NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Technology Appraisal Review Proposal paper

Review of TA311; Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation

Original publication date:	April 2014
Review date	February 2017
Existing recommendations:	Recommended To see the complete existing recommendations and the original remit for TA311, see Appendix A.

1. Proposal

The guidance should be transferred to the 'static guidance list'. That we consult on this proposal.

2. Rationale

Overall, there is no new evidence or ongoing research comparing bortezomib for induction therapy in multiple myeloma with the most relevant comparator identified by the appraisal committee. The company confirmed to NICE that they did not anticipate any changes to the marketing authorisation for this indication and were not aware of any new evidence that may be relevant to this appraisal. Furthermore, there has been no change in the list price since TA311 was published.

No additional NICE technology appraisal guidance has been published since TA311 or are currently scheduled into the technology appraisal work programme for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation.

It is therefore proposed that TA311 is moved to the static list because no evidence has been identified that is likely to alter the conclusions of the guidance (that is, lead to a change in the clinical and cost effectiveness of the bortezomib induction therapy).

3. Summary of new evidence and implications for review

The search strategy from the original ERG report was re-run on the Cochrane Library, Medline, Medline In-Process and Embase. References from September 2012 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 below. See Appendix C for further details of ongoing and unpublished studies.

TA311 compared bortezomib and dexamethasone (with or without thalidomide) to chemotherapy regimens containing thalidomide. In TA311 there was no direct evidence comparing bortezomib and dexamethasone (with or without thalidomide) with the most relevant comparator identified by the committee (cyclophosphamide, thalidomide and dexamethasone). No new evidence or ongoing research has been identified by the searches that are relevant for the comparison of interest.

There is a new phase 3, open label trial assessing induction treatment in people with newly diagnosed multiple myeloma (Moreau et al 2016). However, this trial compares bortezomib, dexamethasone and thalidomide with another bortezomib containing regime. Therefore this trial is not considered directly relevant to TA311.

During the development of TA311 the committee agreed that a robust indirect comparison between the available trials could not be formed. Therefore the committee used further analysis comparing single arms of the available trials to bridge this gap. The addition of this new trial would still not allow a robust indirect comparison of bortezomib and dexamethasone (with or without thalidomide) with cyclophosphamide, thalidomide and dexamethasone. The findings of the new trial support the relationships observed in TA311 (that is, that bortezomib, thalidomide and dexamethasone was more clinically effective than bortezomib, cyclophosphamide and dexamethasone). Therefore any additional analyses that may be possible on the basis of new evidence would be unlikely to change the original recommendation. 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?
There has not been any change to the list price (£762 per 3.5-mg vial) since TA311 was published in April 2014.
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 of bortezomib for induction therapy that would affect the guidance.
Were any uncertainties identified in the original guidance? Is there any new evidence that might address this?
The committee considered cyclophosphamide, thalidomide and dexamethasone, to be the most relevant comparator for decision-making because it was standard clinical practice in England. There was no direct evidence comparing bortezomib and dexamethasone (with or without thalidomide) with cyclophosphamide, thalidomide and dexamethasone. No new evidence has been identified directly comparing bortezomib and dexamethasone (with or without thalidomide) with

cyclophosphamide, thalidomide and dexamethasone. In addition, the new evidence identified would still not allow for a more robust indirect comparison for bortezomib and dexamethasone (with or without thalidomide) compared with cyclophosphamide, thalidomide and dexamethasone.
Are there any related pieces of NICE guidance relevant to this appraisal? If so, what implications might this have for the existing guidance?
NG35 Myeloma: diagnosis and management was published in February 2016 and included recommendations on managing newly diagnosed myeloma. NG35 cross refer to recommendations from TA311 and TA228. There are currently no implications for the existing guidance and it is likely this guideline will be reviewed in 3 years. *See Appendix C for a list of related NICE guidance.*
Additional comments
None.

4. Equalities issues

No equality issues were raised during TA311 that were relevant to the committee's recommendations.

GE paper sign off: **Meindert Boysen, 31 January 2017**

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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 induction therapy prior to high dose chemotherapy and autologous stem cell transplantation for the treatment of multiple myeloma.

6. Current guidance

1.1 Bortezomib is recommended as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

7. Research recommendations from original guidance

N/A

8. Cost information from original guidance

2.3 The cost of bortezomib is £762 per 3.5‑mg vial (excluding VAT; British National Formulary [BNF] edition 66). According to the marketing authorisation bortezomib should be given in combination with dexamethasone (4 cycles of 21 days each) or with dexamethasone and thalidomide (4 cycles of 28 days each; 2 additional cycles of 28 days each for patients with at least partial response after the fourth cycle). Four intravenous infusions or subcutaneous injections of bortezomib are administered per cycle, on days 1, 4, 8 and 11 of each cycle. The average cost of a course of treatment with bortezomib given with dexamethasone is estimated to be £12,261 and the average cost of a course of treatment with bortezomib given with dexamethasone and thalidomide is estimated to be £24,840. Costs may vary in different settings because of negotiated procurement discounts.

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. The review will be conducted through the STA process.	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

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.

Appendix C – other relevant information

1. Relevant Institute work

Published

Myeloma (2016) NICE pathway

Myeloma: diagnosis and management (2016) NICE guideline NG35

Bortezomib and thalidomide for the first‑line treatment of multiple myeloma (2011) NICE technology appraisal 228.

Bortezomib monotherapy for relapsed multiple myeloma (2007) NICE technology appraisal 129.

In progress

Elotuzumab for untreated multiple myeloma [ID966] NICE technology appraisal guidance. Publication expected January 2018.

Bortezomib for treating multiple myeloma after second and subsequent relapse [ID1120] NICE technology appraisal guidance. Publication date to be confirmed.

Suspended/terminated

Lenalidomide for the treatment of newly diagnosed multiple myeloma [ID474] NICE technology appraisal guidance. Publication date to be confirmed. Suspended from the work programme until a Public Access Scheme can be agreed (July 2015).

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 has a UK marketing authorisation for use 'in combination with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation'. The cost of bortezomib is £762 per 3.5-mg vial (excluding VAT; British National Formulary [BNF] edition 66).	**Indication** No change Source: SPC (Jan 2016) and letter from Janssen (Nov 2016) **Cost** £762.38 per vial Source: BNF (November 2016)

3. Details of new products

Drug (company)	Details (phase of development, expected launch date)
Ixazomib (Ninlaro), Takeda	Launched 2016 Multiple myeloma (MM); adults who have received at least one other therapy - combined with lenalidomide & dexamethasone
Melphalan (Evomela), Aspen	Phase 3 clinical trials Launch: [redacted] Multiple myeloma (MM); conditioning treatment prior to transplant

4. Registered and unpublished trials

Trial name and registration number	Details
A phase III study of velcade (bortezomib) thalidomide dexamethasone (vtd) versus velcade (bortezomib) cyclophosphamide dexamethasone (vcd) as an induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma NCT01971658	Study design: randomized, open label Status: completed Enrollment: 358 Completion date: August 2015

5. Relevant services covered by NHS England specialised commissioning

NHS England (2013) Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation

NHS England (2015) National chemotherapy algorithms: multiple myeloma. Draft for public consultation

6. Additional information

Bortezomib Accord (authorised 20 July 2015) – Accord Healthcare

Bortezomib Hospira (authorised 22 July 2016) – Hospira

Bortezomib Sun (authorised 22 July 2016) – SUN Pharmaceutical Industries

Appendix C

European Myeloma Network (2014) European Myeloma Network recommendations on the evaluation and treatment of newly diagnosed patients with multiple myeloma

European Myeloma Network (2015) European Myeloma Network Guidelines for the Management of Multiple Myeloma-related Complications

Appendix D – References

Moreau P, Hulin C, Macro M et al. (2016). VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 127 (21): 2569-2574.