NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using carfilzomib with dexamethasone and lenalidomide 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 against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: September 2020

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 document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using carfilzomib with dexamethasone and lenalidomide 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: Tuesday 13 October 2020

Second appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Carfilzomib with lenalidomide and dexamethasone is not recommended, within its marketing authorisation, for previously treated multiple myeloma in adults.

1.2 This recommendation is not intended to affect treatment with carfilzomib with lenalidomide and dexamethasone that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Clinical trial evidence shows that carfilzomib with lenalidomide and dexamethasone gives longer periods of remission and people live longer than with lenalidomide and dexamethasone. It also suggests that people live longer than 24 months.

However, there is uncertainty about how long the benefit lasts after stopping treatment. This makes the cost-effectiveness estimates uncertain. The most likely cost-effectiveness estimate is higher than what NICE normally considers a cost-effective use of NHS resources. So, carfilzomib with lenalidomide and dexamethasone is not recommended for routine use in the NHS.

Collecting more data is not likely to resolve the uncertainty. So carfilzomib with lenalidomide and dexamethasone cannot be recommended for use within the Cancer Drugs Fund.

2 Information about carfilzomib

Marketing authorisation indication

2.1 Carfilzomib (Kyprolis, Amgen) is indicated ‘in combination with either lenalidomide and dexamethasone or dexamethasone alone for the

treatment of adult patients with multiple myeloma who have received at least one prior therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of carfilzomib is £1,056 for a 60-mg vial (excluding VAT; BNF online, accessed July 2020). Multiple courses of treatment will be used in combination with lenalidomide and dexamethasone. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Amgen, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- The company's positioning of carfilzomib with lenalidomide and dexamethasone is appropriate, whether or not a stem cell transplant is a suitable treatment option (issue 1, see technical report page 19).
- Based on the positioning of carfilzomib in the treatment pathway, the relevant comparator is lenalidomide with dexamethasone (issue 1, see technical report page 19).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 11, page 30), and took these into account in its decision making. It discussed the following issues (issues 2, 3 and 4), which were outstanding after the technical engagement stage.

New treatment option

People with previously treated multiple myeloma would welcome a new second-line treatment option

3.1 The patient expert explained that multiple myeloma is a relapsing and remitting disease with periods of severe symptoms that need treating. He described how difficult it is not knowing when his disease will relapse and that he has to put his life on hold. Treatment options for multiple myeloma after 1 previous treatment depend on what that treatment was and whether a stem cell transplant is suitable. If a stem cell transplant is suitable, treatment options include daratumumab with bortezomib and dexamethasone. If a stem cell transplant is not suitable, NICE guidance recommends the following treatment options:

- bortezomib monotherapy
- carfilzomib with dexamethasone
- lenalidomide with dexamethasone after 1 previous treatment that included bortezomib
- daratumumab with bortezomib and dexamethasone (recommended for use within the Cancer Drugs Fund after 1 previous treatment).

The patient experts explained that there is a need for effective second-line therapies, and the availability of effective combination treatments with different mechanisms of action is highly important when relapse occurs. They explained that the potential for improved quality of life during prolonged remission is important, as well as the potential for improved survival. The committee concluded that people with multiple myeloma

would welcome a new second-line treatment that gives longer periods of remission and improves survival.

Comparators

Lenalidomide and dexamethasone is the only relevant comparator

3.2 The clinical evidence came from ASPIRE, an open-label, randomised multicentre trial of carfilzomib with lenalidomide and dexamethasone compared with lenalidomide and dexamethasone. The company submission included a matched-adjusted indirect comparison of carfilzomib with lenalidomide and dexamethasone against daratumumab with bortezomib and dexamethasone, which is recommended for use within the Cancer Drugs Fund for treating relapsed multiple myeloma after 1 previous treatment. The evidence for this comparison was not presented to the committee because of NICE's position statement on the Cancer Drugs Fund. This states that technologies recommended by NICE for use within the Cancer Drugs Fund cannot be considered established practice and therefore cannot be considered as comparators in new appraisals. The clinical expert explained that many patients have daratumumab with bortezomib and dexamethasone as second-line treatment, so the comparison with lenalidomide and dexamethasone does not fully reflect clinical practice. The committee noted that daratumumab with bortezomib and dexamethasone was recommended for use within the Cancer Drugs Fund because the clinical and cost-effectiveness estimates were too great to make a recommendation for routine commissioning. The committee also noted that technologies recommended for use within the Cancer Drugs Fund might not subsequently be recommended for routine commissioning. It therefore concluded that based on NICE's position

statement on the use of Cancer Drugs Fund comparators in appraisals, lenalidomide and dexamethasone is the only relevant comparator.

Treatment pathway and positioning

The relevant population is people who have had 1 previous bortezomib treatment, whether or not a stem cell transplant is suitable

3.3 The committee noted that the treatment pathway differs depending on whether a person can have a stem cell transplant. It discussed whether a person who has had a stem cell transplant would have poorer outcomes with carfilzomib with lenalidomide and dexamethasone than with lenalidomide and dexamethasone. The clinical expert suggested that there is no clinical reason for treatment to work differently in a person who has had a stem cell transplant compared with someone who has not. The committee understood that the myeloma treatment pathway is continually evolving. It noted that the introduction of carfilzomib with lenalidomide and dexamethasone as a second-line treatment option would help to address the need for effective therapies with alternative mechanisms of action. It agreed that the company's approach of restricting the population to people who have had 1 previous bortezomib treatment is reasonable, provided they were not refractory to it. The committee concluded that the population relevant to this appraisal is people who have had 1 previous treatment with bortezomib, whether or not a stem cell transplant is suitable.

Post hoc subgroups

The subgroup of patients from ASPIRE who had 1 bortezomib treatment and no previous lenalidomide reflects the treatment pathway for multiple myeloma

3.4 The company presented analyses for a subgroup of patients from ASPIRE who had had 1 previous bortezomib treatment. The company considered that in clinical practice a small number of patients may have lenalidomide and bortezomib as first-line treatment and would still be considered

eligible for carfilzomib with lenalidomide and dexamethasone. The ERG highlighted that in the company's subgroup all patients had had 1 previous bortezomib treatment, but some patients also had lenalidomide treatment either at the same time or afterwards in the same treatment phase. The ERG presented analyses from a post hoc subgroup that had a stricter definition of first-line therapy. It was based on the treatment pathway for multiple myeloma and included patients from ASPIRE who only had 1 previous bortezomib treatment and no previous lenalidomide. The clinical expert noted that the definition used in the ERG subgroup is useful for clarifying how carfilzomib would be used in clinical practice, if it were recommended. However future myeloma trials are likely to include a combination of bortezomib and lenalidomide as first-line treatment, which would make it difficult to apply the results to clinical practice. The patient expert advised that people whose disease is not refractory to lenalidomide would welcome carfilzomib with lenalidomide and dexamethasone as a second-line treatment option. The committee heard that it is not current standard practice to have bortezomib and lenalidomide as a first-line treatment. The clinical lead for the Cancer Drugs Fund explained that most patients would have bortezomib as induction therapy before a stem cell transplant, and lenalidomide would only be considered if bortezomib did not provide an adequate response. In this situation, it would be unlikely that a triple regimen of carfilzomib with lenalidomide and dexamethasone would be tolerated as a second-line treatment. The committee concluded that the ERG's subgroup should be used for the basis of its decision, because it reflects current practice in the NHS and is the most likely previous treatment for patients who would have a triple

regimen of carfilzomib with lenalidomide and dexamethasone at second-line.

Overall survival and progression-free survival

Mature data from ASPIRE shows improved progression-free survival and overall survival

3.5 Carfilzomib with lenalidomide and dexamethasone increased median progression-free survival compared with lenalidomide and dexamethasone from 16.6 months to 26.1 months (hazard ratio 0.659; 95% confidence interval 0.553 to 0.784, p<0.0001) in the intention-to-treat population. Carfilzomib with lenalidomide and dexamethasone increased median overall survival compared with lenalidomide and dexamethasone from 40.4 months to 48.3 months (hazard ratio 0.794; 95% CI 0.667 to 0.945, p=0.0045) in the intention-to-treat population. The company did an inverse probability weighted analysis of post hoc subgroup data to account for imbalances in baseline characteristics in the non-randomised groups. Using this inverse probability weighted analysis, the company produced effect-estimates for progression-free survival and overall survival for its own and the ERG's preferred subgroups. The clinical expert explained that clinical practice focuses on whether progression-free survival will translate into overall survival, and that the combinations available in England tend to show only progression-free survival and not overall survival. The clinical expert stated that this is the first multiple myeloma trial with a long follow-up period to provide clear evidence of improved progression-free survival and overall survival. The committee welcomed the mature trial data from ASPIRE and concluded that carfilzomib with lenalidomide and dexamethasone improves progression-

free survival and overall survival compared with lenalidomide and dexamethasone.

Utility values used in the economic model

The choice of utility values has little effect on the cost-effectiveness estimates

3.6 The utility values for the progression-free health state in the company's model include a mean increase in utility from baseline for carfilzomib with lenalidomide and dexamethasone and also for lenalidomide with dexamethasone. From cycle 3 onwards, the model also includes a treatment-specific increase in utility for carfilzomib with lenalidomide and dexamethasone. The committee discussed the clinical plausibility of using differential treatment-specific utility values for patients in the same health state. It noted that treatment-specific utility values were accepted in NICE's technology appraisal of carfilzomib with dexamethasone and that the disease-specific questionnaire (EORTC QLQ-C30 GHS) used in ASPIRE showed a statistically significant difference between the treatment arms. The clinical expert explained that adding carfilzomib to lenalidomide and dexamethasone would not necessarily improve a person's quality of life. But it would increase the effectiveness of controlling the disease, which would improve quality of life. The committee agreed that the company's use of treatment-specific utility values may be reasonable, but it preferred the pre-progression utility values to be the same for both treatment arms. It noted that the ERG's approach of removing the treatment effect and increasing utility from baseline for cycle 3 onwards for the pre-progression health state utility value had little effect on the company's base-case incremental cost-effectiveness ratio (ICER).

The committee concluded that the choice of utility value had little effect on the ICER.

Extrapolation of overall survival

Overall survival can be extrapolated from the mature ASPIRE data

3.7 The company considered that extrapolation from ASPIRE data may underestimate long-term survival, producing conservative results for the lenalidomide with dexamethasone arm compared with estimates presented in related technology appraisals. Because of this, to estimate overall survival for both treatment arms, the company used a combination of extrapolated ASPIRE inverse probability weighted overall-survival data and real-world evidence from a French registry (MyelomaToul) of multiple myeloma patients who had lenalidomide as a second-line treatment. The ERG considered that a clinically plausible extrapolation of overall survival for carfilzomib with lenalidomide and dexamethasone could be estimated entirely from mature ASPIRE data. It noted that the exponential distribution was the best statistical fit for its preferred subgroup. The committee preferred the exponential model for estimating overall survival for both treatment arms because it used data entirely from the ASPIRE trial.

There is uncertainty about how long any treatment benefit lasts after stopping treatment

3.8 The committee noted that a relative treatment effect had been applied to every cycle in the company's model for carfilzomib with lenalidomide and dexamethasone, beyond the observed ASPIRE data. It considered that the ERG's exponential model included a treatment benefit for carfilzomib with lenalidomide and dexamethasone after stopping treatment, although it accepted that the use of mature data from ASPIRE may have captured some waning of treatment effect. The committee discussed whether there would be better prognosis in people who reached 20-years survival with carfilzomib with lenalidomide and dexamethasone compared with

lenalidomide and dexamethasone. The clinical expert confirmed that people who are alive after 20 years only have a better prognosis because they are able to have further treatment, and not necessarily because they previously had one treatment rather than another. The committee agreed it was unclear how long the treatment benefit would last for carfilzomib with lenalidomide and dexamethasone. It considered that the application of a prolonged treatment benefit may potentially overestimate survival and be favourable to carfilzomib with lenalidomide and dexamethasone. It concluded that the effect of any prolonged treatment benefit would need to be explored through additional analyses before it can accept that a treatment benefit for carfilzomib with lenalidomide and dexamethasone would persist after treatment has stopped.

Stopping rule

It is clinically plausible that treatment with carfilzomib would be limited to 18 cycles

3.9 In ASPIRE carfilzomib treatment stopped after 18 cycles, but the marketing authorisation allows for treatment until disease progression or unacceptable toxicity. Carfilzomib's summary of product characteristics states that treatment 'combined with lenalidomide and dexamethasone for longer than 18 cycles should be based on an individual benefit/risk assessment, as the data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited'. The committee noted that treatment costs for carfilzomib after 18 cycles were not included in the company's economic model. The clinical expert stated that because of lack of evidence of efficacy for carfilzomib treatment beyond 18 months, and the associated toxicity, it would be unlikely for treatment to continue beyond this time period. The clinical lead for the Cancer Drugs Fund advised that the NHS would commission a maximum of 18 cycles of carfilzomib based on the evidence from ASPIRE. The committee noted that many cancer treatments are commissioned for a fixed duration of time and clinicians are familiar with this approach. The patient expert highlighted that there

may be some patients who wish to continue treatment with carfilzomib beyond 18 cycles, but most patients would be reassured by the availability of other effective subsequent treatment therapies. The committee concluded that treatment with carfilzomib would be unlikely to continue beyond 18 cycles and that the stopping rule would be enforceable in clinical practice.

Drug wastage

Drug wastage is expected to be minimal

3.10 The committee considered that drug wastage with carfilzomib is expected to be minimal, given that 10 mg dose increments are possible. The company did a scenario analysis to include drug wastage and found that this had little effect on its base-case ICER. The ERG considered that drug wastage is not a primary driver of cost effectiveness in the model and agreed with the company that this assumption does not have a large effect on the ICER. The committee concluded that drug wastage is likely in clinical practice but this is unlikely to have a large effect on the cost-effectiveness results.

Combination therapies

The costs of lenalidomide with dexamethasone should be included in the model

3.11 The company considered that the increased efficacy of adding carfilzomib to lenalidomide and dexamethasone is penalised by the increased costs of lenalidomide with dexamethasone, which are given until disease progression. It did a scenario analysis that excluded the additional cost of lenalidomide with dexamethasone in the carfilzomib with lenalidomide and dexamethasone treatment arm. This reduced its base-case ICER to £16,751 per QALY gained (using the list price for lenalidomide). The committee acknowledged that treatments that extend the use of other high-cost drugs (such as lenalidomide) can lead to additional cost

associated with those other drugs, and that this has been considered in NICE appraisals of other cancer topics. The committee concluded that the costs of lenalidomide and dexamethasone are relevant because the NHS would incur those costs in practice, so they should be included in the model.

Cost-effectiveness estimates

The company's base-case ICER is above £30,000 per QALY gained

3.12 NICE's guide to the methods of technology appraisal notes that above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because of uncertainty in the relative treatment benefit of carfilzomib with lenalidomide and dexamethasone beyond the observed ASPIRE data, the committee agreed that an acceptable ICER would be no higher than the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The company's deterministic base-case ICER for carfilzomib with lenalidomide and dexamethasone compared with lenalidomide and dexamethasone was £43,952 per QALY gained (using the patient access scheme for carfilzomib). The ERG presented 3 analyses using its preferred post hoc subgroup, the same pre-progression utility values for both treatment arms and the exponential distribution from ASPIRE data to extrapolate overall survival for carfilzomib with lenalidomide and dexamethasone beyond the trial data. The ERG's analyses included the confidential commercial arrangement for lenalidomide and for panobinostat and pomalidomide, which are options later in the treatment pathway. The committee preferred the ERG's base case, which combined all 3 of these assumptions (the exact ICERs are confidential and cannot be reported here). The ICERs for all scenarios were above the range NICE considers to be an acceptable use of NHS

resources. The committee therefore could not recommend carfilzomib with lenalidomide and dexamethasone as an option for previously treated multiple myeloma.

End of life

Carfilzomib with lenalidomide and dexamethasone does not meet NICE's end of life criteria

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The committee considered whether carfilzomib with lenalidomide and dexamethasone meets the end of life criteria for people with multiple myeloma who have had 1 previous treatment including bortezomib. The committee noted that the model predicted that patients in the comparator arm lived longer than 24 months, and therefore concluded that carfilzomib in this indication did not meet the criterion for life expectancy. Because it did not meet this criterion, the committee concluded that it did not need to discuss the end of life criteria further.

Cancer Drugs Fund

Carfilzomib with lenalidomide and dexamethasone does not meet the Cancer Drugs Fund criteria

3.14 Having concluded that carfilzomib with lenalidomide and dexamethasone could not be recommended for routine use, the committee then considered if it could be recommended for treating multiple myeloma within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). It discussed the following issue:

- The company considers that mature head-to-head survival data are available from ASPIRE (median 5.5 years of survival follow-up), therefore any uncertainty would not be resolved with additional data

collection as part of a managed access agreement. Because of this, the company did not express an interest in carfilzomib with lenalidomide and dexamethasone being considered for funding through the Cancer Drugs Fund. The committee concluded that carfilzomib with lenalidomide and dexamethasone did not meet the criteria to be considered for inclusion in the Cancer Drugs Fund.

Other factors

There are no equality issues relevant to the recommendations

3.15 The patient expert advised that they were not aware of any equality issues. The committee concluded that no equality or social value judgements are relevant to its decision.

The benefits of carfilzomib are captured in the cost-effectiveness analysis

3.16 The company and the clinical expert consider carfilzomib with lenalidomide and dexamethasone to be innovative because it significantly improves progression-free survival and overall survival compared with lenalidomide and dexamethasone. The committee agreed that these are important benefits of carfilzomib with lenalidomide and dexamethasone. But it concluded that it had not been presented with evidence of any additional benefits that had not been captured in the QALYs.

4 Proposed date for review of guidance

4.1 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.

Stephen O'Brien
Chair, appraisal committee
July 2020

5 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.

Anita Sangha
Technical lead

Sally Doss
Technical adviser

Louise Jafferally
Project manager

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