NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA370; Bortezomib for untreated mantle cell lymphoma

Original publication date:	16 December 2015
Review date	December 2018
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA370, see Appendix A.

1. Proposal

We propose that TA370 should be transferred to the 'static guidance list.'

2. Rationale

No new evidence was identified that is likely to change the existing recommendations in TA370. The lack of mature overall survival data for bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) was identified as an area of uncertainty in TA370. However, we have found no relevant new trial evidence to address this area of uncertainty.

The company has confirmed that no changes in the marketing authorisation are anticipated and is not aware of any new evidence that would change the existing recommendations.

It is therefore considered appropriate to move TA370 to the static list.

3. Summary of new evidence and implications for review

TA370 assessed the use of VR-CAP for previously untreated mantle cell lymphoma. The LYM-3002 trial compared VR-CAP with rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP), which was considered the most relevant comparator at the time the guidance was developed. The committee concluded that the direct evidence from LYM-3002 was sufficient for decision-making.

Since its publication in 2015, no new trial evidence on mature overall survival data in the relevant population has been identified that is likely to change the recommendations.

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We identified 2 additional analyses of LYM-3002 that have been published since TA370 but did not consider these directly relevant because they were post-hoc analyses. However, the results from these analyses support the conclusion in TA370 that VR-CAP is a clinically effective treatment and are unlikely to change the recommendations. A summary of the new evidence is presented in the table below.

Has there been any change to the price of the technology since the guidance was published?
No and the company has confirmed that no change to the price is anticipated.
Are there any existing or proposed changes to the marketing authorisation that would affect the existing guidance?
There are no proposed changes to the marketing authorisation that would affect the existing guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
In TA370, overall survival data from LYM-3002 was immature because the median was not reached in the VR-CAP group. The committee concluded that VR-CAP improved progression-free survival compared with R-CHOP and therefore is likely to improve overall survival. Since the primary analyses from LYM-3002 were published in 2015, 2 further post-hoc analyses were identified. Verhoef et al (2017) examined the association between improved outcomes and quality of responses and Robak (2017) examined the effect of bortezomib dose intensity on overall survival. Verhoef et al (2017) found that within each response category, the median progression-free survival was longer with VR-CAP compared with R-CHOP. Results from Robak et al (2017) suggest that higher bortezomib dose intensity was the strongest predictor of overall survival in patients receiving VR-CAP. The results from the new post-hoc analyses are not directly relevant but support the conclusion in TA370 that VR-CAP is a clinically effective treatment. The findings of these analyses are unlikely to change the recommendations in TA370.
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
The introduction of biosimilar rituximab is unlikely to have a large impact on the cost-effectiveness estimates because it is used as part of the intervention (VR-CAP) and the comparator (R-CHOP).

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The search strategy from the original ERG report was adapted for the Cochrane Library, Medline, Medline In-Process and Embase. References from July 2014 onwards were reviewed. Additional searches of clinical trials registries and other sources were also carried out. The results of the literature search are discussed in the 'Summary of evidence and implications for review' section above. See Appendix C for further details of ongoing and unpublished studies.

4. Equality issues

No equality issues were identified during the development of TA370.

GE paper sign off: **Helen Knight, 06/12/2018**

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Appendix A – Information from existing guidance

5. Original remit

To appraise the clinical and cost effectiveness of bortezomib within its licensed indication for treating previously untreated mantle cell lymphoma.

6. Current guidance

Bortezomib is recommended, within its marketing authorisation, as an option for previously untreated mantle cell lymphoma in adults for whom haematopoietic stem cell transplantation is unsuitable.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

Bortezomib costs £762.38 for a 3.5‑mg vial (excluding VAT; British national formulary [BNF] edition 70).

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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 review of the guidance should be planned into the appraisal work programme.	A review of the appraisal will be planned into the NICE's work programme.	No
The decision to review the guidance should be deferred.	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

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Appendix B

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.	**Yes**
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.

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Appendix C – other relevant information

1. Relevant Institute work – untreated mantle cell lymphoma

Published

Non-Hodgkin's lymphoma: diagnosis and management (2016) NICE guideline NG52

In progress

Ibrutinib for untreated mantle cell lymphoma. NICE technology appraisal guidance. Publication date to be confirmed. *30 May 18: "*Following *an update from the company, the timelines for this appraisal are to be confirmed in order to align with latest regulatory expectations. Therefore, NICE will continue to monitor development and will update interested parties as and when the situation changes."*

Lymphoma (mantle cell) - bendamustine (1st line, with rituximab). NICE technology appraisal guidance. Publication date to be confirmed. *Suspended May 2016 because the company "*will *no longer be pursuing a licensing application for bendamustine in this indication."*

2. Details of changes to the indications of the technology

Indication and price considered in original appraisal	Proposed indication (for this appraisal) and current price
Bortezomib (Velcade, Janssen) has a marketing authorisation for treating adults with previously untreated mantle cell lymphoma for whom haematopoietic stem cell transplantation is unsuitable. Bortezomib costs £762.38 for a 3.5-mg vial (excluding VAT; British national formulary [BNF] edition 70).	The indication is the same, according to the eMC record, accessed 1 Oct 18. The price is the same according to eBNF, accessed 1 Oct 18.

Appendix D – References

Verhoef, Gregor et al. (2017) Association between quality of response and outcomes in patients with newly diagnosed mantle cell lymphoma receiving VR-CAP versus R-CHOP in the phase III LYM-3002 study. Haematologica: 2016.

Robak, Tadeusz et al. (2017) Association between bortezomib dose intensity and overall survival in mantle cell lymphoma patients on frontline VR-CAP in the phase 3 LYM-3002 study. Leukemia & lymphoma: 1-8.

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