOP showed improved overall survival compared with R-FC. The same trial also showed a benefit for the use of subsequent maintenance rituximab, so should this be included in the comparators, particularly if duration of remission or time to next treatment are to be considered in this assessment?	Attendees at the scoping workshop considered the comparators included in the draft scope to be appropriate. Attendees noted that rituximab maintenance therapy may be considered after any initial treatment, and so would not impact the initial treatment decision; it was not necessary to include rituximab maintenance as a comparator.
	Napp Pharmaceuticals	We agree that the range of comparators is correct. We agree that bendamustine plus rituximab (BR) is an established treatment	Attendees at the scoping workshop

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	Limited	in clinical practice. Bendamustine is available through the Cancer Drugs Fund in combination with rituximab for patients unsuitable for standard treatment. The CDF criteria do not define the treatments used as standard of care however we understand that the standard of care for young, fit patients is a cytarabine containing regimen with autologous stem cell transplant. BR vs R-CHOP has been studied in a phase 3 trial in MCL patients who were above the age of 65 (Rummel et al, 2013). R-BAC (Bendamustine, rituximab and cytarabine) is also used in elderly patients unsuitable for bone marrow transplant or high dose therapy. IMS data (imshealth EU Oncology Analyzer Report Q1 2014) shows that bendamustine is used in 1st line Mantle Cell Lymphoma (MCL) in 21% of patients. the use of CHOP is declining and has fallen back to 39%. Br containing regimens are used in over 20% of all MC patients. The same report also stated that BR is the treatment of choice in 2nd-line MCL with 37 % of pateints receiving a BR containing regimen.	considered the comparators included in the draft scope to be appropriate, and noted the rituximab, bendamustine and cytarabine is used in some people with mantle cell lymphoma. This regimen has therefore been added to the comparators.
	RCPath, BSH	The comparators listed are appropriate. However there is no point looking at any studies involving velcade in the context of myeloma as there are no comparisons that are valid.	Comment noted. Attendees at the scoping workshop considered the comparators included in the draft scope to be appropriate.
Outcomes	Janssen-Cilag	No comment.	Noted.
	Lymphoma Association	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes, health-related quality of life is obviously very important to patients being treated for a condition that is	Comment noted. No changes to the scope are required.

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		incurable.	
	Napp Pharmaceuticals Limited	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes	Comment noted. No changes to the scope are required.
	RCPath, BSH	*[Will these outcome measures capture the most important health related benefits (and harms) of the technology?]* Yes	Comment noted. No changes to the scope are required.
Economic analysis	Janssen-Cilag	No comment.	Noted.
	Napp Pharmaceuticals Limited	No comment	Noted.
	RCPath, BSH	Timing seems appropriate	Comment noted. No changes to the scope are required.
Equality and Diversity	Janssen-Cilag	Most patients with MCL are older than 60 years of age. For this group of patients, treatment options are limited due to age and comorbidities. On that basis, bortezomib for first line MCL patients is one of the few options to enable extended progression free survival.	Comment noted. No changes to the scope are required.
	Napp Pharmaceuticals Limited	None	Noted.
	RCPath, BSH	No issues	Noted.

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Innovation	Janssen-Cilag	No comment.	Noted.
	Lymphoma Association	Its mechanism of action is different from existing treatments and it has been trialled in a group of patients for whom existing outcomes are poor. Benefits in PFS will need to be weighed against any additional toxicity however as the condition remains incurable.	Comment noted. The innovative nature of bortezomib will be considered by the Appraisal Committee during the course of the appraisal. No changes to the scope are required.
	Napp Pharmaceuticals Limited	Yes, the innovation is to treat patients with MCL using the combination chemotherapy as detailed in the scope.	Comment noted. The innovative nature of bortezomib will be considered by the Appraisal Committee during the course of the appraisal. No changes to the scope are required.
	RCPath, BSH	This is an advance but not a step change in management	Comment noted. The innovative nature of bortezomib will be considered by the Appraisal Committee during the course of the appraisal. No changes to the scope are required.

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Other considerations	Janssen-Cilag	No comment.	Noted.
	Napp Pharmaceuticals Limited	*[Suggestions for additional issues to be covered by the proposed appraisal are welcome.]* None	Noted.
	RCPath, BSH	*[Suggestions for additional issues to be covered by the proposed appraisal are welcome.]* No	Noted.
Questions for consultation	Janssen-Cilag	No comment.	Noted.
	Lymphoma Association	Stages II to IV seem appropriate. The existing pathway would benefit from revision as it seems inappropriate to split off mantle cell lymphoma but not to separate the low-grade and high-grade forms of lymphoma, guidelines for which are currently all detailed in one box, whereas the pixantrone guidance applies only to high-grade lymphoma.	Comments noted. Attendees at the scoping workshop considered that it would not be necessary to restrict the appraisal to specific states of disease as very few people present with stage I mantle cell lymphoma, and if stage I mantle cell lymphoma is symptomatic treatment may be considered.
	Napp Pharmaceuticals Limited	Should the appraisal be restricted to treating specific stages of mantle cell lymphoma? No. Is bortezomib likely to be used in people for whom bone marrow transplants are appropriate? The trial data would suggest that the patient population is for	Comments noted. Attendees at the scoping workshop considered that it would not be necessary to

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		those unlikely to receive a bone marrow transplant. Is bortezomib expected to only be used in combination with rituximab, cyclophosphamide, doxorubicin and prednisone, or is use in combination with other chemotherapy drugs likely? If the latter, which additional chemotherapy combinations should be included in this appraisal? There is an ongoing trial of bortezomib in combination with BR in elderly patients. (NCT 01415752) Have all relevant comparators for bortezomib been included in the scope? • Which treatments are considered to be established clinical practice in the NHS for mantle cell lymphoma? (See comments above) • Do all people with mantle cell lymphoma who are treated with chemotherapy also receive rituximab? Rituximab is widely used for all NHL patients including mantle cell but we cannot comment on whether all patients actually receive it as part of their treatment regimen.	restrict the appraisal to specific states of disease as very few people present with stage I mantle cell lymphoma and if stage I mantle cell lymphoma is symptomatic treatment may be considered. Since the scoping workshop, bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone received an marketing authorisation for "*the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation*". The scope has been updated accordingly. The appraisal will consider bortezomib in combination regimens consistent with its

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			marketing authorisation.
	RCPath, BSH	1. Do not restrict to specific stages of the disease. 2. Velcade will predominantly be used in the transplant ineligible patient group. It is being trialled in combination with many other chemotherapy combinations and looks to be synergistic. However there is only one randomised trial in de novo patients and this uses R-CHOP as the comparator. So there would not be any data to broaden the remit beyond R-CHOP like therapy. 3. For older patients the treatment comparators listed are appropriate and all patients have treatment that includes Rituximab. 4. PFS and time to next treatment are important in this disease. The first remission is usually the best and patients enjoy a normal quality of life whilst in remission so toxicity is very important as well.	Comments noted. Attendees at the scoping workshop considered that it would not be necessary to restrict the appraisal to specific states of disease as very few people present with stage I mantle cell lymphoma, and if stage I mantle cell lymphoma is symptomatic treatment may be considered. Comment noted. Since the scoping workshop, bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone received an marketing authorisation for "*the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for*

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			haematopoietic stem cell transplantation". The scope has been updated accordingly. Attendees considered the comparators included in the draft scope to be appropriate.
Additional comments on the draft scope	RCPath, BSH	The BCSH guidelines published in the British Journal of Haematology remain up to date and evidence based so should be looked at when considering the background treatment options for these patients.	Comment noted. No changes to the scope are required.

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

Department of Health
Healthcare Improvement Scotland

NATIONAL INSTITUTE FOR HEALTH CARE EXCELLENCE

Single Technology Appraisal (STA)

Bortezomib for previously untreated mantle cell lymphoma [ID724]

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	Proposal made by:		Action taken: Removed/Added/Not included/Noted	Justification:

1	Accord Healthcare (cyclophosphamide doxorubicin)	NICE Secretariat		Added	This organisation makes the agent cyclophosphamide which is a comparator in this appraisal topic. Accord Healthcare (cyclophosphamide doxorubicin) has been added to the matrix list of consultees and commentators under 'comparator companies'.
2	Delete Blood Cancer	NICE Secretariat		Added	This organisation has an interest closely related to the appraisal topic. Delete Blood Cancer has been added to the matrix list of consultees and commentators under 'patient groups'.

3	Hospira UK (cyclophosphamide, doxorubicin, fludarabine, vincristine)	NICE Secretariat		Added	This organisation makes the agent cyclophosphamide which is a comparator in this appraisal topic. Accord Healthcare (cyclophosphamide doxorubicin) has been added to the matrix list of consultees and commentators under 'comparator companies'.
4	Wockhardt UK (doxorubicin, fludarabine, prednisolone)	NICE Secretariat		Added	This organisation makes the agent fludarabine which is a comparator in this appraisal topic. Wockhardt UK (doxorubicin, fludarabine, prednisolone) has been added to the matrix list of consultees and commentators under 'comparator companies'.

5	Janssen-Cilag (doxorubicin)	NICE Secretariat		Amended	The organisation Janssen (doxorubicin) is the comparator in this appraisal topic. An amendment has been made on the matrix list of consultees and commentators under 'comparator companies'
6	Napp Pharmaceuticals (bendamustine, prednisone)	NICE Secretariat		Amended	The organisation Napp Pharmaceuticals (bendamustine), is the comparator in this appraisal topic. An amendment has been made on the matrix list of consultees and commentators under 'comparator companies'

7	Amdipharm Mercury (prednisolone)	NICE Secretariat		Removed	This organisation does not make an agent that is a comparator in this appraisal topic. Amdipharm Mercury (prednisolone) has been removed from the matrix list of consultees and commentators under 'comparator companies'.
8	Aspen Pharma (chlorambucil)	NICE Secretariat		Removed	This organisation does not make an agent that is a comparator in this appraisal topic. Aspen Pharma (chlorambucil) has been removed from the matrix list of consultees and commentators under 'comparators companies'.

9	National Council of Palliative Care	NICE Secretariat		Removed	This organisation does not have an interest related to this appraisal. National Council of Palliative Care has been removed from the matrix of consultees and commentators under 'comparators'.