NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Review Proposal Project (RPP) decision paper

Review of TA457; Carfilzomib for treated multiple myeloma

Final recommendation post consultation
A part review of the guidance should be planned into the appraisal work programme for the triple combination of carfilzomib with lenalidomide and dexamethasone within its marketing authorisation for people who have had at least one prior therapy. The review will be conducted through the single technology appraisal process.

1. Background

This guidance was issued in July 2017

At the Guidance Executive meeting of Tuesday 18 December 2018, it was agreed that we would consult on the recommendations made in the proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

A part review of the guidance should be planned into the appraisal work programme for the triple combination of carfilzomib with lenalidomide and dexamethasone as a third treatment for people who have received two prior therapies and have not received prior lenalidomide. The review will be conducted through the single technology appraisal process. That we consult on this proposal.

3. Rationale for selecting this proposal

The recommendations in TA457 are only for the combination of carfilzomib with dexamethasone and only for people who have had only 1 previous therapy (second line), which did not include bortezomib. The TA457 recommendations were for a population narrower than that covered by the carfilzomib marketing authorisation. This was because:

- The company positioned carfilzomib as a 2nd or 3rd treatment for multiple myeloma, and not later in the disease pathway.

- The committee agreed that the company positioning was in line with clinical practice in England. The TA457 evidence and positioning for carfilzomib was at 2 points and for 2 combinations in the treatment pathway:

    - in a double combination of carfilzomib with dexamethasone in people who have had 1 previous treatment (that is, second line), where the relevant comparator was bortezomib plus dexamethasone, and

  - in a triple combination of carfilzomib with lenalidomide and dexamethasone in people who have had 2 previous treatments (that is, third line) where the relevant comparator was lenalidomide plus dexamethasone (as recommended in TA171 guidance).

- Carfilzomib was found to be cost effective only in a double combination with dexamethasone and when compared with bortezomib plus dexamethasone as a second line treatment for multiple myeloma

- The recommendations for carfilzomib in combination with dexamethasone include only people who had not had previous bortezomib. This is because bortezomib, as a second line treatment was only used in the NHS for people who had not had it at an earlier line of therapy i.e. retreatment with second-line bortezomib was not representative of clinical practice in England at the time.

The company have requested a part review of carfilzomib in combination with lenalidomide and dexamethasone:

- At the time of technology appraisal (TA457) the committee did not recommend the triple combination of carfilzomib with dexamethasone and lenalidomide at third line because the OS data was immature, the life expectancy criterion for the end of life consideration was not met and the ICERs were higher than normally accepted as a cost-effective use of NHS resources. The overall survival trial data for this triple combination versus lenalidomide plus dexamethasone was immature.

- There is more mature overall survival data now available from the clinical trial, for this triple combination at third line position, to allow a part review of TA457 for carfilzomib with lenalidomide and dexamethasone in people who have had 2 previous treatments (that is, third line) compared with lenalidomide plus dexamethasone (as recommended in TA171 guidance) where carfilzomib is currently not recommended.

4. Summary of consultee and commentator responses

Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Respondent: Amgen **Response to proposal:** Disagree Amgen welcome NICE's decision to issue a Proposal Paper to conduct a part-review of TA457 Guidance (July 2017) with respect to carfilzomib in combination with lenalidomide and dexamethasone (CRd), and appreciate the opportunity to provide comments at this stage. Clinicians and key stakeholder's have consistently highlighted the need for more efficacious treatments to be made available to patients for this progressive and heterogeneous disease, and in particular to address the absence of novel therapeutics across the 2nd-line setting. At the time of writing, the part-review of TA171 (ID667) remains ongoing which exacerbates the need for a clinically effective treatment at the early stages of the treatment pathway. Despite the challenges associated with immature survival data and uncertainty in the treatment landscape, we took the important step of engaging with NICE back in July 2016 rather than pursuing a non-submission for CRd. Since that time, new overall survival data with 5.5 years of survival follow-up (double the length originally presented in TA457) has become available. The updated data for CRd demonstrates a statistically significant and clinically meaningful reduction in the risk of death and it is the only novel treatment in multiple myeloma that demonstrates robust overall survival. This new data is an important step-forward in establishing the benefit of CRd and will address a key area of uncertainty present in the original TA457 appraisal. As a result, we are now confident that we can present a comprehensive and robust evaluation of CRd, which can enable patients access to a new treatment option with demonstrably improved outcomes and address a significant unmet need in the treatment pathway. However, Amgen strongly believe that the Review Proposal in its current form is not appropriate. By pro-actively and unnecessarily restricting the proposed population to the 3rd-line setting, this proposal will fail to consider the benefit and cost-effectiveness of CRd with respect to the totality of the evidence base, anticipated use in clinical practice versus relevant comparators, and within specific areas where limitations in the current pathway exist. Amgen therefore suggest that the Review Proposal be amended to reflect the positioning of carfilzomib such that CRd can be considered within its marketing authorisation. The following sub-sections of our response outline in further detail why we believe this is the most appropriate route forward for the part-review. The Review Proposal does not reflect the licensed population of CRd CRd has a therapeutic indication for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. This marketing authorisation was awarded following a large Phase III randomised multi-centre study which evaluated CRd versus Rd in patients with multiple myeloma who had	**Comment from Technology Appraisals** Comments noted. The recommendation has been updated to review carfilzomib in combination with lenalidomide and dexamethasone for people who have had at least one prior therapy, in line with the marketing authorisation. The original proposal anticipated updated overall survival data from the ASPIRE trial for carfilzomib with lenalidomide and dexamethasone as a third line treatment as proposed in Amgen's submission for TA457. A part review of TA457 will appraise carfilzomib in combination with lenalidomide and dexamethasone after at least one prior therapy in line with the marketing authorisation, within a newly issued scope.

received 1–3 prior therapies. Within this population, CRd demonstrated a 31% reduction in the risk of disease progression and a 21% reduction in the risk of death versus Rd. These results were generally consistent across all pre-specified sub-group analyses, including those related to multiple myeloma treatment history. Given these compelling and consistent results, Amgen can see no rationale for why the Review Proposal should limit the population at the outset of the process. The Review Proposal is not aligned with the Final Scope of TA457 with respect to CRd The Final Scope for TA457 outlined the decision problem for CRd to be appraised in line with its marketing authorisation. As before, we believe that this is the most appropriate starting point to conduct a part-review of TA457 and see no rationale for restricting the scope at the outset. The subgroups ultimately presented in our original submission dossier reflected the market landscape at the time. However, given the recent and ongoing changes to the multiple myeloma pathway, including the delayed part-review of TA171 (ID667), we believe it is appropriate for this review to reconsider CRd as per the original scope. Such an approach would allow CRd to be evaluated in populations (and assessed versus relevant comparators) that are reflective of the current landscape and that can take ongoing Technology Appraisals in to account. The Review Proposal would fail to address a significant unmet need in the current multiple myeloma pathway The Review Proposal erroneously states that 'the company has requested a part-review of the evidence for the use of the triplet combination of carfilzomib with dexamethasone and lenalidomide at 3rd line in the treatment pathway'. In our previous communications we have outlined our preference to proceed with a part-review of CRd within its marketing authorisation and consistently highlighted the significant unmet need, particularly within the 2nd-line population where there is an absence of novel therapeutics. The latter point was well reflected during the appraisal for daratumumab in combination with bortezomib and dexamethasone (ongoing, ID974) where clinicians highlighted that 'chemotherapy is the only second-line treatment option for people who had first-line bortezomib' and that they 'did not consider that chemotherapy effectively treats multiple myeloma' at this stage in the treatment pathway. Furthermore, there is a general move towards utilising triplet therapies earlier in the treatment pathway within multiple myeloma, as these offer the advantage of enhancing synergies and targeting multiple pathways to allow for more rapid and deep responses. Capturing the potential for CRd to be used earlier in the pathway than is currently stated in the Review Proposal (ie. within its	Comment noted. NHS England is currently developing a treatment algorithm to allow re-treatment with bortezomib for those patients whose disease respond to first-line treatment with bortezomib, (ID974 FAD)

marketing authorisation) is therefore pivotal to ensure this unmet need can be addressed. Although Amgen welcome the decision to issue a Proposal Paper to conduct a part-review of TA457 Guidance we strongly believe that the positioning of CRd should be amended to reflect both the original scope of TA457 and the marketing authorisation of the triplet regimen. We see no rationale as to why the scope should be restricted at the outset of this process particularly given this would fail to address a significant unmet need in the current multiple myeloma pathway. Amgen has taken every step possible in seeking to deliver this medicine to the patients who urgently need it and are now confident that we are able to present a comprehensive evaluation of CRd and a robust cost effectiveness case in our resubmission using the more mature ASPIRE OS data.	

Respondent: Myeloma UK **Response to proposal:** Disagree We welcome and support the proposal to review guidance on carfilzomib, lenalidomide and dexamethasone. However, we believe strongly that the review should not be restricted to consideration of carfilzomib, lenalidomide and dexamethasone at third line. The scope of the review should be in line with the treatment's marketing authorisation. Issues Final scope of TA457 We note that the published final scope of TA 457 was in line with the marketing authorisation for carfilzomib, that is, adults with multiple myeloma who have had at least one prior therapy. We believe the review should follow this precedent and apply the same scope as the initial appraisal. Myeloma treatment pathway HTA decisions are, of course, informed not just by the efficacy of particular treatments, but by the range of comparator treatments available at any given time. The heterogeneity and relapsing and remitting nature of myeloma, along with an active research pipeline, has led to a complex and constantly changing treatment pathway. We therefore believe it is essential that a review of TA457 not be limited to third line. This would fail to recognise the evolving nature of the treatment pathway and unhelpfully restrict consideration of this treatment to a potentially outdated positioning, which does not properly reflect current patient need or comparators. Unmet need The relapsing and remitting nature of myeloma, along with its heterogeneity and resistance to treatment means that a range of different treatment options at each point in the pathway is especially vital in myeloma. Despite a range of ongoing NICE appraisal activity at second line (first relapse) on the myeloma treatment pathway, there remains a significant and illogical gap in the treatment currently available to patients at this point. This gap means that patients must undergo sub-optimal treatment at a critical time in their disease pathway. There is now considerable research evidence to show that longer and deeper remissions are gained in earlier relapses. Patients therefore deserve access to the widest possible range of effective treatments at the point in their myeloma where it has the greatest chance of delivering the best possible response.	**Comment from Technology Appraisals** Comments noted. The proposal has been updated to review carfilzomib in combination with lenalidomide and dexamethasone after at least one prior therapy in line with the marketing authorisation.

Patients would therefore be very disappointed to see a restriction applied to this review at this stage which would rule out the possibility of patients at second line accessing an effective novel treatment. There is a growing need for flexibility in the HTA process which reflects the constantly evolving nature of the pathway. The review proposal is recognition of this and we welcome it. We strongly recommend that the potential benefits of the review are not unhelpfully limited by applying an unnecessary positioning restriction at the outset of the process.	

Respondent: UK Myeloma Forum **Response to proposal:** Agree This proposal is based on the company assertion that updated overall survival data from the ASPIRE trial will potentially improve the cost effectiveness of the triplet combination carfilzomib / lenalidomide / dexamethasone. The UK Myeloma Forum fully supports the part review of TA457. The recently published extended follow-up from the ASPIRE phase 3 trial of carfilzomib / lenalidomide / dexamethasone versus lenalidomide / dexamethasone (Siegel et al J Clin Onc 2018) confirmed the significantly superior progression free survival for patients receiving the carfilzomib based triplet 26 months v 16months (HR 0.66). This led to a significant improvement in median overall survival for the carfilzomib triplet treated patients (48 months v 40 months; HR 0.79). For patients these are real and meaningful improvements in a disease that remains incurable. Prolonged progression free survival is usually associated with maintained quality of life until progression occurs and this combination is well tolerated for most patients. It should be noted that these improvements were not confined to specific subgroups of patients, in contrast benefit was obtained across all subgroups examined. We note that TA171 is also undergoing part review with the potential for access to lenalidomide at 2nd line therapy if there is a positive outcome. It would be important to ensure that this is reflected in any part review of TA257 – the current access to effective 2nd line therapy for myeloma patients is severely limited at present. Currently very few patients can access TA257 carfilzomib at 2nd line as most will have received bortezomib1st line, TA257 thus far has had limited positive impact for patients. Part review TA257 therefore needs to take the wider picture for myeloma therapy into consideration. In conclusion UK Myeloma Forum fully supports the part review of carfilzomib lenalidomide dexamethasone within its current marketing authorisation and positioned as a 2nd line or 3rd line therapy.	**Comment from Technology Appraisals** Comments noted. The proposal has been updated to review carfilzomib in combination with lenalidomide and dexamethasone after at least one prior therapy in line with the marketing authorisation.

Paper signed off by: Helen Knight, 14 March 2019

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