CONFIDENTIAL

Bortezomib for the treatment of multiple myeloma

Premeeting briefing

This briefing presents key issues arising from the manufacturer's submission (MS), the Evidence review group (ERG) report and personal statements made by nominated clinical specialists and patient experts. Please note that although condensed summary information is included here for ease of reference, this briefing should be read in conjunction with the full supporting documents.

The manufacturer was asked to provide further details of the APEX study, provide results of the economic model incorporating quality-adjusted life years, complete further sensitivity analyses and clarify definitions used in the MS. The questions and responses are given in the addendum of the ERG report (page 54).

Abbreviations

APEX, Assessment of proteasome inhibition for extending remissions
CI, confidence interval
EMEA, European Medicines Agency
ERG, Evidence review group
FDA, Food and Drug Administration
HDD, high dose dexamethasone
HR, hazard ratio
ITT, intention to treat
LYG, life years gained
MM, multiple myeloma
MS, manufacturer's submission
NE, not evaluable
NEJM, New England Journal of Medicine
OS, overall survival
QALY, quality-adjusted life year
RCT, randomised controlled trial
SA, sensitivity analysis
TTP, time to disease progression

Licensed indication

Bortezomib (Velcade, Janssen-Cilag) is indicated as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

Key issues for consideration

Clinical effectiveness

- Is HDD an appropriate comparator and have any comparators been overlooked?
- Does the APEX RCT show clear evidence that bortezomib is more clinically effective than HDD?
- Are the results of the APEX RCT generalisable to the wider UK MM population?

Cost effectiveness

- What is the likely impact of adverse events not being modelled?
- Is the model likely to over-estimate treatment effect and thus under-estimate cost effectiveness?
- Is it more appropriate to consider incremental costs per LYG instead of per QALY gained?
- What is the likely impact of adjusting LYG for health-related quality of life?
- What are the implications of the scenario analyses:
  - first relapse rather than at later relapse?
  - non-responders are limited to three cycles?
  - bortezomib combined with HDD?
- What are the implications of the ERG's analysis on the effects on cost reduction through group/cohort use to minimise wastage?

1 Decision problem

1.1 Decision problem approach in MS

Population	MM patients at first relapse and beyond (MS page 6).
Intervention	1. Bortezomib monotherapy. 2. (Scenario in economic model only): bortezomib in combination with high dose dexamethasone.
Comparators	High dose dexamethasone (HDD). The rationale in the MS for the choice of HDD is that it is commonly used in clinical practice in the UK, there is no UK consensus on best practice, and HDD is the only licensed monotherapy with proven efficacy in first relapse patients and that it was the comparator agreed with the FDA and EMEA as the basis for regulatory approval of the APEX trial.
Outcomes	Primary outcome: time to disease progression (TTP). Secondary outcomes: response rate (responses are defined in MS, page 37, table 8), duration of response, time to new skeletal events, adverse events, 1-year survival, overall survival, quality of life.

1.2 ERG comments

1.2.1 Population

The population defined in the MS does not completely match with the licence population because it does not identify whether patients have already undergone or are unsuitable for bone marrow transplantation. The manufacturer responded that majority of second-line patients meet this description, which was why Committee for Proprietary Medicinal Products requested that it be included in the indication (ERG report, page 70).

1.2.2 Intervention

The regimen in the APEX study was extended compared to the SPC:

APEX: 8 x 3w cycles plus 3 x 5w cycles,

SPC: 3w cycles up to a maximum of 8.

The ERG report highlights (as stated in the MS) that although the UK market authorisation is for monotherapy, clinical advisers and published guidelines suggest that bortezomib is generally used in combination with dexamethasone in the UK.

1.2.3 Comparators

It is not clear whether use of HDD is representative of UK clinical practice. However, the ERG and the MS concur that there is no standard therapy for relapsed MM and treatment is likely to vary according to patients' clinical condition, age, prior treatment regimens and time to relapse. Treatment options include a further chemotherapy regimen leading to a second stem cell transplant, non-transplant-directed therapy with alkylating agents such as melphalan with or without corticosteroids, and thalidomide with or without dexamethasone.

1.2.4 Outcomes

Outcomes stated in MS are appropriate and clinically meaningful. Given the high mortality rate for this condition, the ERG queried whether survival would have been more appropriate than TTP. However, clinical advisers to the ERG indicated that TTP is an appropriate primary outcome (ERG report, pages 21 and 70).

1.3 Clinical specialists' and patient experts' statements

There is no standard of care for patients with relapsed multiple myeloma. However treatment at first relapse will often involve a thalidomide containing regimen and can be followed by a second stem cell transplant. At second and subsequent relapse there is no well established therapy, but these patients often receive high dose steroids or oral cyclophosphamide or melphalan. Patient

pathways through treatment are determined by disease- and patient-specific factors.

There would be no clear clinical rationale for restricting bortezomib to patients who have had any particular number of relapses. Developments in autologous stem cell transplantation and new drugs have led to a change in clinical practice: the therapeutic aim of maximum response is now applicable to each relapse whereas in the past, stable disease was acceptable and the aim of treatment at second and subsequent relapse was mainly palliative. Whereas the response rates and impact on outcome of recently developed combination regimens containing thalidomide, lenalidomide (a thalidomide derivative) and bortezomib are well described, there is currently little evidence to guide the sequence in which these combinations are used. Therefore, it seems likely that during the course of their illness most myeloma patients will receive all of the available therapies.

Patients tend to evaluate treatment effects more in terms of longer time periods spent with reduced paraprotein levels. Achieving complete or near complete response (which is partly defined by a reduction in paraprotein levels, see MS, page 37) is essential for long-term survival of MM patients. To date, given better response rates in studies have translated into better progression-free and overall survival.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in MS

2.1.1 Systematic review results

Table 1 Summary of APEX interim results (8.3 months follow-up)[a]

Outcome measure	Bortezomib (n = 333), ITT	HDD (n = 336), ITT
Median TTP (95% CI) HR TTP (95% CI) P value	6.2 months *(4.6, 6.9)* 0.55 *(0.44, 0.69)* p < 0.001	3.5 months *(2.8, 4.2)*
Overall survival median months (95% CI) HR OS (95% CI) P value	16.6 *(16.6, not evaluable)* 0.57 *(0.40, 0.81)* p = 0.001	Actual figures not reported
1-year survival P value	80% p = 0.003	66%
[a] Additional information from MS in italics (pages 48, 49 of MS and 22 of ERG report)		

Subgroup analysis

Subgroups of patients treated at an early stage (first relapse or one prior therapy), high vs. low risk, and HDD refractory are considered. Better outcomes were achieved with earlier treatment. Efficacy of bortezomib is consistent across all patients irrespective of risk status. Exclusion of patients who were refractory to HDD did not affect the treatment benefits demonstrated by bortezomib over HDD (MS pages 54–56).

2.2 ERG comments

2.2.1 Overall

The ERG identified two main areas of concern (see below and ERG report, page 50):

- the limited evidence base and its relevance to the NHS (clinical evidence reported in the MS is based on the results of a single RCT and a series of abstracts, resulting from a search for studies in which bortezomib monotherapy is compared with either placebo or another comparator in patients with MM at first relapse)
- the interpretation of the included RCT (the lack of detail and clarity in the reporting of the APEX trial makes it difficult to interpret the data with confidence and impossible to check some results for key outcome measures).

However, 'these limitations probably do not significantly affect the overall results especially in the light of clarifications received from the manufacturer'. The APEX RCT is judged to be of reasonable quality according to NICE quality assessment criteria (ERG report, pages 17 and 25).

2.2.2 Subgroup analysis

The data for earlier vs. later treatment reflected the cited abstract. Although the data for high-risk patients reflected the cited abstract, it was not clear where the data for low-risk patients had come from. No data were found to support some statements in this section of the MS (ERG report, page 24).

2.3 Clinical specialists' and patient experts' statements

Based on the results of the APEX RCT it can be concluded that bortezomib is a better treatment than dexamethasone at relapse. Furthermore, in a series of observational studies carried out in patients entered into the APEX study, and two phase II studies, SUMMIT and CREST, it was shown that patients who respond to therapy had improved levels of haemoglobin, decreased transfusion requirements and an improved quality of life.

Responses can be achieved with bortezomib even when myeloma is refractory to other agents or is high risk (e.g., abnormal cytogenetics). In a sub-analysis of the SUMMIT study it was noted that response was independent of the number of

previous lines of treatment, and type of previous treatment, confirming in vitro data that bortezomib works via a different mechanism and overcomes resistance to other treatments.

There is now considerable clinical experience with bortezomib. It has been used along very similar, if not, identical circumstances to the clinical trials and there is widespread agreement that trial results are borne out in clinical practice.

Bortezomib therapy results in a different range of side effects compared with classical chemotherapy. While the range of side effects is wide, the majority are readily manageable. The major side effect of bortezomib is peripheral neuropathy, which can be severe, but appears to be largely reversible with close observation and institution of appropriate measures. It is not clear to what extent neuropathy is attributable to bortezomib because prior therapies and the disease itself also cause it.

A recent position statement on the use of bortezomib in multiple myeloma produced by four experts in the field concluded that the clinical evidence would suggest benefits when combined with dexamethasone as a treatment for second relapse, as well as for patients at first relapse who have been exposed to a range of therapies including thalidomide as either induction therapy or as maintenance treatment.

3 Cost effectiveness evidence

3.1 Cost effectiveness in MS

Analysis	Difference in mean discounted OS (months)	Difference in mean total costs	Estimated cost per LYG	Estimated cost per QALY (provided in response to clarification)
Primary analysis (patients with 1 relapse) *[revised in response to clarification]*	9.9	£25,327	£30,750 *[£31,146]*	£38,452
Primary analysis with probabilistic SA (5th to 95th percentile)			£26,855 to £38,564	£33,992 to £49,894
Scenario (1): only 3 cycles for non-responders	8.2	£19,172	£27,926	Not provided
Scenario (2): overall APEX data (that is, patients with 1 or more relapse)	7.3	£24,165	£39,954	Not provided
Scenario (3): bortezomib + HDD versus HDD alone	11.0	£25,898	£28,281	Not provided

3.2 ERG comments

See appendix for details of selected ERG comments on manufacturer's economic model.

3.2.1 General comments

In general the approach taken to model disease progression and cost effectiveness in this patient group seems reasonable. However, the ERG has identified a number of concerns.

In the original MS no patient related measures of health-related quality of life were applied and the model outcomes were reported in terms of cost per LYG. MM patients have a relatively poor quality of life and the ERG suggested that this should be incorporated. See ERG report, pages 62–65 for the response from the manufacturer where the base-case is reported in cost/QALYs gained. The

content of this response is not commented on in the ERG report, however the ERG identified a number of studies which indicate that a health state value between 0.644 and 0.789 may be appropriate for patient groups with MM (ERG report, page 37).

The ERG suggest that the results presented may underestimate the cost/LYG for treatment with bortezomib compared with HDD where potential UK practice and scenarios are considered and that there may be greater variability in the cost effectiveness of treatment than presented in the MS. The ERG has not undertaken systematic searches; therefore the comments made are for broader consideration by the NICE Appraisals Committee in the context of this single technology appraisal.

3.2.2 Key conclusions

- Bortezomib is more cost effective when the number of treatment cycles is limited to three for non-responders.
- Bortezomib is more cost effective with 100% of patient cohort at first relapse (cost effectiveness decreases when the proportion of cohort patients with more than one relapse increases).
- Combination therapy of bortezomib and HDD is more cost effective than bortezomib monotherapy (though the appropriate dosage regimen for the combination therapy of bortezomib and HDD is not at the moment defined and it does not have a marketing authorisation).
- The most influential factors on cost effectiveness are TTP HR and costs of bortezomib. Cost savings are possible through group/cohort administration to minimise vial wastage.
- There is greater uncertainty in both deterministic and probabilistic cost effectiveness estimates than suggested in MS.

4 Authors

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Appendix

Selected ERG comments on the manufacturer's economic model	Potential impact
Model structure: The model structure covers the treatment of MM, rather than depicting the natural history of disease. It predicts treatment experience, rather than disease progression.	It may not capture important issues such as the relevance of 'time to relapse' (for example, 1 month treated the same as 10 months to relapse). Adverse events have not been included in the MS model, either in terms of loss of quality of life or increased resource use.
Cost data inputs: The ERG considered the cost impact of wastage due to packaging; a 3.5 mg vial (cost £762.38) is enough for 2.7 m^2 body surface area which is more than average.	Group/cohort treatment of MM patients may yield costs savings. Assuming 0.5 mg of each 3.5 mg vial is wasted; estimated costs savings is about £2350 per patient (over 24 doses/6 cycles).
External consistency: Comparisons of survival estimates from MS model with Kaplan Meier survival curves in the MS (figure 1, page 42 ERG report).	These comparisons indicate that the model, after the first year, may overestimate the treatment effect.
One-way SA: MS states that the most influential parameters are duration of treatment and TTP HR.	ERG amended SA with alternative parameter ranges showed TTP HRs and cost of bortezomib to be the most influential parameters (ERG report, page 44, table 9).
Scenario analysis: limit to three cycles for non-responders.	ERG concurs that this reduces cost/LYG and is reflective of current UK practice but points out that approx. 15% of those who had a response in APEX did so *after* the 3rd cycle and those people would have their treatment stopped before that in this scenario.
Scenario analysis: In the scenario with one or more relapses, the MS model uses a HR for OS of 0.43 for the 2nd and 3rd years, whereas 0.83 is used in the baseline scenario. ERG re-ran using 0.83 instead.	ICER increases from £40K to £46K/LYG (ERG report, page 45).
Scenario analysis: ERG performed combined analysis of treatment scenarios in MS (ERG report, page 46). The three scenarios in MS are likely to be used in clinical practice.	The most cost effective scenario is treating all patients at first relapse. As the proportion of patients treated at 2nd and 3rd relapse increases, the ICER of bortezomib increases significantly. Results range from £27K to £45K/LYG depending on % assumed to be treated in 1st, 2nd, 3rd regimen (ERG report, page 46, table 10).
Probabilistic SA: limited parameter ranges used in MS. ERG maintained distributions in MS and used 95% CIs for hazard ratios and a range of ±25% for cost data. ERG ran another PSA where cost of bortezomib varies by ±50%.	Range from amended PSA: £23K/LYG to £47K/LYG (5th to 95th percentile). Range from amended PSA £20K to £50K/LYG.