NICE National Institute for Health and Care Excellence

NICE guidance

Carfilzomib with dexamethasone and lenalidomide for previously treated multiple myeloma

Technology appraisal guidance
Published: 28 April 2021

www.nice.org.uk/guidance/ta695

Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance partially replaces TA657.

1 Recommendations

1.1 Carfilzomib plus lenalidomide and dexamethasone is recommended as an option for treating multiple myeloma in adults, only if:

- they have had only 1 previous therapy, which included bortezomib, and
- the company provides carfilzomib according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with carfilzomib plus 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 plus lenalidomide and dexamethasone gives longer periods of remission and people live longer, compared with lenalidomide plus dexamethasone. This treatment benefit appears to continue for up to 6 years. However, there is uncertainty about how long the benefit lasts after this.

The most likely cost-effectiveness estimates are within what NICE normally considers a cost-effective use of NHS resources. So, carfilzomib plus lenalidomide and dexamethasone is recommended.

2 Information about carfilzomib

Marketing authorisation indication

2.1 Carfilzomib (Kyprolis, Amgen) 'in combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone is indicated 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 January 2021). Multiple courses of treatment may be used in combination with lenalidomide and dexamethasone. The company has a commercial arrangement. This makes carfilzomib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

2.4 The list price of lenalidomide per 21-capsule pack varies according to capsule size: £3,426.00 (2.5 mg), £3,570.00 (5 mg), £3,675.00 (7.5 mg), £3,780.00 (10 mg), £3,969.00 (15 mg), £4,168.50 (20 mg) and £4,368.00 (25 mg) (excluding VAT; BNF online, accessed January 2021). The company has a commercial arrangement. This makes lenalidomide available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

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

New treatment option

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

3.1 The patient experts explained that multiple myeloma is a relapsing and remitting disease with periods of severe symptoms that need treating. They described how difficult it is not knowing when their disease will relapse and that they have to put their 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 (NICE's technology appraisal guidance on daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma). If a stem cell transplant is not suitable, NICE technology appraisal 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 new effective second-line treatments, and the availability of effective combination treatments with different mechanisms of action is 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 plus lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone. The company submission included a matched-adjusted indirect comparison of carfilzomib plus 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 (NICE's technology appraisal guidance on daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma). 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 plus bortezomib and dexamethasone as second-line treatment, so the comparison with lenalidomide plus dexamethasone does not fully reflect clinical practice. The committee noted that daratumumab plus bortezomib and dexamethasone was recommended for use within the Cancer Drugs Fund because the uncertainties in the clinical evidence 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 role of technologies recommended for use in the Cancer Drugs Fund as comparators in appraisals, lenalidomide plus dexamethasone is the only relevant comparator.

Treatment pathway and positioning

The relevant population is people who have had only 1 previous treatment containing bortezomib, 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 plus lenalidomide and dexamethasone than with lenalidomide plus dexamethasone. The clinical expert suggested that there is no clinical reason for carfilzomib 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 plus 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. The committee concluded that the population relevant to this appraisal is people who have had only 1 previous treatment containing bortezomib, whether or not a stem cell transplant is suitable.

Subgroup data

The subgroup of patients from ASPIRE who had 1 bortezomib

treatment and no previous lenalidomide reflects the current treatment pathway

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 plus lenalidomide and dexamethasone. The ERG highlighted that in the company's subgroup, all patients had 1 previous bortezomib treatment, but not all patients had bortezomib as part of their last treatment regimen. Some patients also had lenalidomide 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 current NICE-recommended treatment pathway for multiple myeloma and included patients who only had 1 previous bortezomib treatment and no previous lenalidomide. The committee heard from clinical experts 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 plus lenalidomide and dexamethasone would be tolerated as a second-line treatment. The company did not submit new evidence to support its choice of post-hoc subgroup in response to the appraisal consultation document. The committee noted that the first-line treatments in the ERG's subgroup are appropriate for patients who would be offered carfilzomib plus lenalidomide and dexamethasone as second line in the NHS. It concluded that the ERG's subgroup should be the basis of its preferred analyses.

Overall survival and progression-free survival

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

3.5 Carfilzomib plus lenalidomide and dexamethasone increased median

progression-free survival compared with lenalidomide plus 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 plus lenalidomide and dexamethasone increased median overall survival compared with lenalidomide plus dexamethasone from 40.4 months to 48.3 months (hazard ratio 0.794; 95% confidence interval 0.667 to 0.945, p=0.0045) in the intention-to-treat population. For both its own and the ERG's preferred post-hoc subgroups, the company did an inverse probability weighted analysis to account for imbalances in baseline characteristics in the non-randomised groups. The subgroup results are considered confidential by the company and cannot be reported here, but the results for the ERG's preferred post-hoc subgroup showed a similar size benefit as for the intention-to-treat population. 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 improvements only in 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 plus lenalidomide and dexamethasone improves progression-free survival and overall survival compared with lenalidomide plus dexamethasone.

Utility values used in the economic model

Analyses with and without treatment-specific utility values were considered

3.6 From cycle 3 in the company's model, the utility values for the progression-free health state increased from baseline for carfilzomib plus lenalidomide, and dexamethasone and also for lenalidomide plus dexamethasone. However, the increase in utility is greater for carfilzomib plus 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 included in the company's model, which was accepted in

NICE's technology appraisal guidance on carfilzomib with dexamethasone. The company highlighted that the general cancer health-related quality of life (HRQoL) questionnaire (EORTC QLQ-C30) used in ASPIRE showed a statistically significant difference in the global health status scores between the treatment arms over 18 cycles of treatment. However, the committee noted that there were no significant differences between treatment arms on the other HRQoL domains assessed, including the myeloma-specific EORTC QLQ-MY20 instrument that was also used to collect quality of life data in ASPIRE. The clinical expert explained that adding carfilzomib to treatment with lenalidomide and dexamethasone would not necessarily improve a person's quality of life. But it increases the effectiveness of controlling the disease, which would improve quality of life. The company did not submit any new evidence to support its approach of using treatment-specific utility values in response to the appraisal consultation document. The company's clinical experts considered that patients in the progression-free health state having carfilzomib treatment are likely to experience reduced symptoms (such as bone pain and fatigue), a higher response rate and a faster response. This would improve their quality of life. The committee noted that the ERG's clinical expert considered there may be a quicker response to treatment for patients having carfilzomib in addition to lenalidomide and dexamethasone. But there is no clinical reason for there to be a treatment-specific utility benefit in addition to the benefit provided by any gains in progression-free survival. The ERG noted that ASPIRE was an open-label trial, and knowing which treatment they were having could have influenced patient's responses to the HRQoL questionnaires. It therefore preferred to use the same utility value for both treatments, with no increase from baseline. The committee considered that it had not been presented with strong evidence to support the company's use of treatment-specific utility values. It noted that using the same values for both treatments may be more clinically plausible because of possible confounding of the treatment-specific values. But it also noted that applying either choice of utility values resulted in carfilzomib plus lenalidomide and dexamethasone being cost effective. The committee concluded that it would consider treatment-specific values and equal values for both treatments in its decision making.

Extrapolation of overall survival

Overall survival should be extrapolated from the mature ASPIRE data

3.7 The company considered that extrapolating from ASPIRE data may underestimate long-term survival, producing conservative results for the lenalidomide plus 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 plus 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 company did not provide any new evidence to support its preferred overall-survival extrapolations in response to the appraisal consultation document. The committee concluded that it preferred to estimate overall survival for both treatment arms using data from the ASPIRE trial only.

Stopping rule

In clinical practice, treatment with carfilzomib would be limited to 18 cycles

3.8 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 NHS England 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. In particular, carfilzomib with dexamethasone alone is commissioned and used for a maximum of 18 cycles in the NHS. 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 not continue beyond 18 cycles because further treatment would not be commissioned by NHS England after this period.

It is uncertain how long any treatment benefit lasts after stopping treatment

3.9 The committee noted that a constant relative treatment effect had been applied to every cycle in the company's model for carfilzomib plus lenalidomide and dexamethasone, beyond the observed ASPIRE data. This is despite the fact that the company proposes carfilzomib is stopped after 18 cycles of treatment. The committee considered that the ERG's exponential model of overall survival also included a treatment benefit for carfilzomib plus lenalidomide and dexamethasone after stopping treatment. However, 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 plus lenalidomide and dexamethasone compared with lenalidomide plus 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 1 treatment rather than another. The committee agreed it was unclear how long the treatment benefit would last for carfilzomib plus lenalidomide and dexamethasone. It considered that the application of a prolonged treatment benefit may

potentially overestimate survival and be favourable to carfilzomib plus lenalidomide and dexamethasone. The company provided some additional analyses in response to the appraisal consultation document that aimed to resolve the committee's concerns that the treatment effect may wane over time. The committee agreed that the new evidence clearly showed that a treatment benefit is maintained for carfilzomib plus lenalidomide and dexamethasone after 18 cycles of carfilzomib treatment (28 days of treatment per cycle) and during the entire trial follow-up period (72 months). However, it was not convinced there was sufficient evidence or clinical rationale to support the assumption of a continued treatment benefit beyond the observed ASPIRE data. Therefore, the committee concluded that it is uncertain how long any treatment benefit with carfilzomib plus lenalidomide and dexamethasone lasts after stopping treatment. It considered that the treatment effect is likely to diminish over time in the extrapolated period. The committee concluded that accepting a constant treatment benefit during this period may result in optimistic cost-effectiveness estimates in favour of carfilzomib.

Combination therapies

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

3.10 The company considered that the increase in progression-free survival from adding carfilzomib to lenalidomide and dexamethasone is penalised because lenalidomide and dexamethasone are given until disease progression. This increases the costs associated with these drugs compared with using them without carfilzomib. The company did an exploratory analysis that excluded the additional cost of lenalidomide and dexamethasone in the carfilzomib plus lenalidomide and dexamethasone treatment arm. This improved the cost effectiveness of the carfilzomib regimen. 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. It 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 committee's preferred incremental cost-effectiveness ratios are likely to be below £30,000 per quality-adjusted life year gained

3.11 NICE's guide to the methods of technology appraisal notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per quality-adjusted life year (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.

3.12 The company's deterministic base-case ICER for carfilzomib plus lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone was £43,952 per QALY gained (using the patient access scheme for carfilzomib, which the company revised in response to consultation). The ERG presented analyses combining its preferred assumptions including choice of post-hoc subgroup, using the same pre-progression utility values for both treatment arms and using the exponential distribution to extrapolate overall survival based on the ASPIRE data only. It also presented analyses for its base-case assumptions without the treatment-specific utility values. The ERG's analyses included the confidential commercial arrangements for lenalidomide and for panobinostat and pomalidomide, which are options later in the treatment pathway. The committee considered analyses with and without the treatment-specific utility values (see section 3.6). The ICERs for all scenarios were below £30,000 per QALY gained for carfilzomib plus lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone. The committee discussed that the cost-effectiveness estimates may be optimistic because some waning of treatment benefit with carfilzomib plus lenalidomide and dexamethasone is likely to occur beyond the observed ASPIRE data. Based on the evidence presented and with the discount agreed in the commercial

arrangement, the committee concluded that the most plausible ICERs are within the range that NICE normally considers an acceptable use of NHS resources. Although the committee's preferred analyses were based on the ERG's post-hoc subgroup (see section 3.4), it did not consider it needed to specify that people should not have previously had lenalidomide in the recommendation. This was because it noted the company's argument that this may exclude a small number of people from accessing carfilzomib plus lenalidomide and dexamethasone. It was also aware that recommendations for the comparator in this appraisal, lenalidomide plus dexamethasone, do not specify no previous lenalidomide. Therefore, it recommended carfilzomib plus lenalidomide and dexamethasone for multiple myeloma in adults who have had only 1 previous therapy, which included bortezomib.

End of life

Carfilzomib plus 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 plus 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.

Other factors

There are no equality issues relevant to the recommendations

3.14 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

3.15 The company and the clinical expert consider carfilzomib plus 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 plus 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 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – a new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously treated multiple myeloma and the doctor responsible for their care thinks that carfilzomib plus lenalidomide and dexamethasone is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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Accreditation