NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Carfilzomib for previously treated multiple myeloma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using carfilzomib in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination versus any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using carfilzomib in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 5pm, Wednesday 30 November 2016

Second appraisal committee meeting: Wednesday 15 February 2017

Details of membership of the appraisal committee are given in section 7.

1 Recommendations

1.1 Carfilzomib, in combination with lenalidomide and dexamethasone or dexamethasone alone, is not recommended for treating multiple myeloma in adults who have had at least 1 prior therapy.

1.2 This guidance is not intended to affect the position of patients whose treatment with carfilzomib was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

2 The technology

Description of the technology	Carfilzomib (Kyprolis, Amgen) is an irreversible proteasome inhibitor that binds to the N-terminal threonine site, causing degradation of the proteins in the cell. It is given intravenously.
Marketing authorisation	Kyprolis 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.
Adverse reactions	The most common adverse reactions (in more than 20% of patients) were: anaemia, fatigue, diarrhoea, thrombocytopenia, nausea, pyrexia, dyspnoea, respiratory tract infection, cough and peripheral oedema. For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule for carfilzomib (1 cycle=28 days)	<u>In combination with lenalidomide and dexamethasone</u> • Carfilzomib is given on 2 consecutive days, each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17 to 28) for the first 12 cycles. • From cycle 13, the day 8 and 9 doses of carfilzomib are omitted. • Carfilzomib is administered at a starting dose of 20 mg/m^2 (maximum dose 44 mg) in cycle 1 on days 1 and 2. • If tolerated, the dose should be increased to 27 mg/m^2 (maximum dose 60 mg) from day 8 of cycle 1. <u>In combination with dexamethasone alone</u> • Carfilzomib is given on 2 consecutive days, each week for 3 weeks (days 1, 2, 8, 9, 15, and 16) followed by a 12-day rest period (days 17 to 28). • Carfilzomib is administered at a starting dose of 20 mg/m^2 (maximum dose 44 mg) in cycle 1 on days 1 and 2. • If tolerated, the dose should be increased to 56 mg/m^2 (maximum dose 123 mg) from day 8 of cycle 1. For further details, see the summary of product characteristics.
Price	The list price of carfilzomib is £1,056 for a 60-mg vial

	(excluding VAT; MIMS online, accessed October 2016). In combination with lenalidomide and dexamethasone From cycle 1 to 12: £5,127 (no wastage), £6,336 (wastage) From cycle 13: £3,418 (no wastage), £4,220 (wastage) In combination with dexamethasone alone £10,644 (no wastage), £12,627 (wastage) The company has agreed a patient access scheme with the Department of Health. If carfilzomib had been recommended, this scheme would provide a simple discount to the list price of carfilzomib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Evidence

The appraisal committee considered evidence submitted by Amgen and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of carfilzomib, having considered evidence on the nature of multiple myeloma and the value placed on the benefits of carfilzomib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

Clinical need

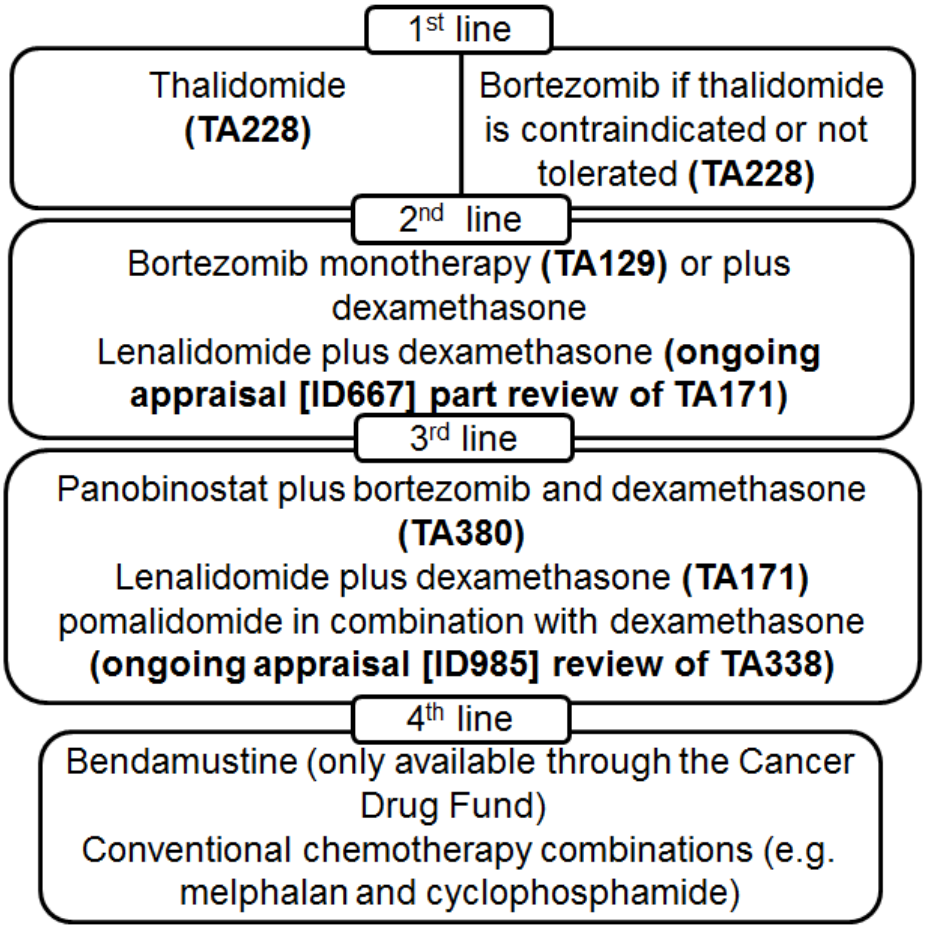
4.1 The committee noted the emotional impact and burden of disease on patients, their families and carers and the value of carfilzomib because it provides an additional treatment option that is well tolerated. The

committee understood that there are effective treatments at earlier stages of the disease but there is a need for novel chemotherapeutic agents at later stages of the disease. The clinical experts emphasised the problem of emergent cells that are resistant to current treatment options; because of this, double and triple therapies are often used at later stages of the treatment pathway because a combination of different mechanisms is needed to control the resistant cells. The committee heard from the patient expert that although carfilzomib is given intravenously, which often deters patients, it offers important benefits over existing treatments. In particular, carfilzomib does not appear to be associated with neuropathic adverse reactions to the same extent as standard treatment and offers an increased remission time so patients are willing to have an intravenous administration. The committee concluded that patients and clinicians would welcome carfilzomib as there is a need for effective treatments after relapse and because it offers a number of quality-of-life improvements over current treatment options.

Decision problem and treatment pathway

4.2 The committee considered the current treatment pathway for people who have relapsed after receiving 1 prior therapy, including current NICE-recommended treatments and other agents used in practice.

Figure 1 Treatment pathway for multiple myeloma in people who cannot have a stem cell transplant

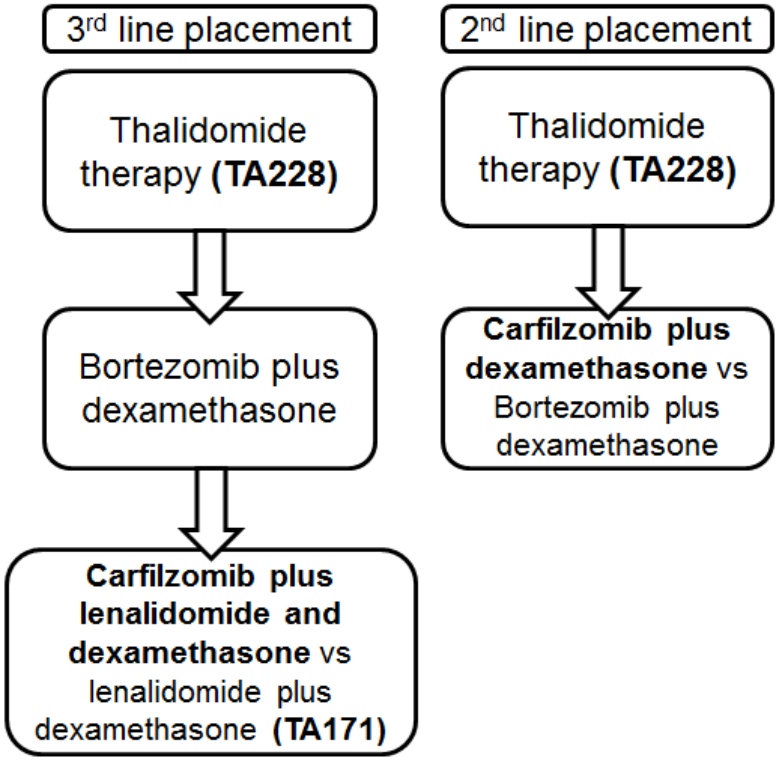


4.3 The committee noted that the NICE scope specified comparator treatments that are currently used at second, third and fourth line (see figure 1). The committee noted that the marketing authorisation for carfilzomib is for people who have had at least 1 previous therapy (and therefore includes fourth line treatment), but the comparisons presented by the company restricted placement to second and third line only, based on the previous treatments received (based on current NICE guidance and the most commonly used treatment regimens in practice; see figure 2). The committee heard from the clinical expert that the company's approach was clinically rational and carfilzomib would mainly be used at second and third line. The committee accepted this opinion and concluded

that the company's placement of carfilzomib at second or third line was appropriate.

4.4 In the company's treatment route, having carfilzomib depended on whether people had previously had thalidomide or bortezomib at first line. The committee understood that for people who cannot have a stem cell transplant, NICE recommends thalidomide at first line (with bortezomib reserved only for people who cannot have thalidomide). It therefore concluded that thalidomide is the therapy most often used at first line for people who cannot have a stem cell transplant.

Figure 2 Company's comparators and treatment route to receive carfilzomib



4.5 The company considered a number of comparators in the NICE scope to be irrelevant. These were bortezomib alone (for people who have had 1 previous therapy), panobinostat with bortezomib and dexamethasone, and pomalidomide with dexamethasone and combination chemotherapy (for people who have had 2 previous therapies). Because of the emergence of

resistant cells (see section 4.1), clinicians prefer to alternate between treatments; ideally, between immunomodulators (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib and carfilzomib). So bortezomib alone is not a valid comparator because carfilzomib with dexamethasone would only replace bortezomib with dexamethasone at second line if people had not had bortezomib therapy at first line (and instead had thalidomide therapy at first line, as the most commonly used regimen; see section 4.4). The committee also heard that clinicians prefer to use combinations of treatments which have different mechanisms of actions (such as immunomodulators with proteasome inhibitors and dexamethasone; see section 4.1). So, when placing carfilzomib at third line, carfilzomib with lenalidomide and dexamethasone would only replace lenalidomide with dexamethasone if people had not had carfilzomib previously (at second line had bortezomib therapy instead) or lenalidomide. The committee understood that panobinostat was not considered an appropriate comparator because unlike lenalidomide with dexamethasone its use is not established in England at third line. It also understood that the company did not consider pomalidomide to be appropriate comparator for the same reason (that is, it is not yet established practice in England). The committee agreed that conventional chemotherapy is no longer used because of the availability of newer agents. The committee accepted the rationale for the company's treatment route to receive carfilzomib; that is:

- carfilzomib and dexamethasone compared with bortezomib and dexamethasone at second line
- carfilzomib, lenalidomide and dexamethasone compared with lenalidomide and dexamethasone at third line.

Clinical effectiveness

4.6 The committee noted that the trials for carfilzomib were of good quality and included active comparators that are relevant to the appraisal,

thereby providing direct head-to-head evidence. It noted the overall survival data had not yet matured, so considered in detail the progression-free survival estimates for the overall population. It agreed that the estimates were compelling in favour of carfilzomib over the comparator treatments. It noted that, compared with bortezomib and dexamethasone, carfilzomib and dexamethasone doubled the progression-free survival to 18.7 months. When compared with lenalidomide and dexamethasone, carfilzomib with lenalidomide and dexamethasone increased the progression-free survival to 26.3 months (a gain of 8.7 months). The committee concluded the trial evidence showed a progression-free survival benefit for carfilzomib combinations over the comparators in the overall population.

4.7 The committee understood that to estimate the efficacy of carfilzomib at second and third line, the company specified post hoc subgroups for:

- people who had 1 prior therapy, not bortezomib (second line compared with bortezomib and dexamethasone)
- people who had 2 prior therapies, not lenalidomide (or carfilzomib; third line compared with lenalidomide and dexamethasone).

The committee was aware of the limitations and the uncertain outcomes associated with subgroups that were not prespecified. It recognised the company's attempt to counter the uncertainties by adjusting for imbalances in the baseline characteristics with additional covariates by using a Cox proportional hazards model to estimate efficacy (as hazard ratios) of carfilzomib and its comparators. But the committee heard from the evidence review group (ERG) that the choice of these covariates was unclear without sufficient justification. The committee noted that the choice of variables to adjust the model should be those that are prognostic of the outcome, including an adjustment for the treatment effect. It concluded that the adjusted hazard ratios for the subgroups were not reliable estimates of the efficacy of carfilzomib and its comparators.

4.8 The committee noted that the median age of people in the ENDEAVOUR trial (comparing carfilzomib and dexamethasone with bortezomib and dexamethasone) and the ASPIRE trial (comparing carfilzomib, lenalidomide and dexamethasone with lenalidomide and dexamethasone) was 64 and 65 respectively. Patients had an average Eastern Cooperative Oncology Group (ECOG) status of between 0 and 2. In comparison, data collected in the UK by the Haematological Malignancy Research Network (HMRN) from 2001 to 2012 showed that the median age at diagnosis was 73. The committee was therefore concerned that the results of the trials may not be generalisable to UK clinical practice. The committee understood from the clinical expert that patients in myeloma trials are generally younger because they are more willing and able to travel to the treatment centre. It also understood that patients are being diagnosed earlier and, as a result, the average age at diagnosis in the UK is younger than that recorded by the HMRN. The committee concluded that the patient characteristics in the trials could be generalised to UK clinical practice.

4.9 The committee noted a discrepancy between the length of treatment stipulated in the marketing authorisation and the stopping rule applied in ASPIRE. It understood that in ASPIRE, carfilzomib was stopped after 18 cycles whereas the marketing authorisation allows for treatment until progression or unacceptable toxicity. The committee heard from the company that no stopping rule was applied in ENDEAVOUR but the average length of treatment was 16.5 cycles, which the clinical experts stated would be reflective of clinical practice. The committee concluded that the length of treatment in the trials was reflective of clinical practice in the UK.

4.10 The committee noted the adverse reactions listed in the summary of product characteristics. It heard that in practice, serious adverse reactions and toxicity are managed through dose reduction and concomitant medication. It also heard that people taking carfilzomib find it tolerable and

that neuropathic adverse reactions are less evident than with other chemotherapeutic agents. The committee was satisfied that although carfilzomib is associated with serious adverse reactions, these are not any more significant than those experienced with other chemotherapeutic agents and are manageable in practice.

Cost effectiveness

4.11 The committee considered the economic model presented by the company to estimate the cost effectiveness of carfilzomib. It identified several areas of uncertainty, specifically:

- the survival model to estimate long-term effects
- the length of treatment and dosing schedule of bortezomib
- derived health state utility values.

4.12 The committee had concerns about the company's approach to survival modelling, which used 2 separate regression models (for the intervention and comparator arms of the trials) to extrapolate the effects over the full model time horizon (40 years). It was aware the model to extrapolate the carfilzomib arm was based on the subgroup post hoc estimate hazard ratios (see section 4.7), and noted that this assumes the hazard ratios for both arms to be constant over time (benefits of treatment continue until the end of the time horizon or death; proportional hazards). The committee discussed whether this assumption was valid and noted that the Kaplan-Meier estimated curves for the subgroups showed visual points of departure from proportionality (showing non-constant hazards over time). The committee recognised the ERG's attempt to remove some of the uncertainty by using unadjusted estimates in the extrapolation model (thereby assuming no imbalance between the treatment groups), but noted that this also required the assumption of proportional hazards and was not more robust than the company's approach. The committee agreed that the post hoc subgroup estimates were a key driver for the survival model but no robust evidence had been provided to demonstrate

the long-term benefit of carfilzomib. The company had not fully explored the uncertainty of the cost-effectiveness results by fitting all standard distributions (parametric models), exploring the effect of non-proportionality, exploring different extrapolation methods, and exploring the plausibility of the projection estimates to the observed data from the trials. The committee concluded that without exploring such uncertainties, it had no confidence that the chosen model was the best fit to the trial data and if the long-term estimates are reliable. The committee further concluded that it would have liked to have seen:

- Plausible efficacy estimates for all comparisons, adjusted by covariates, including a treatment effect, and to explore the plausibility of different combinations of covariates on the efficacy estimates. The covariates to adjust the model, presented with a rationale for why they had been chosen.
- The effects of fitting different parametric models, including covariate-adjustments, to both arms of the ENDEAVOUR and ASPIRE trials; in line with published technical guidelines, such as NICE DSU Technical Support Document 14.
- An assessment of the resulting predictions from the model and the corresponding covariate-adjusted estimates from the trial.
- The effect of different extrapolation techniques, including exploring a weighted covariate-adjusted model.
- A robust justification for the final preferred model for the cost-effectiveness results.

4.13 The committee noted that there were discrepancies between the model and clinical practice in the dosing schedule and length of treatment for bortezomib. It noted that the marketing authorisation for bortezomib states that it can be given twice weekly for 8 cycles (21-day cycles equal to a total of 32 doses), whereas the model assumed bortezomib would be given twice weekly as an intravenous infusion until progression. The

clinical experts clarified that in practice they prefer to give bortezomib once weekly and subcutaneously, because this is associated with fewer adverse reactions, and to give the full 32 doses. The committee concluded that the assumptions in the model for bortezomib did not accurately reflect its use in NHS clinical practice.

4.14 The committee discussed how the company had derived the health state utility values used in the model. It noted that the company had used a mixed method, using published utility values from Agthoven et al. (2004) and mapped utility values from the trials. The committee heard that the company had used the ERG's preferred approach in the sensitivity analysis. This derived utility values straight from trial data, using a mapping algorithm from Proskorovsky et al (2014). The committee noted that using values derived straight from trial data was more plausible and more closely followed the NICE reference case. It concluded that the utility values used in the company's base case were not appropriate, and it would have preferred to see values mapped from the trial data.

4.15 The committee discussed the incremental cost-effectiveness ratios (ICERs) presented by the company and the ERG. It noted that the company did not include the patient access scheme for bortezomib for the comparison of carfilzomib and dexamethasone with bortezomib and dexamethasone. The committee agreed that the inclusion of the patient access scheme would decrease the cost of bortezomib and therefore increase the ICERs for carfilzomib. However, it could not be confident that the most plausible cost-effectiveness estimate of carfilzomib had been presented; given the uncertainties in the estimation of long-term survival (see section 4.12). The committee concluded that the cost effectiveness of carfilzomib had not been adequately demonstrated.

End-of-life considerations

4.16 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods.

4.17 The committee reasoned that if carfilzomib at third line did not meet the end-of-life criteria, it would not meet them at second line when treatment is expected to be more effective and survival is longer. With that in mind, the committee considered whether survival after a second relapse was less than 24 months while on current treatment. It noted that the company presented data from the HMRN showing that median survival on lenalidomide and dexamethasone at third line is 1.3 years. The committee discussed that it is preferable to have mean estimates for survival over the entire expected lifetime horizon. It noted that the modelled overall survival was 4.93 years, which is well beyond 24 months, but the committee had already expressed that the estimates from the model were uncertain (see sections 4.12 and 4.15). Therefore, it could not reliably conclude that carfilzomib therapy met the first end-of-life criterion.

4.18 The committee discussed whether carfilzomib with lenalidomide and dexamethasone increases survival by 3 months compared with lenalidomide and dexamethasone. It again could not rely on the mean estimates from modelling, but noted that in the overall trial population the median progression-free survival showed a median gain of more than 3 months (see section 4.6). The committee thought it reasonable to assume that if the progression-free survival was more than 3 months compared with the next best treatment, then it is likely that overall survival would also be greater than 3 months. The committee therefore concluded carfilzomib therapy meets the second end-of-life criterion.

4.19 Based on the uncertainty of the clinical and cost-effectiveness results and carfilzomib not meeting the 24-month extension criterion for end-of-life, the committee concluded that it could not recommend carfilzomib, in

combination with lenalidomide and dexamethasone or dexamethasone alone, as a cost-effective use of NHS resources.

Summary of appraisal committee's key conclusions

TAXXX	**Appraisal title: carfilzomib for previously treated multiple myeloma**	**Section**
Key conclusion		
Based on the uncertainty of the clinical and cost-effectiveness results and carfilzomib not meeting the 24-month extension criterion for end-of-life, the committee did not recommend carfilzomib, in combination with lenalidomide and dexamethasone, or dexamethasone alone, as a cost-effective use of NHS resources; for treating multiple myeloma in adults who have had at least 1 prior therapy.		1.1, 4.19
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee noted the emotional impact and burden of disease on patients, their families and carers and the value of carfilzomib because it provides an additional treatment option that is well tolerated. The clinical experts emphasised the problem of emergent cells that are resistant to current treatment options; because of this, double and triple therapies are often used at later stages of the treatment pathway because a combination of different mechanisms is needed to control the resistant cells. The committee concluded that there is a need for effective treatment options for people after relapse.	4.1

The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from the patient expert that although carfilzomib is given intravenously, which often deters patients, it offers important benefits over existing treatments. In particular, carfilzomib does not appear to be associated with neuropathic adverse reactions to the same extent as standard treatment. The committee concluded that patients and clinicians would like to have access to carfilzomib because it offers quality-of-life improvements over current treatment options.	4.1
What is the position of the treatment in the pathway of care for the condition?	Carfilzomib therapy would be used at second and third line (after first and second relapse).	4.3
Adverse reactions	The committee noted the adverse reactions listed in the summary of product characteristics. It heard that in practice serious adverse reactions and toxicity are managed through dose reduction and concomitant medication. People also find it tolerable and that neuropathic adverse reactions are less evident than with other chemotherapeutic agents. The committee was satisfied that although carfilzomib is associated with serious adverse reactions these are not any more significant than those experienced with other chemotherapeutic	4.10

	agents and are manageable in practice.	
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	Evidence was from 2 trials. ENDEAVOUR trial (comparing carfilzomib plus dexamethasone with bortezomib plus dexamethasone) and the ASPIRE trial (comparing carfilzomib plus lenalidomide and dexamethasone with lenalidomide plus dexamethasone	4.8
Relevance to general clinical practice in the NHS	Comparators in both trials are used in NHS clinical practice for treating multiple myeloma.	-
Uncertainties generated by the evidence	The committee was aware of the limitations and the uncertain outcomes associated with subgroups that were not prespecified. It recognised the company's attempt to counter the uncertainties by adjusting for imbalances in the baseline characteristics with additional covariates by using a Cox proportional hazards model to estimate efficacy (as hazard ratios) of carfilzomib and its comparators. But, it heard from the ERG that the choice for these covariates was unclear and without sufficient justification. The committee agreed that the choice of variables to adjust the model were not appropriately validated and discussed that the choice of variables to adjust the model should be those that are prognostic of the outcome, including an	4.7

	adjustment for treatment effect.	
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee was aware of the limitations and the uncertain outcomes associated with subgroups that were not prespecified.	4.7
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The committee discussed that the choice of variables to adjust the model should be those that are prognostic of the outcome, including an adjustment for treatment effect. It concluded that the adjusted hazard ratios for the subgroups were not reliable estimates of the efficacy of carfilzomib and its comparators	4.7
Evidence for cost effectiveness		
Availability and nature of evidence	The committee had concerns about the company's approach to survival modelling , which used 2 separate regression models (for the intervention and comparator arms of the trials) to extrapolate the effects over the full model time horizon (40 years). It was aware the model to extrapolate the carfilzomib arm was based on the subgroup post hoc estimate hazard ratios (see section 4.7), and noted that this assumes the hazard ratios for both arms are constant over time (benefits of treatment continue until the end of the time horizon or death; proportional hazards).	4.12

Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee discussed whether the proportional hazard assumption was valid and noted that the Kaplan-Meier estimated curves for the subgroups showed visual points of departure from proportionality (that is showing non-constant hazards over time).	4.12
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?	The company's used a mixed method, using published utility values from Agthoven et al. (2004) and mapped utility values from the trials. The committee noted that using values derived straight from trial data was more plausible and more closely followed the NICE reference case. It concluded that the utility values used in the company's base case were not appropriate, and it would have preferred to see values mapped from the trial data.	4.14
Are there specific groups of people for whom the technology is particularly cost effective?	No specific considerations.	-
What are the key drivers of cost	The committee agreed that the post hoc subgroup estimates were a key driver for the	4.12

effectiveness?	model.	
Most likely cost-effectiveness estimate (given as an ICER)	The committee could not agree on the best cost-effectiveness estimate, because both the company's and the ERG's approach to modelling were highly uncertain.	4.15
Additional factors taken into account		
Patient access schemes (PPRS)	The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of any of the technologies in this appraisal.	-
End-of-life considerations	The committee concluded that carfilzomib therapy, after first or second relapse, did not qualify for end-of-life. It agreed that the trial data showed that carfilzomib increased progression-free survival of more than 3 months compared to lenalidomide plus dexamethasone. But the modelled overall survival for lenalidomide plus dexamethasone estimates were uncertain so could not conclude that the life-expectancy on current treatment is less than 24 months.	4.17, 4.18
Equalities considerations and social value judgements	No equality issues raised.	-

5 Proposed date for review of guidance

5.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Professor Eugene Milne
Chair, appraisal committee C
November 2016

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Hamish Lunagaria

Technical lead

Joanne Holden

Technical adviser

Stephanie Yates

Project manager

ISBN: [to be added at publication]