NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Part review of TA457; Carfilzomib for previously treated multiple myeloma

Original publication date:	July 2017
Review date in guidance	July 2020
Existing recommendations:	Optimised only for the double combination of carfilzomib with dexamethasone in people who had 1 previous therapy that did not include bortezomib (second line). To see the complete existing recommendations and the original remit for TA457, see Appendix A.

1. Proposal

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.

2. Rationale

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.

3. Summary of new evidence and implications for review

Has there been any change to the price of the technology(ies) since the guidance was published?
No
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
No
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
Yes. The company has requested a part review of the evidence for the use of the triple combination of carfilzomib with dexamethasone and lenalidomide at 3rd line in the treatment pathway. The TA457 uncertainties and new evidence for this population are described below. **A third line treatment for patients who have received two prior therapies**. Carfilzomib in combination with dexamethasone and lenalidomide was not found to be cost effective for this population in TA457. The most plausible ICER was

determined to be above £41,429 The estimates were uncertain because the overall survival data used in the model was immature, whether the effect of carfilzomib was maintained over the long term (whether it was appropriate to assume proportional hazards) and which method was appropriate to extrapolate the trial overall survival data. In addition, the life expectancy criterion for end of life was not met and the ICERs were higher than normally accepted as a cost-effective use of NHS resources. The company has noted that more mature trial data is available, which it suggests supports a proportional hazards assumption being appropriate. At this stage, the company have not provided comment on the fit of its preferred extrapolation method to the more mature overall survival data from ASPIRE or whether the more mature data suggest better outcomes than modelled in TA457.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
See Appendix C for a list of related NICE guidance.
Additional comments
None

4. Equality issues

No equality issues were raised in the original guidance.

GE paper sign off: **Helen Knight, 13.12.18**

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of carfilzomib in combination with dexamethasone within its marketing authorisation for treating multiple myeloma in people who have received at least 1 prior therapy.

6. Current guidance

1.1 Carfilzomib in combination with dexamethasone is recommended as an option for treating multiple myeloma in adults, only if:

- they have had only 1 previous therapy, which did not include bortezomib and
- the company provides carfilzomib with the discount agreed in the patient access scheme.

1.2 These recommendations are not intended to affect treatment with carfilzomib that was started in the NHS before this guidance was published. People having treatment outside these recommendations 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.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

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. This scheme provides 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.

Appendix B – Explanation of options

When considering whether to review one of its Technology Appraisals NICE must select one of the options in the table below:

Options	Consequence	Selected – 'Yes/No'
A part review of the guidance should be planned into the appraisal work programme. The review will be conducted through the STA process.	A part review of the appraisal will be planned into the NICE's work programme for the triple combination of carfilzomib with lenalidomide and dexamethasone in people who have had 2 previous treatments (that is, third line) compared with lenalidomide plus dexamethasone where carfilzomib is currently not recommended in TA457	**Yes**
The decision to review the guidance should be deferred to a specific date or trial.	NICE will reconsider whether a review is necessary at the specified date.	No
A review of the guidance should be combined with a review of a related technology appraisal. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the specified related technology.	No
A review of the guidance should be combined with a new technology appraisal that has recently been referred to NICE. The review will be conducted through the MTA process.	A review of the appraisal(s) will be planned into NICE's work programme as a Multiple Technology Appraisal, alongside the newly referred technology.	No
The guidance should be incorporated into an on-going clinical guideline.	The on-going guideline will include the recommendations of the technology appraisal. The technology appraisal will remain extant alongside the guideline. Normally it will also be recommended that the technology appraisal guidance is moved to the static list until such time as the clinical guideline is considered for review. This option has the effect of preserving the funding direction associated with a positive recommendation in a NICE technology appraisal.	No

Options	Consequence	Selected – 'Yes/No'
The guidance should be updated in an on-going clinical guideline[1].	Responsibility for the updating the technology appraisal passes to the NICE Clinical Guidelines programme. Once the guideline is published the technology appraisal will be withdrawn. Note that this option does not preserve the funding direction associated with a positive recommendation in a NICE Technology Appraisal. However, if the recommendations are unchanged from the technology appraisal, the technology appraisal can be left in place (effectively the same as incorporation).	No
The guidance should be transferred to the 'static guidance list'.	The guidance will remain in place, in its current form, unless NICE becomes aware of substantive information which would make it reconsider. Literature searches are carried out every 5 years to check whether any of the Appraisals on the static list should be flagged for review.	No
The guidance should be withdrawn	The guidance is no longer relevant and an update of the existing recommendations would not add value to the NHS. The guidance will be stood down and any funding direction associated with a positive recommendation will not be preserved.	No

[1] Information on the criteria for NICE allowing a technology appraisal in an ongoing clinical guideline can be found in section 6.20 of the guide to the processes of technology appraisal.