National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Carfilzomib for previously treated multiple myeloma (part review of TA457) [ID1493]

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 [sic]	Action
Wording	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Yes	No action required.
	Myeloma UK	Yes	No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	No comments	No action required
	Amgen Ltd	Yes, the wording of the remit reflects the marketing authorisation of carfilzomib in combination with lenalidomide plus dexamethasone (CRd).	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Timing Issues	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Combination therapy for relapsed myeloma improves survival outcomes. Therefore this treatment for relapsed myeloma, which is an incurable malignancy, should be considered relatively urgent	Comment noted. No action required.
	Myeloma UK	Myeloma is a very challenging illness to live with and to treat. It is a relapsing and remitting and very heterogeneous cancer which means that a wide range of treatments with different mechanisms of action are especially vital. There have been welcome recent approvals at second line in the myeloma treatment pathway which has addressed to some extent what was a chronic unmet need. However, the need for an effective triplet combination, combining a proteasome inhibitor and an immunomodulatory drug remains.	Comment noted. No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	No comments	No action required.
	Amgen Ltd	It is our view that this topic should be considered with high urgency and the currently proposed timelines are suitable. In the multiple myeloma landscape, there is a clear need for triplet therapies that enable deeper and more durable responses earlier in the pathway.	Comment noted. No action required.
Additional comments on the draft remit	Janssen-Cilag Ltd	No comment	No action required.
	Celegene Ltd	No additional comments	No action required.
	Amgen Ltd	NA	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Draft scope should specify that NICE TA 573 recommendation of Daratumumab/ Bortezomib/ dexamethasone is not an option for patients who are Bortezomib refractory	Comment noted. No action required. The background section includes only an overview of previous NICE guidance in the specific disease area. Detailed NICE guidance can be found on NICE's website.
	Myeloma UK	No comment	No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	No comments	No action required.
	Amgen Ltd	No comment	No action required.
The technology/ intervention	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Yes	No action required.
	Myeloma UK	Yes	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	No comments	No action required
	Amgen Ltd	Yes, accurate.	No action required.
Population	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Yes	No action required. However, the wording has been changed in line with other comments on the population.
	Myeloma UK	We strongly disagree with the patient population being restricted to patients who were not previously treated with lenalidomide. In our comments on the review of this appraisal we argued that the scope should be in line with the marketing authorisation for the treatment. We continue to believe that this is the case. Excluding patients who have had previous lenalidomide is also not consistent with existing practice and decisions, eg the NHS England Cancer Drugs Fund list does not stipulate that patients must be lenalidomide naïve to receive treatment with ixazomib, lenalidomide and dexamethasone – only that they must not be refractory. Patients who have been exposed to lenalidomide are clearly eligible. This is the correct approach. The decision on whether a lenalidomide exposed patient may benefit from retreatment with lenalidomide as part of a treatment combination should be one for physicians to make. Patients and their families feel strongly that the treatment pathway should not unfairly restrict treatment options that their physician may feel has clinical benefit. At this stage, prior to the appraisal taking place, we can see no clinical rationale for this restriction being applied.	Comment noted. The wording has been changed.

Section	Consultee/ Commentator	Comments [sic]	Action
	Janssen-Cilag Ltd	We note that the licenced indication is broader than the population defined in the draft scope (i.e. not based on prior exposure to lenalidomide)	Comment noted. The wording has been changed.
	Celgene Ltd	Current 2nd line therapies recommended in the UK are: • Combinations of bortezomib: o with dexamethasone, VD, or o with daratumumab and dexamethasone, DVDex (via Cancer Fund); • Combination of lenalidomide and dexamethasone (RD) • Carfilzomib in combination with dexamethasone (KD) in people who received 1 prior therapy (but not 2) (TA457) A clarification of the decision problem population is appropriate, and should concern: 1. Whether the requirement that carfilzomib 2nd line is given to people who are naïve to bortezomib is also applicable to the population in this appraisal in 3rd line, i..e whether retreatment with carfilzomib is admissible. 2. Whether the appraisal covers relapsed or refractory patients, or both	Comment noted. No action required. However, the wording has been changed in line with other comments on the population.
	Amgen Ltd	The wording of the remit and background section accurately captures the population for which CRd has a marketing authorisation – ie. *for treating adults with multiple myeloma who have had at least 1 prior therapy*. However, we believe there is an error in the description of the population within the draft scope.	Comment noted. The wording has been changed.

Section	Consultee/ Commentator	Comments [sic]	Action
		Currently the draft scope states that the population to be considered in the decision problem is "*Adults with multiple myeloma who have had at least 1 previous therapy which did not include lenalidomide"*. This population is inconsistent with the marketing authorisation of CRd and does not reflect the associated NICE Guidance of relevant comparators. In particular, the most relevant comparator for this appraisal, lenalidomide plus dexamethasone, is recommended in NICE TA586 as a treatment option for adults who had only 1 previous therapy which included bortezomib. Although we acknowledge the important consideration of prior therapies in optimising subsequent treatment lines in clinical practice, it is Amgen's strong view that the population considered in the decision problem scope should be aligned with the MA and not pro-actively restricted.	
Comparators	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	It is unlikely that this treatment will be used for patients who have had 3 or more previous lines of therapy. Comparators listed for 1 previous lines of therapy are appropriate. But there are differences in the population. For patients who have received 1 prior line of therapy, Carfilzomib and dexamethasone is only allowed as a choice of therapy, if patients are naïve to Bortezomib. Lenalidomide and dexamethasone is only allowed as a choice of therapy, if patients have had prior Bortezomib therapy. Bortezomib can only be prescribed after 1 prior therapy If patients have not had Bortezomib before. Comparators for 2 previous lines of therapy does not include Ixazomib/ Lenalidomide and dexamethasone the most widely used therapy in England (TA 505).	Comment noted. No action required. As per NICE's position statement technologies that have been recommended by NICE for use in the Cancer Drugs Fund cannot be considered established practice and are therefore not considered as comparators in new appraisals.
	Myeloma UK	No comment	No action required.

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	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	In addition to the combination of panobinostat + bortezomib + dexamethasone in third line in relapsed and refractory people, as per NICE recommendations (TA380). The triplet ixazomib + lenalidomide + dexamethasone (IRD) is also available (via Cancer Fund) for people who received no less than 2 prior therapies. Are comparisons with products funded via CDF also going to be assessed? These treatments seem appropriately described as best alternative care	See response to comment on comparators by UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists.
	Amgen Ltd	The most appropriate comparator for this appraisal will be lenalidomide plus dexamethasone (Rd, TA586) given the likely use of CRd in clinical practice. Additional comparators highlighted in the scope accurately reflect current NICE approved treatments in this disease area. We also note that the guidance of TA573 which recommends daratumumab plus bortezomib and dexamethasone (DVd) for use within the Cancer Drugs Fund as a treatment option for adults who have had 1 previous therapy is acknowledged in the draft scoping document also. Consistent with the NICE Position Statement on the consideration of products recommended for use in the Cancer Drugs Fund as comparators, January 2019, DVd has not been included as a comparator. However, given the need for more effective treatments earlier in the pathway, and the likely use of DVd in clinical practice, this treatment may realistically reflect a significant proportion of the standard of care in this setting. For this reason Amgen would consider a	See response to comment on comparators by UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists.

Section	Consultee/ Commentator	Comments [sic]	Action
		comparison versus DVd to be pertinent to the decision problem and informative for a Committee to consider.	
Outcomes	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Yes	No action required.
	Myeloma UK	Yes	Comment noted. No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	The proposed outcomes seem appropriate	Comment noted. No action required.
	Amgen Ltd	Yes	Comment noted. No action required.
Economic analysis	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Yes. Carfilzomib is given for a fixed duration of therapy and there is statistically significant improvements in overall survival, on long term follow up. This would help with certainty of the costs involved in delivering this therapy.	Comment noted. No action required.
	Myeloma UK	The question of time horizons for overall survival impact in myeloma, say over 10 or 20 years, has often led to disagreements between NICE and the ERG and submitting companies. Our role is not to comment on the applicability of	Comment noted. No action required.

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		specific health economic models. However, we do want to note our view that companies must be realistic and considered in relation to the overall long term survival claims they make. No one is well served if companies come to the table with inflated claims about the long term OS impact of their product. Equally, the system should acknowledge the limitations of any model predicting OS gains that far into the future, when the pathway is subject to constant change, and should factor that into its consideration of long term OS impact.	
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	A lifetime horizon would be most appropriate	Comment noted. No action required.
	Amgen Ltd	No comment, as per reference case.	Comment noted. No action required.
Equality and Diversity	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Nil	No action required.
	Myeloma UK	No comments	No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	No comment	No action required.

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	Amgen Ltd	NA	No action required.
Other considerations	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	Carfilzomib has to be delivered parenterally in day units 2 days a week in tandem. Treatment will be delivered in secondary care day units across the country. Patients with poor kidney function require close monitoring on therapy. Hypertension, anaemia, cardiac issues are key considerations when monitoring patients on therapy. Biggest advantage with the technology is the lack of neuropathy as a side effect. This has been a significant issue with previous therapies (thalidomide & Bortezomib). Quality of life is improved on the ASPIRE trial on the carfilzomib arm despite a use of triplet combination. This is very encouraging, as this is a continuous therapy and treatment toxicities can frequently emerge with cumulative doses.	Comment noted. No action required.
	Myeloma UK	No comments	No action required
	Janssen-Cilag Ltd	The following subgroups will be important to consider as part of this appraisal as prior treatment is an important prognostic marker: • Velcade naïve • Velcade experienced • Lenalidomide naïve • Lenalidomide experienced	Comment noted. No action required.
	Celgene Ltd	No additional issues	Comment noted. No action required.
	Amgen Ltd	NA	No action required.
Innovation	UK Myeloma Forum/ British	Combination therapies in myeloma are a step change. Some of these have already been appraised by NICE and currently on Cancer drug fund (Ixazomib Lenalidomide Dexamethasone and Daratumumab Bortezomib	Comment noted. No action required.

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	Society of Haematology/ Royal College of Pathologists	dexamethasone). This technology adds to the list of treatment combination which improve progression free survival and data are suggestive of improvement in overall survival	
	Myeloma UK	While this is an effective and important treatment option for patients we do not consider it a “step change” in management of myeloma.	Comment noted. No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	No comment	No action required.
	Amgen Ltd	At present, there is a significant unmet need in the treatment of MM patients and a requirement for a greater number of potential treatment regimens available. It is widely acknowledged that there is no standard approach for MM management, and that treatment decisions are influenced by both disease- and patient-related factors. Whilst some patients may be more suited to doublet regimens, triplet regimens are more suitable in other patients due to the advantages they afford. Triplet therapies have been shown to be superior to doublet therapies in terms of both the response and duration of PFS achieved in MM patients, and in development of resistance, due to the enhanced synergies and targeting of multiple cellular pathways. As the first triplet therapy to be approved at 2L in MM and having demonstrated substantially improved clinical outcomes over the comparator, CRd would offer greater clinical benefit in these patient populations. In addition to offering greater clinical benefit, inclusion of CRd in the treatment pathway for MM would expand the treatment armamentarium currently available for the treatment of this disease. As MM is not a homogenous disease, and a consistent response to different regimens is not observed	Comment noted. No action required.

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		across the whole patient population, this would enable greater numbers of patients to receive potentially more appropriate therapy.	
Questions for consultation	UK Myeloma Forum/ British Society of Haematology/ Royal College of Pathologists	*Is carfilzomib plus lenalidomide and dexamethasone likely to be used for treating multiple myeloma after 1, 2 or 3 previous therapies in clinical practice?* Yes. Likely to be used after 1 or 2 previous lines of therapy *Is re-treatment with lenalidomide an option in people who have received lenalidomide earlier in therapy?* Yes 20% of patients included in the ASPIRE trial had prior lenalidomide exposure. Patients who are not refractory to Lenalidomide should be considered for a combination of Carfilzomib, Lenalidomide and dexamethasone. *Which treatments are considered to be established clinical practice in the NHS for multiple myeloma following at least 1 prior therapy?* Daratumumab, Bortezomib dexamethasone, Carfilzomib dexamethasone and Lenalidomide and dexamethasone for Bortezomib refractory patients. *Are there any other subgroups of people in whom carfilzomib plus lenalidomide and dexamethasone expected to be more clinically effective and cost effective or other groups that should be examined separately?* No	Comment noted. No action required.

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		Do you consider that the use of carfilzomib plus lenalidomide and dexamethasone can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No *Where do you consider carfilzomib plus lenalidomide and dexamethasone will fit into the existing NICE pathway, 'Myeloma'?_* First or second relapse Myeloma treatment	
	Myeloma UK	No comments	No action required.
	Janssen-Cilag Ltd	No comment	No action required.
	Celgene Ltd	*Is carfilzomib plus lenalidomide and dexamethasone likely to be used for treating multiple myeloma after 1, 2 or 3 previous therapies in clinical practice?* Likely to be used after 1 or 2 previous therapies *Have all relevant comparators for carfilzomib plus lenalidomide and dexamethasone been included in the scope?* Yes *Is re-treatment with lenalidomide an option in people who have received lenalidomide earlier in therapy?*	Comment noted. No action required.

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		Where "re-treatment" is defined as the cessation of one line of treatment, and the introduction/starting of another, then retreatment with lenalidomide is not allowed, in line with licence and recommended usage. *Which treatments are considered to be established clinical practice in the NHS for multiple myeloma following at least 1 prior therapy?* See above A*re the subgroups suggested in 'other considerations appropriate?* Data permitting – relapsing or refractory disease *Are there any other subgroups of people in whom carfilzomib plus lenalidomide and dexamethasone expected to be more clinically effective and cost effective or other groups that should be examined separately?* No comment *Where do you consider carfilzomib plus lenalidomide and dexamethasone will fit into the existing NICE pathway, 'Myeloma'?* No comment *Would it be appropriate to use the cost comparison methodology for this topic?* ○ *Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?*	

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		○ *Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?* ○ *Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?* No comment	
	Amgen Ltd	*Is carfilzomib plus lenalidomide and dexamethasone likely to be used for treating multiple myeloma after 1, 2 or 3 previous therapies in clinical practice?* The most appropriate line of therapy for CRd is in patients who have received one prior treatment . There is a general move in clinical practice towards utilising triplet therapies earlier in the treatment pathway within multiple myeloma, as these offer the advantage of synergistic mechanisms of action and target multiple pathways to allow for deeper and more durable responses. *Have all relevant comparators for carfilzomib plus lenalidomide and dexamethasone been included in the scope? Is re-treatment with lenalidomide an option in people who have received lenalidomide earlier in therapy?* See above. The most appropriate comparator for this appraisal is Rd (TA586) given the likely use of CRd in clinical practice. It is Amgen's view that DVd is also pertinent and informative to the decision problem, despite being currently available through the CDF. *Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom carfilzomib plus lenalidomide and*	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		dexamethasone expected to be more clinically effective and cost effective or other groups that should be examined separately? Subgroup analyses pertinent to the decision problem include type and number of lines of previous therapy – this is consistent with the previous TA457 appraisal and those outlined in the draft scope.	
Additional comments on the draft scope	Janssen-Cilag Ltd	No comment	No action required.
	Celegene Ltd	No additional comments	No action required.
	Sanofi UK	We have no comments on the draft scope and remit. However, in the 'Related NICE recommendations and NICE Pathways' section, we would highlight that isatuximab appraisals are currently under development: Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma [ID1477] Isatuximab with carfilzomib and dexamethasone for treating relapsed or refractory multiple myeloma [ID1620] We would also like to add that the following appraisal should feature under Appraisals in development (including suspended appraisals): Elotuzumab with pomalidomide and dexamethasone for treating multiple myeloma after 2 therapies [ID1467]	Comment noted. The relevant sections have been updated.

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

- Leukaemia Care
- Novartis