MyelomaUK

informing
understanding
supporting

Leukaemia CARE
supporting a quality of life

cancerbackup

Myeloma UK, Cancerbackup, Leukaemia CARE

Appeal against Final Appraisal Determination

Bortezomib monotherapy for relapsed multiple myeloma

We are appealing against this FAD in line with the following two grounds:

1) NICE has failed to act in accordance with the appraisal procedure
2) NICE has prepared guidance that is perverse in the light of the evidence submitted

1. Procedure

1.1 *The appraisal process was not adhered to with regard to the scoping exercise as set out in paragraph 1.3 of the 'Guide to the Methods of Technology Appraisal'*

The Appraisal Committee did not consult relevant stakeholders on the scope of the appraisal thus denying the right of consultees to comment on the appropriateness of the questions to be asked within the appraisal.

The '*Guide to the single technology appraisal (STA) process*', which requires that a consultative scoping exercise takes place in paragraph 3.1.1.1, was not available until September 2006, after the relevant time for the bortezomib appraisal. However, it is unfair that other appraisals conducted via the STA system have been subject to a fully consultative scoping process. A scoping exercise should have been granted to bortezomib by merit of paragraph 1.3 in the *'Guide to the Methods of Technology Appraisal'*.

Had Myeloma UK and its partners been consulted as part of the scoping process, we would have commented on the use of dexamethasone as a comparator drug, and the special consideration that needed to be taken into account with respect to the use of bortezomib used in combination with dexamethasone; the current clinical practice.

1.2 *The FAD has given undue weight to cost effectiveness in contradiction to paragraph 6.2.6.4 of the 'Guide to the Methods of Technology Appraisal'*

Paragraph 6.2.6.4 states that the appropriateness of the comparator treatment is crucial to the weighting of cost effectiveness evidence.

The FAD notes in paragraph 4.2 that it "accepted that HDD was an appropriate comparator." We understand that this is because HDD, as the *only available comparator*, was by default, deemed appropriate.

Dexamethasone (HDD) is currently the only licensed comparator for relapsing myeloma patients, yet was proven in the APEX trial to be less effective than bortezomib. Patients taking bortezomib had a significantly longer median time to disease progression compared with people receiving dexamethasone and, as stated in the FAD in paragraph 3.2, "the independent data monitoring committee deemed it unethical to continue with the trial, and

recommended that people in the HDD arm should be offered bortezomib." This is evidence of the unsuitability of HDD as a comparator.

Further, the FAD is not determining the value for money of the benefits of bortezomib in comparison with treatments actually used in clinical practice. If bortezomib is explicitly disallowed while other treatments are being allowed because they have not faced NICE scrutiny, then there is a real possibility that the NHS is wasting money on less effective treatments. Again, had there been the opportunity to comment on the scope of the appraisal, such points would have been drawn to the Committee's attention.

We therefore believe the Appraisal Committee to have given undue weight to cost effectiveness in this FAD. The weighting that cost-effectiveness receives within the bortezomib analysis should be appropriately reduced in recognition that the only alternative for patients is proven to be significantly less clinically effective than bortezomib.

1.3 *The Chief Executive of NICE acted outwith the appraisal procedure as set out in 6.3.3.1 of the 'Guide to the Methods of Technology Appraisal'*

In response to many MPs' letters of concern regarding the pending FAD on bortezomib, the Chief Executive of NICE wrote and distributed a stock letter. The final paragraph states:

"Cost is a consideration in our appraisals, but what really drives the judgement that needs to be made about the value of a new drug is the extent of the additional therapeutic benefit it brings. In the case of Velcade, there just is not enough additional benefit, relative to its cost and based on current evidence, to support its widespread use". (First instance attached, dated 23 August 2006, to John Redwood MP).

We believe the NICE Chief Executive acted outwith the appraisal procedure in his letter by committing to paper a conclusion that cannot legitimately have been reached before the final outcome of the appraisal, and takes no account of the public consultation responses. This is in direct contravention to paragraph 6.3.3.1 of the NICE document 'Guide to the Methods of Technology Appraisal' which sets out the guidance for reviewing the consultation responses and considering appropriate changes to the ACD.

Further, regardless of whether the decision had been made in lieu of the consultation responses or second appraisal discussion, this statement should not have been released into the public domain, where it was inevitably going to be shared with patients for whom the decision is of paramount importance.

2. Perversity

2.1 *It is perverse that appropriate efforts were not made to address distorted results generated from the significant cross over between study arms in the APEX trial*

The ERG argued that the model submitted by the manufacturer overestimated the treatment effects of bortezomib shown in the APEX trial (FAD paragraph 3.5). However, the ERG does not appear to acknowledge that the APEX study was subject to a predetermined interim analysis at which point the Independent Data Monitoring Committee (IDMC) deemed it

unethical to withhold bortezomib from the dexamethasone arm. This resulted in significant cross over between study arms; consequently the APEX study did not provide a balanced estimate of the benefits of bortezomib, and was in fact a comparison of early versus late bortezomib.

The IDMC unblinds trials early on ethical grounds when a treatment proves highly effective against its comparator; this event should have been appropriately assimilated into the evaluation by the ERG and the Appraisal Committee.

It is perverse that an independent committee can deem a treatment so effective that it is unethical to withhold from patients receiving standard care, but that the committee's actions ultimately result in the treatment being withheld from many more terminally ill patients by a Health Technology Appraisal Committee on cost-effectiveness grounds. Had the APEX trial been allowed to continue as planned then the true survival advantages over dexamethasone would have been established and the cost-effectiveness been the subject of less uncertainty.

We urge the Appraisal Committee to reconsider their decision in light of the IDMC's actions. Moreover, we urge NICE to establish a standard process to more justly assess treatments which are penalised by the current technology appraisal process for being the focus of trials unblinded early because of their outstanding clinical effectiveness.

2.2 *The FAD contains perverse and contradictory recommendations about future research as cited in paragraphs 4.10 and 6.1.*

The FAD notes that no further trials of bortezomib in its licensed indication are planned (paragraph 4.10). The FAD, for valid ethical reasons, withdraws the preliminary recommendation stated in paragraph 1.1 of the ACD to make bortezomib available only in the context of clinical trials. Yet paragraph 6.1 of the FAD recommends further studies to focus on "comparisons with other agents that are currently used in clinical practice in the NHS in England and Wales". This is a contradictory recommendation to the accepted reality regarding clinical trials.

The lack of planned trials means that there will be no further evidence to be able to adequately reassess the treatment in October 2007. If the Appraisal Committee insists in the 2007 review on only considering comparisons with licensed treatments there are likely to be no new data which satisfy this restriction.

The clinical efficacy of bortezomib has been confirmed. We feel that the treatment should be endorsed, with retrospective analyses made to generate additional data that can be assessed in a year's time.

2.3 *The fact that the Rule of Rescue was not applied to this treatment is perverse.*

The NICE Citizens Council Report on the 'Rule of Rescue', published in July 2006, states the Council were in majority agreement with the premise of the Rule, which if applied, would mean that the NICE's advisory bodies could be prepared to accept higher costs per QALY. In particular the Council were of the opinion that:

- That cost effectiveness is not the most important and overriding factor (page 14)
- The Rule of Rescue could apply to a new drug that would help extend a cancer patient's life and should be applied in certain situations (page 8 and 11)
- The existing QALY criteria used by NICE should be expanded
- If there were limited treatment options for an 'exceptional case' (what the Council re-termed Rule of Rescue) the new treatment should receive more serious consideration than it may otherwise receive (page 14)

In accordance with the Citizen Council's opinion, which "should underpin NICE's guidance", we believe that the Appraisal Committee should apply the Rule of Rescue to bortezomib as it is the only licensed treatment specifically available for relapsing myeloma patients; it is proven to extend life for an incurable cancer; and its ICER per QALY is below that of other therapies that have been positively endorsed by NICE.

Chief Executive Myeloma UK	Chief Executive Cancerbackup	Chief Executive Leukaemia CARE