

National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the and draft scope

Section	Consultees	Comments	Action
Background information	Celgene Ltd	No comment	
	Myeloma UK	No comment	
	NCRI/RCP/RCR /ACP/JCCO	In general, this is accurate.	Comment noted.
	UK Myeloma Forum	In general this is accurate.	Comment noted.
The technology/ intervention	Celgene Ltd	Yes	No action required.
	Myeloma UK	Yes. The description of the technology is accurate.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	Yes	No action required.
	UK Myeloma Forum	Yes	No action required.

Section	Consultees	Comments	Action
Population	Celgene Ltd	The population as currently defined is not appropriate and Celgene suggests that it be reworded to state "multiple myeloma patients who have had high dose chemotherapy and autologous stem cell transplantation and whose disease has achieved an appropriate response. No specific subgroups have been identified.	Comment noted. The population section has been updated to reflect the characterisation of treatment response.
	Myeloma UK	The population is not defined appropriately. It is important that the sentence "and whose disease has had a response to treatment with high-dose chemotherapy" is reworded. Instead the population should read "People with multiple myeloma who have had high dose chemotherapy and autologous stem cell transplantation and whose disease has achieved an appropriate response (i.e. stable disease or better)." This is for two principle reasons: 1. There is no clinical rationale to measure response to high-dose chemotherapy prior to autologous stem cell transplantation. 2. Some patients may have reached their maximal response to treatment following induction therapy and experience no further response following high-dose therapy and autologous stem cell transplantation.	Comment noted. The population section has been updated to reflect the characterisation of treatment response.
	NCRI/RCP/RCR /ACP/JCCO	Suggest re-wording of this to read ' and whose disease is at least stable following high dose chemotherapy.' This is because some patients will have reached their maximal response following induction therapy and no further response is seen following treatment with high dose chemotherapy.	Comment noted. See above.
	UK Myeloma Forum	Suggest re-wording of this to read " and whose disease is at least stable following high dose chemotherapy." This is because some patients will have reached their maximal response following induction therapy and no further response is seen following treatment with high dose chemotherapy.	Comment noted. See above.

Section	Consultees	Comments	Action
Comparators	Celgene Ltd	'Best supportive care' / 'watchful waiting' is considered the most appropriate comparator. At this point, there are no other licensed treatments in this area of high unmet need. Thalidomide is not an appropriate comparator as it is rarely used in clinical practice.	Comment noted. It is recognised that best supportive care can vary, and the comparator section in the scope has been updated to reflect the range of potential treatment options.
	Myeloma UK	<p>Best supportive care' is an appropriate comparator as currently there are no licensed drugs in this setting or standard approach to maintenance in the UK.</p> <p>'Best supportive care' should include 'active monitoring' of paraprotein levels, symptoms and general quality of life.</p> <p>Patients who are not currently receiving anti-myeloma treatment are likely to still be receiving a number of supportive treatments such as bisphosphonates, antibiotics, anti-fungals and analgesics.</p> <p>Thalidomide has been used to a limited extent as a maintenance treatment within clinical study settings. However, it is not used routinely in clinical practice due to patient intolerance and its deleterious impact on the quality of life of patients. It is therefore not an appropriate comparator.</p>	Comment noted. See above.
	NCRI/RCP/RCR /ACP/JCCO	<p>There are no standard treatments that can be considered comparators, so best supportive care would be regular monitoring with bisphosphonate therapy, analgesia and antibiotics as appropriate.</p> <p>Thalidomide is generally not used due to patient intolerance.</p>	Comment noted. See above.

Section	Consultees	Comments	Action
	UK Myeloma Forum	There are no standard treatments that can be considered comparators, so best supportive care would be regular monitoring with bisphosphonate therapy, analgesia and antibiotics as appropriate. Thalidomide is generally not used due to patient intolerance.	Comment noted. See above.
Outcomes	Celgene Ltd	Yes. Progression-free survival is a valuable end point in itself even in the absence of overall survival (given that the data has not yet matured).	Comment noted.
	Myeloma UK	These are all appropriate outcome measures. Progression-free survival (PFS) is a particularly important outcome measure in myeloma, a cancer which is incurable and characterised by repeated relapses and remissions. Without additional effective treatment, periods of remission become increasingly shorter as the myeloma cells become resistant to treatment. The primary objective of maintenance treatment is to extend the duration of response to treatment and to achieve as long a period of PFS as possible. PFS is usually associated with improved quality of life as active myeloma is slowed down or prevented from returning.	Comment noted.
	NCRI/RCP/RCR /ACP/JCCO	These are appropriate, with perhaps the addition of 'Time to next treatment' or TTNT, as health related QOL in general is lower during treatment periods.	Comment noted. Time to next treatment has been included an outcome.
	UK Myeloma Forum	These are appropriate, with perhaps the addition of 'Time to next treatment' or TTNT, as health related QOL in general is lower during treatment periods.	Comment noted. See above.
Economic	Celgene Ltd	A life time model will be appropriate for any economic analysis.	Comment noted.

Section	Consultees	Comments	Action
analysis	Myeloma UK	No comments	
	NCRI/RCP/RCR /ACP/JCCO	The time horizon should be sufficiently long to reflect any difference in survival outcomes	Comment noted.
	UK Myeloma Forum	The time horizon should be sufficiently long to reflect any difference in survival outcomes	Comment noted.
Equality and Diversity	Celgene Ltd	Myeloma mostly affects the elderly population, who often face other concomitant conditions. Such patient populations may also have mobility issues. Equality of access may be achieved by ensuring that the benefits of newer treatments reach these patients.	Comment noted. The Committee will discuss and decide on all potential equality issues during this appraisal.
	Myeloma UK	No comments	
	NCRI/RCP/RCR /ACP/JCCO	No comments	
	UK Myeloma Forum	No comments	
Innovation			
Other considerations	Celgene Ltd.	None	
	Myeloma UK	None	

Section	Consultees	Comments	Action
	NCRI/RCP/RCR /ACP/JCCO	None	
Questions for consultation	Celgene Ltd	<p>Yes, lenalidomide maintenance treatment of newly diagnosed multiple myeloma patients can be viewed as an innovative technology, with an immunomodulatory mode of action.</p> <p>Benefits of lenalidomide maintenance (in the context of clinically meaningful improvements) can likely not be captured since QoL data on lenalidomide maintenance was not collected in either IFM 2005-02 and CALGB 100104. Therefore, only rudimentary QoL proxy data will be available, which might not capture all treatment-specific QoL benefits.</p> <p>Lenalidomide is an oral therapy and therefore can be self-administered. This can be of immense help to patients who have mobility problems. However this benefit is unlikely to be reflected in the standard QALY measure.</p> <p>Data is available from 2 phase III trials - IFM 2005-02 and CALGB 100104 for patients following stem cell transplant. In these trials, progression-free survival (PFS) was used as primary endpoint, while response rates and overall survival, OS, amongst others, were collected as secondary endpoints.</p>	Comment noted.

Section	Consultees	Comments	Action
	NCRI/RCP/RCR /ACP/JCCO	Yes, this technology is innovative, and represents a 'step-change' in the management of this incurable cancer. This technology is able to double the time to disease progression following stem cell transplantation, and as such is the most significant innovation in the management of these patients since the adoption of high dose therapy. Results of the CALGB phase 3 study also indicate a survival benefit. A significant health related benefit that is unlikely to be captured in the QALY calculation is the fact that prolongation of progression free survival and delaying relapse would afford the opportunity to receive treatment with newer technologies which would not have been available previously. Such a consideration would be supported by the number of new technologies that have become available for the treatment of myeloma over the past 5 years.	Comment noted.
	UK Myeloma Forum	Yes, this technology is innovative, and represents a 'step-change' in the management of this incurable cancer. This technology is able to double the time to disease progression following stem cell transplantation, and as such is the most significant innovation in the management of these patients since the adoption of high dose therapy. Results of the CALGB phase 3 study also indicate a survival benefit. A significant health related benefit that is unlikely to be captured in the QALY calculation is the fact that prolongation of progression free survival and delaying relapse would afford the opportunity to receive treatment with newer technologies which would not have been available previously. Such a consideration would be supported by the number of new technologies that have become available for the treatment of myeloma over the past 5 years.	Comment noted.

Section	Consultees	Comments	Action
	Myeloma UK	<p>The use of maintenance treatment is widely regarded as having the potential to make a substantial impact on the duration and quality of response (in particular progression free survival) experienced by patients following autologous stem cell transplantation.</p> <p>The CALGB Phase III study has also recently reported that lenalidomide maintenance post-autologous stem cell transplantation may also have a benefit in improving survival.</p> <p>There is currently an unmet need with regard to an approved, standard maintenance strategy for myeloma patients in the UK.</p> <p>The evidence suggests that lenalidomide is an effective maintenance treatment in this patient population. As the first treatment to receive an anticipated licence for maintenance, it offers a potential step-change in the management of myeloma in the UK.</p> <p>*Please see 'Comparators' section for a response to the 'Questions for consultation' on the most appropriate comparators for lenalidomide maintenance treatment.</p>	Comment noted.
Additional comments on the draft scope.	Myeloma UK	No comments	
	NCRI/RCP/RCR /ACP/JCCO	<p>Thalidomide is not routinely used in this context, even for people whose disease has not achieved a VGPR after stem cell transplantation.</p> <p>Best supportive care should be defined as regular clinical review, including monitoring of paraprotein and administration of bisphosphonates unless contra-indicated, antibiotics and analgesia as appropriate.</p> <p>A group of people for whom the technology would be especially beneficial are those with neuropathy that is grade 2 or greater, according to the NCI CTCAE (common terminology criteria for adverse events), because they would not be able to receive bortezomib or thalidomide at relapse, hence any therapy that delays relapse would be especially beneficial.</p>	Comment noted. Thalidomide has been removed as a potential comparator, and is no longer listed in the matrix.

Section	Consultees	Comments	Action
	UK Myeloma Forum	<p>Thalidomide is not routinely used in this context, even for people whose disease has not achieved a VGPR after stem cell transplantation.</p> <p>Best supportive care should be defined as regular clinical review, including monitoring of paraprotein and administration of bisphosphonates unless contraindicated, antibiotics and analgesia as appropriate.</p> <p>A group of people for whom the technology would be especially beneficial are those with neuropathy that is grade 2 or greater, according to the NCI CTCAE (common terminology criteria for adverse events), because they would not be able to receive bortezomib or thalidomide at relapse, hence any therapy that delays relapse would be especially beneficial.</p>	

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

Healthcare Improvement Scotland, Marie Currie, Royal College of Nursing, Department of Health, Janssen