National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lenalidomide with rituximab for previously treated follicular lymphoma and marginal zone lymphoma

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

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Wording	Celgene	Yes, however this should also refer specifically to marginal zone lymphoma, the combination with rituximab and specify that patients are previously treated. Suggested alternative wording of the remit is; "To appraise the clinical and cost effectiveness of lenalidomide in combination with rituximab within its marketing authorisation for treating previously treated follicular lymphoma and marginal zone lymphoma" It is suggested that the title of the appraisal is also modified to "Lenalidomide in combination with rituximab for previously treated follicular lymphoma and marginal zone lymphoma"	Thank you for your comment. The remit is broad but the appraisal committee will only be able to make recommendations in line with the final marketing authorisation. The remit has been reworded to reflect the combination with rituximab and marginal zone lymphoma has also been added in line with the appraisal title.
	Janssen	No comment	Noted.

Section	Consultee/ Commentator	Comments	Action
	Lymphoma Action	It may be clearer to specify at least one previous course of chemo-immunotherapy, unless this treatment is to be considered following a short course of rituximab alone? Consider whether to specify that previous treatment should have include rituximab.	Thank you for your comment. The remit is broad but the appraisal committee will only be able to make recommendations in line with the final marketing authorisation. No changes have been made.
Timing Issues	Celgene	No comments.	Noted.
	Janssen	No comment	Noted.
	Lymphoma Action	There are a number of possible treatments for relapsed and refractory mantle cell lymphoma and as there is not currently an accepted standard, it is important that new treatments are evaluated at the earliest opportunity in order to better define the most appropriate treatment pathway.	Thank you, your comment has been noted. No changes have been made.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Celgene	As per the response to question 2 in planning for potential guidance/advice production, [redacted]	Thank you for your comment. A summary of TA472 has been added to the background section to cover disease that is refractory to rituximab.

Section	Consultee/ Commentator	Comments [sic]	Action
		As such, NICE Guidance for treating refractory disease is relevant to this appraisal.	
	Janssen	No comment	Noted.
	Lymphoma Action	Consider explaining in the background that patients who are asymptomatic at diagnosis may be managed with an active monitoring strategy as, in practice, short-course rituximab is not used for all asymptomatic patients.	Thank you for your comment. The background section is intended to provide a very brief summary of the topic, therefore no changes have been made.
The technology/ intervention	Celgene	The description of rituximab should specify that it can also be administered subcutaneously. The description should also capture that lenalidomide with rituximab is also being studied in the MAGNIFY study (NCT01996865) which includes patients with relapsed/refractory follicular, marginal zone or mantle cell lymphoma. Data from the induction phase of this study will provide evidence on the efficacy and safety of lenalidomide with rituximab for relapsed/refractory follicular and marginal zone lymphoma, including rituximab refractory patients.	Thank you for your comment. Subcutaneous administration of rituximab and a brief summary of the MAGNIFY trial have been added to the technology section.
	Janssen	No comment	Noted.
	Lymphoma Action	The duration of treatment is not described.	Thank you for your comment.
Population	Celgene	The definition should specify that patients are 'previously' treated. As per the response to question 2 in planning for potential guidance/advice production,	Thank you for your comment. The population and title have

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		[redacted] Patients who are refractory to rituximab vs. those who are not should be examined separately.	been amended to refer to 'previously treated disease.'
	Janssen	No comment	Noted.
	Lymphoma Action	Are sub-groups being analysed as part of the AUGMENT trial?	Thank you for your comment. The clinical trials summary of AUGMENT does not currently include details of subgroups. The appraisal committee will consider subgroups based on the availability of evidence. No changes have been made.
Comparators	Celgene	As per the response to question 2 in planning for potential guidance/advice production, [redacted] As such, treatments for refractory disease are also relevant to this appraisal.	Thank you for your comment. obinutuzumab in combination with bendamustine is only used as part of the Cancer Drugs Fund therefore it is not considered a relevant comparator for disease that is refractory to rituximab.
	Janssen	NICE pathways specify the following treatments for "treating relapse or refractory disease:	Thank you for your comment. obinutuzumab in combination with bendamustine is only

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		- Rituximab, within its marketing authorisation, in combination with chemotherapy (CVP, CHOP, MCP, CHVPi or chlorambucil) is recommended as an option for the induction of remission in people with relapsed stage III or IV follicular non-Hodgkin's lymphoma. - Rituximab monotherapy as maintenance therapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed stage III or IV follicular non-Hodgkin's lymphoma in remission induced with chemotherapy with or without rituximab. - Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy). - Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is recommended for use within the Cancer Drugs Fund as an option for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen." CVP - cyclophosphamide, vincristine and prednisolone; CHOP - cyclophosphamide, doxorubicin, vincristine and prednisolone; MCP - mitoxantrone, chlorambucil and prednisolone; CHVPi - cyclophosphamide, doxorubicin, etoposide, prednisolone and interferon-α	used as part of the Cancer Drugs Fund therefore it is not considered a relevant comparator for disease that is refractory to rituximab.
	Lymphoma Action	Obinutuzumab with chemotherapy Idelalisib is under appraisal	Thank you for your comment. obinutuzumab in combination with bendamustine is only used as part of the Cancer

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		Consider explaining that chemotherapy choice is based on individual circumstances such as fitness and co-morbidities.	Drugs Fund therefore it is not considered a relevant comparator for disease that is refractory to rituximab.
Outcomes	Celgene	No comments.	Noted.
	Janssen	No comment	Noted.
	Lymphoma Action	PFS is the primary outcome measure, so consider listing first. Consider including time to next treatment, as this may be important to patients in terms of quality of life. Also consider complete response rates, if these could give an indication of length of remission.	Thank you for your comment. The list of outcomes are examples and are not intended to be an exhaustive list. They are in line with other scopes in the same disease area. No changes have been made.
Economic analysis	Celgene	No comments.	Noted.
	Janssen	No comment	Noted.
Equality and Diversity	Celgene	No comments.	Noted.
	Janssen	No comment	Noted.
Other considerations	Janssen	No comment	Noted.

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Innovation	Celgene	Lenalidomide in combination with rituximab represents a chemotherapy-free approach to the treatment of relapsed/refractory follicular and marginal zone lymphoma, which remains an area of high unmet medical need with limited treatment options. The only currently reimbursed treatment alternatives in England and Wales are chemotherapy-based, and the combination of lenalidomide and rituximab represents a targeted, synergistic, immunomodulatory approach that is a step change away from chemotherapy, offering a different class of treatment. The addition of lenalidomide to rituximab results in a complimentary mechanism of action in indolent NHL, that causes enhanced immunomodulatory and direct anti-tumour activity compared to either agent used alone, as a result of increased natural killer cell function, increased immune synapse formation, increased apoptosis and increased antibody-dependent cell-mediated cytotoxicity. Additionally, the combination of lenalidomide and rituximab may reduce administrative burden compared to rituximab plus chemotherapy for both the patient and the NHS, as lenalidomide is an oral therapy.1-10	Thank you, your comments have been noted. No changes have been made.
	Janssen	No comment	Noted.
	Lymphoma Action	Comparators are generally a choice of different chemo-immunotherapy regimens. Lenalidomide has a different mode of action from existing therapies so may have different benefits, particularly for those already treated with chemo-immunotherapy. Most therapies are intravenous so this has the added advantage of being oral, making it possible to give it over a prolonged period of time. In contrast to targeted drugs used for some other lymphomas, treatment with lenalidomide is stopped after 1 year in the AUGMENT	Thank you, your comments have been noted. No changes have been made.

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		trial. Having a defined end point of treatment, rather than ongoing treatment, could improve compliance.	
Questions for consultation	Celgene	Should chemotherapy regimens without rituximab be included? As per the response to question 2 in planning for potential guidance/advice production, [redacted] As such, options for treating follicular lymphoma refractory to rituximab are relevant to this appraisal. We understand lenalidomide in combination with rituximab is not expected to be used to treat follicular or marginal zone lymphoma that is refractory to rituximab, is this correct? No. As per the response to question 2 in planning for potential guidance/advice production, [redacted] Where do you consider lenalidomide in combination with rituximab will fit into the existing NICE pathway, Non-Hodgkin's lymphoma? Lenalidomide with rituximab is expected to fit into the existing NICE pathway as an option for the treatment of relapsed or refractory follicular or marginal zone lymphoma	Thank you for your comments. The scope has been amended to include disease that is refractory rituximab.
	Janssen	No comment	Noted.

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

Merck Sharpe & Dohme and Napp