National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Bendamustine in combination with rituximab for the first-line treatment of indolent non-Hodgkin's lymphoma

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft scope

Section	Consultees	Comments	Action
Background information	Napp Pharmaceuticals Ltd	No comments	No action required.
	Royal College of Pathologists/BSH	Adequate	No action required.
	Lymphoma Association	No comment.	No action required.
	North of England Cancer Network on behalf of North of Tyne PCTs	Background information is thorough and is delivered in a very clear, concise language. However, no mention of examples of what symptoms are observed (e.g. painless swellings in the neck, groin etc)	Comment noted. The background section of the scope aims to give a brief and clear definition of the spectrum of disease relevant to the new technology. Complete details related to the disease will be included in the appraisal.
The technology/ intervention	Napp Pharmaceuticals Ltd	No comments	No action required.

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	Royal College of Pathologists/BSH	Adequate	No action required.
	Lymphoma Association	No comment.	No action required.
	North of England Cancer Network on behalf of North of Tyne PCTs	Yes, but there is no mention about the rituximab. What is the benefit of the rituximab with the bendamustine? Why is solely based on the bendamustine? Should it state that a phase III study was conducted that compared bendamustine and rituximab in comparison to R-CHOP, as opposed to simply stating a clinicl trial	The technology under appraisal is bendamustine. The background section of the scope has been amended to include a brief description of rituximab. The technology section states that bendamustine in combination with rituximab has been studied in a clinical trial in comparison with R-CHOP.
Population	Napp Pharmaceuticals Ltd	No comments	No action required.

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	Royal College of Pathologists/BSH	No- the text should read “People with previously untreated advanced stage follicular lymphoma that requires therapy.” Note that many people with indolent follicular lymphoma don’t require any therapy, hence the importance of this point. Second, not all indolent lymphomas are the same- the population should be defined according to histologic sub-type- this was commented on previously but has had no impact.	Comment noted. The population has been amended to reflect the therapy requirements. The population section of the scope is determined by the therapeutic indications specified in the marketing authorisation. (See comment from the Lymphoma Association below).
	Lymphoma Association	The population is appropriately defined. The Lymphoma Association does not feel that groups within this population should be considered separately. Narrowing down to sub-groups risks excluding patients with rare subtypes who might be just as likely to benefit.	Comment noted. No action required.

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	North of England Cancer Network on behalf of North of Tyne PCTs	Yes, but why are NICE not considering its use for patients with relapsed Low Grade Non Hodgkins Lymphoma, especially since bendamustine is licensed in people who have progressed during or within six months following treatment with rituximab. BR has been reported to have activity, but with no comparator available to assess improvement in Progression Free Survival (PFS) or response rate. Response rates of 80% have been reported with median TTF of 19 months and Overall survival 25 months. These trials were not controlled. Using bendamustine alone as a control group the TTF was around 10 months, so it may be reasonable to assume in this cohort that rituximab + bendamustine extends TTF (PFS) by 9 months.	This remit/appraisal is focused on bendamustine in combination with rituximab for the treatment of people with previously untreated advanced indolent NHL. Bendamustine for the treatment of indolent NHL that is refractory to rituximab or rituximab containing regimen was the focus of Technology Appraisal No. 206 (TA206). TA206 was terminated because no evidence submission was received from the manufacturer or sponsor of the technology and therefore, NICE was unable to make recommendations.
Comparators	Napp Pharmaceuticals Ltd	Napp Pharmaceuticals ("We") agree that chlorambucil is only really used as standard for people in whom combination chemotherapy is not considered to be an appropriate treatment. Therefore it is not a relevant comparator given the proposed indication under review.	Comment noted. The comparators section has been amended and chlorambucil in combination with rituximab has been specified in the comparators list.

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	Royal College of Pathologists/BSH	No- R-CVP and R-CHOP are suitable comparators but chlorambucil monotherapy is not an appropriate comparator. In the absence of an oral preparation of bendamusitne it is not appropriate to compare these two agents for a group of patients who cannot tolerate R-CVP.	Comment noted. The comparators section has been amended and chlorambucil in combination with rituximab has been specified in the comparators list.
	Lymphoma Association	These are the correct comparators. However, in view of the inclusion of chlorambucil in combination with rituximab in TA243, the comparators should include R-chlorambucil rather than just chlorambucil. The use of the comparators depends not so much on the type of low-grade NHL but on other factors such as clinical behaviour/high FLIPI score. Therefore none of these can be described as 'best alternative care'.	Comment noted. The comparators section has been amended and chlorambucil in combination with rituximab has been specified in the comparators list.
	North of England Cancer Network on behalf of North of Tyne PCTs	In most regions bendamustine monotherapy (without the rituximab) is an available treatment option via CDF and Although chlorambucil is listed as a comparator, chlorambucil + rituximab is also a treatment option. R-CVP is the standard of care in the North East and is the same regimen as R-CHOP without the anthracycline , hence R-CVP is no more superior to R-CHOP.	Comment noted. Bendamustine monotherapy is licensed in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen. The comparators section has been amended and chlorambucil in combination with rituximab has been specified in the comparators list.

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Outcomes	Napp Pharmaceuticals Ltd	No comments	No action required.
	Royal College of Pathologists/BSH	Adequate	No action required.
	Lymphoma Association	As well as the improvements in complete response rate and progression-free survival, the technology has advantages over the standard treatments in terms of reduced adverse effects of treatment and therefore improved health-related quality of life. These measures are extremely important to patients and it is important they are taken fully into account when assessing the overall benefits of the technology.	Comment noted. No action required.
	North of England Cancer Network on behalf of North of Tyne PCTs	Yes	No action required.
Economic analysis	Napp Pharmaceuticals Ltd	No comments	No action required.
	Royal College of Pathologists/BSH	Adequate	No action required.
	Lymphoma Association	No comment.	No action required.

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	North of England Cancer Network on behalf of North of Tyne PCTs	Cost/ impact on resources? Delivery of the service? There is an expected impact on patient admissions as there will be longer patient stays in order for patients to receive rituximab. There will also be an impact on preparation time of the rituximab and bendamustine (additional pharmacy tme)	The economic analysis section in the scope states the potential impact on resource costs and savings for the NHS and personal social services (PSS) that would be expected from the introduction of the technology and that will be assessed during the appraisal. Section 2.2.7 of the Guide to the methods of technology appraisal http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
Equality and Diversity	Napp Pharmaceuticals Ltd	No comments	No action required.
	Royal College of Pathologists/BSH	Not applicable	No action required.

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	Lymphoma Association	The technology is particularly helpful for older patients and those with more co-morbidities as its toxicity profile means it is well tolerated. This may allow more effective treatment to be delivered to some patients who would not previously have been considered fit enough for combination therapy.	Comment noted. It is noted in the Equality Impact Assessment Form that choice of treatment is influenced by the general health and comorbidities of the patient and these, in turn, are related to age. However, age itself does not determine choice of treatment.
	North of England Cancer Network on behalf of North of Tyne PCTs	None	No action required
Other considerations	Napp Pharmaceuticals Ltd	No comments	No action required.
	Royal College of Pathologists/BSH	None	No action required.
	Lymphoma Association	None	No action required

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	North of England Cancer Network on behalf of North of Tyne PCTs	mention recommended dosages? What are the advantages to this treatment in terms of other treatments available? (claims of less neutropenia and infections than R-CHOP)	The technology will be appraised within the boundaries of the marketing authorisation. The technology will be compared with the specified comparators.
Questions for consultation	Napp Pharmaceuticals Ltd	No comments	No action required.
	Royal College of Pathologists/BSH	Bendamustine in combination with rituximab is a very exciting combination of therapy that appears to have a similar response rate to R-CHOP but with lower toxicity and an improved overall survival. However, it is difficult to provide definitive advice on this question as the pivotal study by Rummel et al, comparing R-CHOP vs R-Bendamustine has not yet been through the peer-review process and been published. It has been presented many times and alluded to by many, but given the importance of NICE's work I believe that the information should not only be in the public domain but have passed the test of peer-review. To my knowledge, this has not yet happened.	Comment noted. No action required.

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	Lymphoma Association	Bendamustine-R has the potential to be an important development in the initial management of low-grade lymphomas. It appears to offer longer progression-free survival than the alternatives (e.g. 69.5 months vs. 31.2 months for R-CHOP in the StiL NHL1 trial), which means that patients can look forward to a good quality of life in a prolonged period of time off treatment. In addition it has a significantly more favourable toxicity profile. It causes less haematotoxicity than other combination regimens, so patients are less likely to suffer infections or bleeding. It is less likely to cause peripheral neuropathy (a side effect that can be permanent and disabling in some) or severe constipation than R-CVP or R-CHOP. Avoidance of the cardiotoxic drug doxorubicin in R-CHOP is also a significant health benefit. The fact that it is less likely to cause hair loss, a side-effect that is especially traumatic for many people having chemotherapy, is also important to patients. Encouragingly, the risk of second malignancies does not appear to be significantly greater than with other regimens. Because of the favourable toxicity profile, it is also likely to be well tolerated in older people, who make up the majority of people with low-grade lymphoma but are often difficult to treat because of significant co-morbidities. For example, it avoids the use of steroids which can cause problems with CVP and CHOP for people with diabetes. Choice of treatments is particularly important to clinicians and patients, especially given the wide variations in individual health status and preferences. It is already included in the NCCN practice guidelines. The Lymphoma Association would therefore support the addition of bendamustine-R to the current therapeutic options for patients in England too. *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* *National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)* *http://www.nccn.org/professionals/physician_gls/f_guidelines.asp*	Comment noted. No action required.

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	North of England Cancer Network on behalf of North of Tyne PCTs	Due to the large cost difference of this treatment in comparison to other treatment options available, is there a clear need for a pathway that distinguishes that this should be used in patients who are not suitable for standard treatment (R-CHOP etc). Is this actually a third choice first line treatment?	The technology will be appraised within the boundaries of the marketing authorisation.
Additional comments on the draft scope.	Napp Pharmaceuticals Ltd	No comments	No action required.
	Royal College of Pathologists/BSH	The apparent ease with which stem cell mobilisation can be conducted following therapy with bendamustine would also be helpful in comparing the choices. As the marketing information suggests the chemical structure of bendamustine offers nucleoside analogue properties, comments about the risk of secondary myelodysplasia and transfusion associated graft-versus host disease would also be useful.	Comment noted. No action required. The scope is intended to be a brief description of the disease relevant to the new technology. Further and complete details will be investigated in the appraisal.
	Lymphoma Association	None	No action required.
	Dr Patrick Cadigan on behalf of NCRI/RCP/RCR/ACP/JCCO	The NCRI/RCP/RCR/ACP/JCCO is grateful for the opportunity to comment. Our experts advise that the data that could justify the approval of this technology is likely to be published shortly (in the LANCET). We believe that this will need to be carefully considered as part of any on-going appraisal.	Comment noted. No action required.

Section	Consultees	Comments	Action
	North of England Cancer Network on behalf of North of Tyne PCTs	Any additional comments on the draft scope	No action required.

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

Pfizer LTd
Roche Products Ltd
The Royal College of Nursing