National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lenalidomide for treating relapsed or refractory mantle cell lymphoma

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

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 [sic]	Action
Appropriateness	Celgene	NA	Comment noted. No change to scope required.
	Leukaemia CARE	Leukaemia CARE considers it appropriate to refer this topic to NICE for appraisal.	Comment noted. No change to scope required.
	RCPath	Yes	Comment noted. No change to scope required.
	Roche Products Ltd	Yes	Comment noted. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Celgene	Yes	Comment noted. No change to scope required.
	Leukaemia CARE	The document does not make it clear whether lenalidomide is being used as a monotherapy or in combination with other therapies. Leukaemia CARE would suggest that this is clarified.	Comment noted. The marketing authorisation for lenalidomide is yet to be confirmed by the European Medicines Agency. This will detail how lenalidomide should be administered.
	RCPath	It does	Comment noted. No change to scope required.
	Roche Products Ltd	-	-
Timing Issues	Celgene	Similar to other life-threatening cancers	Comment noted. No change to scope

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			required.
	Leukaemia CARE	Mantle Cell Lymphoma (MCL) is a relapsing, remitting and relentless disease which is very difficult to treat. The duration of remission is short, with patients soon relapsing. As stated, there is no accepted standard of treatment for relapsed and refractory MCL. This indicates that there is an urgency for a more effective drug to treat (and improve the survival of) patients with MCL and therefore, the NICE scoping of lenalidomide is both timely and necessary.	Comment noted. No change to scope required.
	RCPath	Lenalidomide will obtain a license in MCL soon so this is timely.	Comment noted. No change to scope required.
	Roche Products Ltd	-	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Celgene	The precise epidemiology estimates may of course be open to critique, i.e.; if there are alternative sources for this information. In addition to the BCSH guidelines, guidance exists from other bodies,	Comment noted. The background section of the scope provides an

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		including ESMO (Ref: Dreyling et al, 2014). Some of the information on treatment patterns may be inaccurate or irrelevant. Our detailed comments are provided in the Population and Comparators sections below. For fitter MCL patients at diagnosis, first line treatment of choice involves a cytarabine-based combination chemotherapy regimen, which is usually consolidated with an autologous stem cell transplant. For second line treatment of these patients, there is no agreed standard of care. An allogenic stem cell transplant can be considered for younger patients. Alternatively, a different immuno-chemotherapeutic regimen from that used first line is given (such as R-CHOP, ibrutinib or R-bendamustine). For third line treatment, these patients are generally unfit for further combination chemotherapy, and this is where monotherapies and newer targeted agents (including lenalidomide, bortezomib and ibrutinib) are recommended by current guidelines. There is currently no agreed sequencing of these targeted agents. (Ref Campo & Rule, 2015) For less fit MCL patients at diagnosis (the majority), in whom an intensive approach is not feasible, first line treatment options include R-CHOP, R-Bendamustine, R-CVP and R-Chlorambucil, usually with rituximab maintenance therapy. These patients are generally not fit for these combination chemotherapy regimens second line, therefore for these patients, monotherapies and newer targeted agents (including lenalidomide, bortezomib and ibrutinib) are recommended by current guidelines in the second line space. Again however, there is no standard of care and no agreed standard sequencing of these agents. (Ref: Campo & Rule, 2015).	overview of the disease area and is not intended to cover all details.
	Leukaemia	We consider the background information to be largely accurate.	Comment noted. The background section of

Section	Consultee/ Commentator	Comments [sic]	Action
	CARE	That said, it is worth noting that the appraisal should refer to the condition as “non-Hodgkin lymphoma” opposed to the stated “non-Hodgkin’s lymphoma”.	the scope has been updated.
	RCPath	I would delete the sentence (3rd paragraph in the background section) starting ‘The BCSH guidelines recommend that treatment with Rituximab with or without’ This is incorrect but the next part does summarise the front line therapeutic approach correctly.	Comment noted. The background section of the scope has been updated.
	Roche Products Ltd	-	-
The technology/ intervention	Celgene	Yes	Comment noted. No change to scope required.
	Leukaemia CARE	-	-
	RCPath	Yes	Comment noted. No change to scope required.
	Roche Products Ltd	-	-

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Population	Celgene	Broadly, yes – the current definition reflects the anticipated indication for this technology. However, as indicated in the Background section – and our comments above - there will be distinct patient sub-groups and treatment pathways that can be defined, and which should be considered separately. MCL is a very heterogeneous condition ranging from indolent to highly aggressive disease. A primary distinction can be made according to the overall aim of therapy, i.e.; either to get eligible patients to stem cell transplant (SCT), or achieve extended remission, or palliation. Tumour load, plus patient age and frailty determine treatment choice/intensity, and thus which of these therapeutic aims are viable. So in general, more intense therapeutic regimens or monotherapies are selected when possible (e.g.; fitter patients, pre-SCT) and less intense regimens otherwise (e.g.; less fit patients, to extend remission or palliate). At this later stage of the pathway there are limited proven and licensed treatment options and there is no clear standard of care. Lenalidomide should not be considered to fall within the category of 'intense' chemotherapies. The profile and expected clinical performance of lenalidomide has allowed clinical opinion leaders to predict the relative effectiveness – and thus place in therapy – of this technology. The pivotal clinical trial population were patients ineligible for SCT and intensive chemotherapy, and clinicians have indicated that they would not position lenalidomide for use in these SCT/intense therapy patients. Instead, they have advised that the optimal position for lenalidomide is likely to be in patients who are ineligible for intensive or combination chemotherapy (R-CHOP), or bendamustine+rituximab.	Comment noted. The population is in line with the expected marketing authorisation. No change to scope required.

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		Therefore, the population for which Celgene advise this technology will be suitable is: patients who are not/no longer eligible for SCT or combination chemotherapy, as a second, third or fourth-line treatment. Correspondingly, other aspects of the Background information – including a description of the epidemiology, and survival prognoses – could be amended to reflect this specific patient population. For example: • Median age is likely to be higher (e.g.; 73 compared to 63) • Patients are likely to be less fit • Tumour burden is likely to be higher, with a poorer prognosis • Median survival decreases to 1-2 years (rather than 3-5 years) in patients ineligible for SCT (Ref: Dietrich et al, 2011). Patient numbers will obviously also be lower.	
	Leukaemia CARE	The treatment may be more suitable for those who are older or have comorbidities that prevent them receiving some of the more aggressive therapies such as SCT or chemotherapy.	Comment noted. No change to scope required.
	RCPath	No sub-groups	Comment noted. No change to scope required.
	Roche Products Ltd	-	-

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Comparators	Celgene	For the population of patients who are not/no longer eligible for SCT or combination chemotherapy, UK drug utilisation data and market research indicates that the following treatments have been most routinely used in the NHS: • Bortezomib + rituximab (although this is no longer available as it has been removed from the CDF) • Ibrutinib • Monotherapies This could result in lenalidomide being used as either a '2L' or '3L' therapy in the treatment pathway (but in either case, the displaced therapy – and thus relevant comparator – would likely remain unchanged). The use of some of these therapies may be dependent upon evolving funding statuses. E.g.; the historical funding of bortezomib(+rituximab) via the Cancer Drugs Fund (CDF) has been removed. As usage consequently declines, this therapy may no longer be an appropriate comparator. Additionally, there is no agreed standard sequencing of these monotherapy agents. For example, we have been advised by clinical experts that they are likely to sequence lenalidomide post-ibrutinib, but for some patients they might prefer to sequence lenalidomide prior to ibrutinib. Therefore, the group of remaining monotherapy options appear to be the therapies most definitely likely to be displaced by use of lenalidomide, and are thus the primary comparator/s.	Comment noted. Consultees at the scoping workshop agreed that comparators listed in the scope were appropriate. No change to scope required.
	Leukaemia CARE	-	-

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	RCPath	With the exception of Rituximab and Ibrutinib single agent therapy would not be used in this disease.	Comment noted. Consultees at the scoping workshop agreed that comparators listed in the scope were appropriate. No change to scope required.
	Roche Products Ltd	For patients with relapse or refractory Mantle Cell Lymphoma there is no standard of care, therefore all therapeutic options in this setting must be considered relevant comparators. The current list of comparators omit the following options : Bortezomib, temsirolimus and stem cell transplant (in patients who are fit enough and who have not received a SCT previously) If the licence states that prior treatment with one of these therapies is required, then re-challenge with them may not be appropriate.	Comment noted. Consultees at the scoping workshop agreed that comparators listed in the scope were appropriate. Bortezomib has been removed from the Cancer Drugs Fund for this indication, the Consultees considered that temsirolimus is not commonly used in the NHS and the people in the lenalidomide trial were ineligible for stem cell transplant. No change to scope required.

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Outcomes	Celgene	Yes	Comment noted. No change to scope required.
	Leukaemia CARE	We consider the outcome measures to be correct.	Comment noted. No change to scope required.
	RCPath	Yes	Comment noted. No change to scope required.
	Roche Products Ltd	-	-
Economic analysis	Celgene	The technology may be demonstrated to be cost-effective, by being cost-saving (ie; in the SW quadrant of the cost-effectiveness plane) compared to other regimens.	Comment noted. No change to scope required.
	Leukaemia CARE	-	-

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	RCPath	No comment	-
	Roche Products Ltd	This section typically states that for treatments funded by the CDF, cost incurred by the CDF should be used in any economic analysis rather than list price. Bendamustine and Ibrutinib are listed in the scope as funded by the CDF.	Comment noted. The scope has been updated and this has been removed from the economic analysis section.
Equality and Diversity	Celgene	-	-
	Leukaemia CARE	-	-
	RCPath	No issues with this	Comment noted. No change to scope required.
	Roche Products Ltd	-	-

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Innovation	Celgene	No, we doubt the technology will be considered innovative according to these definitions.	Comment noted. No change to scope required.
	Leukaemia CARE	Lenalidomide as a different mode of action from existing therapies so is likely to bring additional benefits and is therefore considered to be an innovative treatment. Most therapies are intravenous so this has the added advantage of being an oral tablet, a method more suited to some patients It also differs in being given as an ongoing therapy, which may be of particular benefit given that mantle cell lymphoma often relapses early after initially responding to other therapies.	Comment noted. No change to scope required.
	RCPath	Lenalidomide is an active drug in the context of mantle cell lymphoma. Whilst ibrutinib is a game changing drug in this condition patients who respond to lenalidomide obtain a very similar duration of response, there are just fewer of them as a percentage. The other important point is one of sequencing therapies. MCL is an incurable disease and it is important to maintain good QOL for as long as possible. Both ibrutinib and lenalidomide are well tolerated, ibrutinib invariably works following lenalidomide, the converse is not true.	Comment noted. No change to scope required.
	Roche Products Ltd	-	-

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Other considerations	Celgene	See additional comments below	Comment noted. No change to scope required.
	Leukaemia CARE	-	-
	RCPath	-	-
	Roche Products Ltd	It may be appropriate to consider sub groups according to number of lines of prior therapy	Comment noted. No change to scope required.
Questions for consultation	Celgene	Please see our comments on the 'Population(s)' and 'Comparators' sections above.	Comment noted. No change to scope required.
	Leukaemia CARE	-	-
	RCPath	There is no clear treatment paradigm in MCL. Front line you use R-chemo (plus autograft in young patients), second line you will use a different R-chemo regimen. Commonly one uses R-CHOP then R-Bendamustine or vice versa. After second line there are a host of options which will depend very much on the age and fitness of the patient, the response to prior therapies, what is available, and patient wishes. Lenalidomide would be one of the	Comment noted. No change to scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		drugs (like Ibrutinib) that would be used when the patient has exhausted chemotherapy or is clearly resistant to that approach.	
	Roche Products Ltd	-	-

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

Lilly UK

Healthcare Improvement Scotland

Janssen

Pfizer UK

NATIONAL INSTITUTE FOR HEALTH CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Lenalidomide for treating relapsed or refractory mantle cell lymphoma [ID739]

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.	Afyia Trust	NICE Secretariat		Removed	This organisation interests are not related to technology appraisal topics. Afyia Trust have been removed from the list of consultees and commentators under 'Patient/carers group'

1.	Alliance Pharmaceuticals (prednisolone)	NICE Secretariat		Removed	This organisation does not hat an interest related to the appraisal topics. **Alliance Pharmaceuticals (prednisolone)** have been removed from the list of consultees and commentators under 'Comparator companies'
2.	Muslim Health Networks	NICE Secretariat		Removed	This organisation is no longer operational and. have been removed from the list of consultees and commentators under 'Patient / carer groups