National Institute for Health and Care Excellence

Single Technology Appraisal

Lenalidomide for the maintenance treatment of newly diagnosed multiple myeloma after autologous stem cell transplantation

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Celgene	The remit should read "To appraise the clinical and cost effectiveness of lenalidomide *monotherapy* within its marketing authorisation, i.e. "Revlimid as monotherapy is indicated for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation"	This topic was referred before the marketing authorisation was gained. The remit covers lenalidomide being appraised within its marketing authorisation. Elsewhere in the scope it has been clarified that the population is people with newly diagnosed multiple myeloma and that lenalidomide will be used as a monotherapy rather than a combination therapy for this indication.

Section	Consultee/ Commentator	Comments [sic]	Action
	Janssen- Cilag	No comment	Comment noted.
	Myeloma UK	Yes.	Comment noted.
	UK Myeloma Forum	Wording is appropriate	Comment noted.
Timing Issues	Celgene	No comment	Noted.
	Janssen- Cilag	No comment	Noted.
	Myeloma UK	This appraisal is extremely important to myeloma patients and their families and should be progressed with urgency. There has already been too long a delay in the company moving forward with this appraisal which has been licensed for some time. There is now strong data demonstrating a doubling of remission time and overall survival gains for this treatment, at a point in the pathway when patients have the most chance of and the most to gain from a deep and prolonged remission. Around 1,300 myeloma patients undergo a stem cell transplant each year. This means that with every month that passes more than100 patients are missing out on the opportunity to access treatment which could help them live significantly longer.	Comments noted.
	UK myeloma Forum	This is a technology that improves overall survival and progression free survival in this indication and is in standard usage in most EU countries and USA in the post transplant setting.	Comment noted.
Additional comments on the draft remit	Celgene	No comments	Noted.
	Janssen- Cilag	No comment	Noted.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Celgene	No comment	Noted.
	Janssen- Cilag	No comment	Noted.
	Myeloma UK	No comment	Noted.
	UK Myeloma Forum	The background is accurate. It would be useful to highlight that the decision that patients are eligible for high dose therapy supported with autologous stem cell therapy (ASCT) is determined by patient medical fitness/ medical co-morbidities and performance status. There is not a chronological age cut off. However less than half newly diagnosed myeloma patients would be considered ASCT eligible.	Thank you for your comments. The background section of the scope is intended to give a top-level summary of the disease area. The characteristics of people who could have a stem cell transplant and would be eligible for lenalidomide is anticipated to be explored during the appraisal.
The technology/ intervention	Celgene	The sentence “Lenalidomide has a marketing authorisation for the treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation” Should be replaced by	This sentence has been updated in the scope. It is not necessary to state monotherapy in the interventions section of the table because if lenalidomide is indicated to be taken

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		"Lenalidomide has a marketing authorisation for the *maintenance* treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation" The table (pp 2) should be changed as follows: Intervention(s): 'Lenalidomide *as monotherapy*'.	in combination with other drugs those drugs would be stated in this table. The description of the marketing authorisation has been updated to state that lenalidomide is taken as a monotherapy.
	Janssen- Cilag	No comment	Noted.
	Myeloma UK	Yes	Noted.
	UK Myeloma Forum	This is accurate. Please note that lenalidomide is currently approved by NICE as a 2nd line (if prior bortezomib treatment), 3rd or 4th line therapy i.e. for relapsed patients.	Comment noted. The technology section has listed the marketing authorisation for the indication which will be considered in the current appraisal only
Population	Celgene	Table (pp2) should be changed as follows: Population(s) A*dults with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation*.	The population section has been updated to include 'newly diagnosed' in line with the marketing authorisation.
	Janssen-Cilag	No comment	Noted.

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	Myeloma UK	While we would want the widest possible application of an approval for this treatment, NICE may wish to consider reviewing this wording to ensure that it is consistent with the marketing authorisation which is for newly diagnosed patients.	The population section has been updated to include 'newly diagnosed' in line with the marketing authorisation.
	UK Myeloma Forum	The population is accurate	The population section has been updated to include 'newly diagnosed' in line with the marketing authorisation.
Comparators	Celgene	Celgene will be making a submission comparing best supportive care to maintenance in people who received ASCT. The appropriate comparator is best supportive care (monitoring and follow up) after ASCT until disease progression. Currently, no other licensed treatment or recommendations exist for maintenance therapy after ASCT: • Bortezomib (in combination with dexamethasone or with dexamethasone and thalidomide) is indicated for the induction treatment of adult patients with previously untreated MM who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation. In this indication, bortezomib is recommended in the UK for people who have not received ASCT. Bortezomib is also indicated (in combination with doxorubicin or with dexamethasone) in people who with progressive MM who have received at least one prior therapy and are either unsuitable or have progressed after ASCT. In	The comparator section has been updated to 'Established clinical management without lenalidomide maintenance therapy (including monitoring and follow up)'.

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		this indication, bortezomib is recommended in the UK after first relapse. • Carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. In this indication, carfilzomib is recommended in the UK in people who have progressed as long as they did not receive prior bortezomib. In summary, any combinations of bortezomib, or carfilzomib or thalidomide or melphalan are not comparators for post-ASCT maintenance with lenalidomide. In addition, people who undergo an ASCT and do not receive maintenance with lenalidomide (in the best supportive care arm) remain eligible for lenalidomide after second relapse, therefore the wording 'without lenalidomide' is misleading and should be deleted.	The wording has been updated to "without lenalidomide maintenance therapy"
	Janssen Cilag	No comment	Noted.

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	Myeloma UK	No comment.	Noted.
	UK Myeloma Forum	The comparators listed are not accurate. It is not standard practice / NICE approved to offer any alternative therapy post ASCT. The comparator is no therapy.	The comparator section has been updated to 'Established clinical management without lenalidomide maintenance therapy (including monitoring and follow up)'
Outcomes	Celgene	Yes	Comment noted.
	Janssen- Cilag	No comment	Noted.
	Myeloma UK	Yes	Comment noted.
	UK Myeloma Forum	Overall survival, progression free survival and Quality of life are the key outcome measures	Comment noted.
Economic analysis	Celgene	A lifetime time horizon is appropriate to model multiple myeloma treatment and is consistent with the NICE reference case.	Comment noted.
	Janssen- Cilag	No comment	Comment noted.
	Myeloma UK	Yes	Comment noted.
	UK Myeloma Forum	The appropriate time horizon for consideration should be between 5 – 10 years	Comment noted.

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Equality and Diversity	Celgene	No comments	Noted.
	Janssen- Cilag	No comment	Noted.
	Myeloma UK	No comment.	Noted.
	UK Myeloma Forum	There are no specific equality issues	Noted.
Other considerations	Celgene	No comments	Noted.
	Janssen- Cilag	• Important to understand the evidence supporting lenalidomide maintenance therapy in patients with renal impairment. • What are the risks of developing secondary primary malignancies with continuous lenalidomide maintenance versus current standard of care after autologous stem cell transplant?	Comments noted.
	UK Myeloma Forum	Lenalidomide based treatment is approved by NICE for patients with relapsed myeloma at 2nd line (TA586) or 3rd line (TA171, TA505). It is expected that those patients treated with lenalidomide maintenance post transplant would not access lenalidomide later in their treatment course (which currently is the vast majority of patients) thereby offsetting the cost of earlier lenalidomide.	Comment noted
Innovation	Celgene	Maintenance with lenalidomide is a step-change in the treatment of people with NDMM who undergo transplantation. Maintenance with continuous lenalidomide monotherapy after transplant until disease progression significantly improves PFS, reduces the risk of death, improves health-related quality of life compared with the standard of care, observation until progression. Maintenance with lenalidomide monotherapy brings about a	Comment noted.

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		clinically significant advantage for people who are at risk of progressive disease. Currently, no maintenance treatments are in use, which results in faster progression to subsequent treatment with decreased efficacy and higher probability to develop refractory disease. Lenalidomide monotherapy is an all oral regimen and patients have shown a preference for oral combinations in numerous studies[4]. As an oral therapy, lenalidomide can be self-administered at home, with only outpatient consultations during maintenance.	
	Janssen- Cilag	No comment	Comment noted.
	Myeloma UK	While this technology will deliver significant benefit for this patient population in this new indication the treatment itself is not innovative having been a "backbone" treatment in myeloma for a decade.	Comment noted.
	UK Myeloma Forum	This is an innovative therapy. There are no approved maintenance approaches in England and Wales post ASCT. The use of maintenance treatment post transplant is associated with a significantly longer disease control compared to no therapy and this leads to significant improvements in overall survival. This has been demonstrated in several phase 3 trials including UK led trials and meta-analysis.	Comment noted.
Questions for consultation	Celgene	Only best supportive care is a relevant comparator for this assessment. No current pharmacological therapy is licensed to be used in maintenance after ASCT. Carfilzomib is licensed for use after one prior therapy. It is currently available in the UK only for people who have had one relapse and have not received prior bortezomib.	Comments noted. The comparator section has been updated to 'Established clinical management without lenalidomide maintenance therapy (including monitoring and follow up)'.

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		Bortezomib is used in combination with other agents (alkylating agents, corticosteroids) either for induction before transplant, or in people who are not eligible for transplant. Treatment combinations with thalidomide and melphalan are used either for induction before transplant, or in patients who are not eligible for transplant. Specifically, usage of these products is not indicated for continuous use.	
	Celgene	Clinical management for multiple myeloma after ASCT essentially consists of monitoring for disease progression. Consolidation regimens are sometimes used after ASCT. Consolidation consists in a course of chemotherapy intended to be short and aimed to enhance response following ASCT. Consolidation regimens are mostly made up of bortezomib in combination with lenalidomide and dexamethasone (VRD). Sometimes, VTD (bortezomib + thalidomide + dexamethasone, used for 2 cycles) or dexamethasone alone (4 cycles) are used after ASCT. However, the use of all the aforementioned treatments with bortezomib, thalidomide, and lenalidomide as consolidation therapy post ASCT are not within their respective labels. Other regimens (bortezomib + thalidomide + dexamethasone, VTD) are sometimes used after ASCT, in the context of so called 'tandem transplant' which consists of two rounds of stem dell reinfusion after one induction course. This therapeutic approach is not in use in the UK.	Comments noted

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		Although many regimens may have a potential for use after first ASCT, none have a license, or are used in practice after ASCT for indefinite use before progression. Supportive care (or observation) consists of follow up after ASCT and monitoring for disease progression. People with myeloma also receive concomitant care for the prevention and management of disease associated issues such as bone disease, prevention of fractures, infections, peripheral neuropathy and thrombosis. [Are the outcomes listed appropriate?] Yes No subgroups are relevant for this assessment. [Equality issues] No comments [lenalidomide innovative?] See above. No additional benefits that cannot be captured [barriers to adoption?] No. Access to maintenance with lenalidomide has been advocated by the clinical community on grounds of efficacy benefits and ease of administration. The Myeloma XI study, a large randomised clinical trial conducted entirely in the UK, proved that maintenance is a step change in the therapy of multiple myeloma. [redacted]	

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		[redacted] The STA process is appropriate.	
	Janssen- Cilag	No comment	
	UK Myeloma Forum	1. There are no specific treatments used as maintenance therapy post transplant at present None of the “alternative” therapies listed are appropriate as it is not current practice to administer chemotherapy post transplant unless relapse has occurred. There is specific NICE guidance that is applicable following relapse e.g TA586, TA573, TA457, TA129 all apply to 2nd line treatment.	Comments noted. The comparators have been updated to ‘Established clinical management without lenalidomide maintenance therapy (including monitoring and follow up)’.
Additional comments on the draft scope	Janssen- Cilag	In terms of related NICE recommendations and NICE Pathways, an appraisal in development not included in the draft scope is Ixazomib with lenalidomide and dexamethasone for untreated multiple myeloma [ID1170]; https://www.nice.org.uk/guidance/indevelopment/gid-ta10254	Comment noted. This has not been included because that appraisal will cover a population for whom stem cell transplant is not suitable.
	UK Myeloma Forum	This is an extremely important appraisal. Lenalidomide maintenance has clear significant benefits for patients in terms of disease control duration, overall survival and quality of life benefits at a time in the disease course	Comment noted.

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		when patients are at their most medically well. It is considered the standard of care in EU and USA on the basis of the robust phase 3 trial data and metanalysis.	

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