National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Carfilzomib for treated multiple myeloma

Response to consultee and commentator comments on the draft remit and draft scope (post-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
Appropriateness	UKMF	Yes	Comment noted. No action required.
	Myeloma UK	Myeloma UK considers this to be an appropriate topic to refer to the NICE appraisal committee.	Comment noted. No action required.
	Amgen	This topic is appropriate for a NICE appraisal.	Comment noted. No action required
Wording	UKMF	Yes	Comment noted. No action required.
	Myeloma UK	The wording of the remit accurately reflects the issues of clinical and cost-effectiveness at this stage in the appraisal process and conforms to the European marketing licence authorisation for carfilzomib and to a subsequent licence application currently going through the European Medicines Agency.	Comment noted. No action required.

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	Amgen	The wording of the remit is appropriate.	Comment noted. No action required.
Timing Issues	UKMF	Multiple myeloma remains an incurable cancer and hence new technologies that have shown benefit in phase 3 studies should be made available on the NHS as soon as possible	Comment noted. No action required.
	Myeloma UK	We consider a NICE appraisal of carfilzomib to be very timely for relapsed myeloma patients, particularly given the delay that was occurred to the appraisal process in December 2015.	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	UKMF	This is adequate	Comment noted. No action required.
	Myeloma UK	We consider this background information to be largely accurate.	Comment noted. No action required.
The technology/ intervention	UKMF	Yes	Comment noted. No action required.
	Myeloma UK	The description of the technology is accurate.	Comment noted. No action required
	Amgen	Carfilzomib is an epoxyketone proteasome inhibitor. Although carfilzomib and bortezomib both act on the proteasome, there are critical mechanistic differences in how these drugs affect cell signalling pathways (attributable to carfilzomib's	Comment noted. No action required.

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		unique chemical structure). Carfilzomib is a tetrapeptide epoxyketone–based, irreversible proteasome inhibitor; bortezomib which makes carfilzomib a fundamentally different drug than bortezomib with a different molecular mechanism of action, despite having the same site of action. In contrast with bortezomib, carfilzomib is highly selective and inhibits the proteasome with minimal off-target activity (peripheral neuropathy is a well-known dose-limiting toxicity of bortezomib), inhibits the proteasome irreversibly leading to sustained inhibition, and is cytotoxic in cells that are resistant to bortezomib.	
Population	UKMF	Yes	Comment noted. No action required.
	Myeloma UK	The population is defined appropriately.	Comment noted. No action required.
	Amgen	The population is defined appropriately.	Comment noted. No action required.
Comparators	UKMF	Currently in patients treated with Bortezomib based therapy at diagnosis (based on TA 311) when they relapse after 1 prior therapy use of bortezomib as per TA129 is denied in certain trusts. Thalidomide based therapy is the appropriate comparator here. Lenalidomide and dexamethasone after 1 prior therapy was delisted by the cancer drug fund. But is subject of an ongoing appraisal TA 171 For patients who have had 2 prior therapies, bendamustine based therapy is available through the cancer drugs fund.	Comment noted. The list of comparators has been amended to include bendamustine.
	Myeloma UK	As the most likely approved indications of carfilzomib are likely to be at first (second line) and second relapse (third line), we consider the main comparators to be as follows:	Comments noted. The committee will appraise

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		At first relapse: Bortezomib in combination with dexamethasone (NICE first relapse guidance TA129). Please note that Myeloma UK is aware that retreatment with Velcade is being restricted at first and subsequent relapse. Until recently, Revlimid and dexamethasone was approved via the CDF in this setting – however, this is no longer routinely available. At second relapse: Lenalidomide (Revlimid®) in combination with dexamethasone (NICE second relapse guidance and subject to NICE assessment at first relapse TA171). We do not consider standard chemotherapy (melphalan and cyclophosphamide) to be a major comparator in this appraisal as this is mainly used in a setting beyond currently approved national guidance. We also do not consider pomalidomide (Imnovid®) and dexamethasone to be an appropriate comparator. Carfilzomib is likely to be appraised at earlier stages of relapse and would not cover the same group of patients as pomalidomide. Pomalidomide is most likely to be used at fourth line (third relapse), where a patient has become refractory to Revlimid. Panobinostat (Farydak®), bortezomib and dexamethasone is a relevant comparator – however, this has only just been made available within NHS England so it is not clear how it is widely being used in clinical practice. It is likely to be used once a patient has received prior treatment with Velcade and Revlimid – the order these are given in depends on the individual patient and treatment pathway (i.e. it will be given at third or fourth relapse depending on prior treatment)	carfilzomib in accordance with its marketing authorisation. The marketing authorisation for carfilzomib specifies that it for people with relapsed multiple myeloma who have had at least 1 prior therapy. The list of comparators in the scope reflect the possible positioning of carfilzomib in the treatment pathway as specified in its marketing authorisation. No action required.
	Amgen	The carfilzomib-based regimens included in the scope are positioned in England and Wales at 1st and 2nd relapse. 1. For patients who have received one prior therapy the choice of treatment at 1st relapse will be dependent on the nature of the 1st line regimen used:	Comment noted. The committee will appraise carfilzomib in accordance with its

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		• For patients treated with an immunomodulatory drug (IMiD) e.g. thalidomide (TA228) at 1st line, bortezomib-based treatments are standard of care at 1st relapse. 2. For patients treated with a bortezomib-based regimen (TA228 and TA311) at 1st line, clinicians typically favour using an IMiD-based treatment such as lenalidomide in combination with dexamethasone at 1st relapse. Until recently this was possible via the cancer drugs fund. Since closure of the current cancer drugs fund, future access is dependent on the outcome of the ongoing part-review of TA171. Alternatively, patients may be retreated with bortezomib (TA129), but retreatment is not routinely funded by commissioners and where retreatment is given, it is typically only in patients who did not experience peripheral neuropathy (grade 2 and above) and who had a response to prior bortezomib of at least 6 months. For patients who have received two prior therapies, the nature of the prior treatment similarly impacts the therapeutic choice at 2nd relapse: • For patients who have received a bortezomib-based treatment at 1st relapse, lenalidomide in combination with dexamethasone is the current standard of care (TA171) at 2nd relapse. • For patients who have received prior treatment with bortezomib and an IMiD, panobinostat is combination with bortezomib and dexamethasone is also an option at 2nd relapse (TA380). Pomalidomide in combination with dexamethasone is currently not recommended by NICE, and where used it is typically in later lines of therapy. As such it does not constitute a relevant comparator for carfilzomib-based regimens at 1st or 2nd relapse. Similarly chemotherapy-based regimens will only be used at later lines of treatment and do not constitute a relevant comparator for carfilzomib-based regimens at 1st or 2nd relapse.	marketing authorisation. The marketing authorisation for carfilzomib specifies that it for people with relapsed multiple myeloma who have had at least 1 prior therapy. The list of comparators in the scope reflect the possible positioning of carfilzomib in the treatment pathway as specified in its marketing authorisation. No action required. The committee will be aware that there is an ongoing appraisal of pomalidomide and will take into account any relevant NICE guidance draft

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			documents, as appropriate No action required.
	Celgene	We do not believe that the appraisal of pomalidomide will be concluded in time to allow inclusion as a comparator in this review. Bendamustine should be a comparator for 4th line treatment (after 3 prior therapies).	Comment noted. The list of comparators has been amended to include bendamustine.
Outcomes	UKMF	We would suggest that, in addition to the response rate, complete response should also be included, as this is an indication of the quality of response, and the deeper the response, the greater the benefit in terms of disease free and overall survival.	Comment noted. Complete response is listed as an example of response rate. No action required.
	Myeloma UK	We consider these outcome measures to capture the most important health related benefits and harms of the technology.	Comment noted. No action required.
Equality and Diversity	UKMF	We do not believe there are any considerations here	Comment noted. No action required.
	Myeloma UK	We consider the equality issues to be accurately captured by the scoping document.	Comment noted. No action required.
Innovation	UKMF	Yes, carfilzomib is a proteasome inhibitor with improved target specificity and hence tolerability, compared to existing licensed PI Bortezomib. Given the central importance of PI-based therapy in the treatment of myeloma, the availability of this new generation agent is a ‘step-change’. With an improved safety profile	The innovative nature of carfilzomib will be considered by the

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		observed in trials (particularly lack of neuropathy) patients can receive planned treatment, with less discontinuations for adverse events, thus increasing overall response rates and duration of response. Carfilzomib in combination with dexamethasone was compared with Bortezomib and dexamethasone in a large randomised Phase III trial in relapsed/ refractory myeloma patients, who had 1-3 prior therapies (NCT01568866), which forms part of the submission. Median progression free survival was almost doubled in the carfilzomib arm vs Bortezomib arm (18.7 vs 9.4 months), which is an accepted surrogate marker for overall survival in the relapsed setting, with an increase in serious adverse events reported in the carfilzomib arm. This benefit was maintained in patients who have had prior bortezomib therapy. This trial confirms that Carfilzomib is a superior proteasome inhibitor for response in relapsed myeloma patients. Drug discontinuation rates is a surrogate of tolerability and should be taken into account across both trials (NCT01080391, NCT01568866)	committee during the appraisal. No action required.
	Myeloma UK	Myeloma UK considers carfilzomib to be innovative in the treatment of myeloma. As myeloma is a relapsing and remitting cancer, it is important that clinicians have a range of treatments available to them to use flexibly in their patients and according to their individual needs. Having new treatments available, with demonstrable evidence of prolonging progression free survival and with a reduced side-effect profile compared to already approved drugs, is important to ensure that patients are able to live longer with myeloma and with a better quality of life. Given the efficacy and effectiveness data on carfilzomib that has been published to-date from the Phase III ASPIRE and ENDEVOUR Trials, it is clear that patients gain considerable survival benefit from receiving carfilzomib in combination with dexamethasone and with or without the addition of Revlimid, at all stages of	The innovative nature of carfilzomib will be considered by the committee during the appraisal. No action required.

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		relapse. It is therefore important that carfilzomib is made available as soon as possible for patients.	
	Amgen	Multiple myeloma (MM) is an incurable disease and deadly disease. As such there is an unmet need to prolong disease free survival in these patients. MM is relapsing and progressive in nature and returns more aggressively and quicker with each relapse. Despite advances in therapy with the availability of bortezomib and IMiDs, progression free survival (PFS) remains limited and novel agents and combinations are needed to achieve deeper and durable remissions. Carfilzomib is a unique proteasome inhibitor with irreversible binding to the proteasome. Carfilzomib when combined with lenalidomide and dexamethasone demonstrated a 26.3 month median PFS in the ASPIRE study, a statistically significant and clinically meaningful 8.7 month improvement versus lenalidomide in combination with dexamethasone, which represents the longest PFS reported in relapsed and/or refractory MM to date. In addition in a second large randomised phase III trial comparing carfilzomib + dexamethasone versus bortezomib + dexamethasone (ENDEAVOR), carfilzomib + dexamethasone demonstrated an 18.7 months median PFS, compard to the 9.4 months for bortezomib+dexamethasone.	The innovative nature of carfilzomib will be considered by the committee during the appraisal. No action required.
Questions for consultation	UKMF	Based on published evidence use of Carfilzomib as set out in the current remit will not benefit any particular sub groups of myeloma patients. We note the analysis will be performed based on previous lines of therapy. When such an analysis is made, type of previous therapies e.g. IMID or proteasome inhibitor should be taken into account.	Comment noted. No action required.
	Myeloma UK	Is carfilzomib in combination with lenalidomide and dexamethasone likely to be used for treating myeloma after 1, 2 or 3 prior therapies? Depending on the treatment pathway that myeloma patients are on (i.e. whether	Comments noted. No action required.

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		they are eligible or ineligible for stem cell transplantation) and whether they started with a thalidomide or bortezomib-based treatment combination – we anticipate that both carfilzomib and dexamethasone and carfilzomib, lenalidomide and dexamethasone – will be used in myeloma patients at first or second relapse. For people previously treated with one prior therapy, specifically bortezomib (with or without dexamethasone), is retreatment with bortezomib used in clinical practice in the NHS? For myeloma patients at first relapse, retreatment with Velcade is used in line with NICE TA380 which approved panobinostat, Velcade and dexamethasone for myeloma patients after two or more prior therapies. NICE TA129, which approved Velcade at first relapse, previously allowed myeloma patients to access Velcade retreatment at this stage – however, we have become aware of informal NHS England guidance stating that this is no longer commissioned on the NHS since it was removed from the Cancer Drug Fund. Velcade retreatment is therefore not a routine option for the vast majority of myeloma patients. For people previously treated with 2 prior therapies, specifically lenalidomide and bortezomib is retreatment with lenalidomide used in clinical practice in the NHS? This is not a clinical situation that would take place. NICE TA171 specifies that myeloma patients can receive Revlimid after two or more prior therapies. Lenalidomide and dexamethasone is given on a treatment until progression basis, so at this stage (i.e. when they stop responding) patients are considered refractory to lenalidomide. Retreatment with lenalidomide is therefore not routinely done on the NHS.	Comment noted. No action required. Comment noted. No action required.
	Amgen	Is carfilzomib in combination with lenalidomide and dexamethasone and carfilzomib in combination with dexamethasone likely to be used for treating multiple myeloma after 1, 2 or 3 prior therapies in clinical practice?	Comments noted. No action required.

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		It is anticipated that carfilzomib in combination with dexamethasone (Cd) will be used: • At 1st relapse for patients who have received an IMiD-based regimen (e.g. thalidomide-based regimen) at 1st line • At 1st relapse for patients who have received a bortezomib-based regimen at 1st line and are eligible for re-treatment with bortezomib based treatment (no grade 2 and above peripheral neuropathy and response to prior bortezomib was at least 6 months) • At 2nd relapse for patients who have received an IMiD at 1st relapse It is anticipated that carfilzomib in combination with lenalidomide and dexamethasone (CRd) will be used: • At 1st relapse for patients who have received bortezomib-based regimen at 1st line • At 2nd relapse for patients who have received a bortezomib-based regimen at 1st relapse For people previously treated with 1 prior therapy, specifically bortezomib (with or without dexamethasone), is retreatment with bortezomib used in clinical practice in the NHS? Although bortezomib is recommended as a treatment option by NICE for patients who have received 1 prior therapy (TA129), bortezomib retreatment is not routinely funded by commissioners, and in clinical practice clinicians typically prefer to alternate treatment between proteasome inhibitor- and IMiD-based therapies. Furthermore, retreatment with bortezomib is typically not considered if patients have experienced peripheral neuropathy (grade 2 and above) and/or have had a short duration of response (less than 6 months) with prior bortezomib therapy. For people previously treated with 2 prior therapies, specifically lenalidomide and	Comments noted. No action required.

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bortezomib, is retreatment with lenalidomide used in clinical practice in the NHS?

It is unlikely that retreatment with lenalidomide would be used at 2nd relapse in patients who had received prior lenalidomide (since it is given until progression).

Have all relevant comparators for carfilzomib in combination with lenalidomide and dexamethasone and carfilzomib in combination with dexamethasone been included in the scope? Which treatments are considered to be established clinical practice in the NHS for multiple myeloma following at least 1 prior therapy?

The appropriate comparators at 1st and 2nd relapse have been included (see table below). Pomalidomide in combination with dexamethasone and chemotherapy-based regimens are typically only used in clinical practice (where available) at 3rd relapse and beyond, and should not be considered relevant comparator for this appraisal given the 1st and 2nd relapse positioning of carfilzomib.
<table>
<tr><td></td><td>Patients treated with thalidomide at 1st line</td><td>Patients treated with bortezomib at 1st line</td></tr>
<tr><td>1st relapse</td><td>Bortezomib-based regimen (e.g. bortezomib in combination with dexamethasone)</td><td>• Lenalidomide in combination with dexamethasone (subject to ongoing NICE appraisal [part review of technology appraisal 171])
• Bortezomib-based regimen if funding possible and clinically indicated (no PN and not refractory)</td></tr>
<tr><td>2nd</td><td colspan="2">Lenalidomide in combination with dexamethasone for the great majority</td></tr>
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</td><td>Comment noted. No action required.

Comments noted. The list of comparators have been amended accordingly.</td></tr>
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<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
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<tr><td>relapse</td><td>Panobinostat in combination with bortezomib and dexamethasone, could become a relevant comparator if lenalidomide in combination with dexamethasone is recommended as an option at 1st relapse for patients treated with bortezomib at 1st line.</td></tr>
<tr><td>3rd relapse and beyond</td><td>Panobinostat in combination with bortezomib and dexamethasone
Chemotherapy combination regimen (e.g. melphalan, cyclophosphamide, bendamustine), pomalidomide in combination with dexamethasone</td></tr>
</table>
</td><td></td></tr>
<tr><td>Additional comments on the draft scope</td><td>UKMF</td><td>Treatment will be delivered in secondary care day units across the country. Carfilzomib is currently widely used in clinical trials (Myeloma XI, MUK 5, CARDAMON) across the UK. Myeloma XI trial alone has over 100 centres across the UK, with over 30 sites have MUK 5 trial opened and up to 10 sites have opened the CARDAMON trial. All these trials use Carfilzomib in varying combinations but trial participation would equip the day unit staff with sufficient experience to roll out this technology following approval. Carfilzomib in combination with cyclophosphamide and dexamethasone is tested against Bortezomib, cyclophosphamide and dexamethasone, as typically used in the UK, in myeloma patients exposed to one prior therapy. Results reported at ASH 2015 after 208 patients were recruited in this ongoing study, demonstrated safety of this treatment combination.</td><td>Comment noted. No action required.</td></tr>
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The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Novartis
Royal College of Nursing