NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Appraisal of bortezomib for the treatment of multiple myeloma

Decision of the Panel

1. Introduction

An Appeal Panel was convened on 8th February 2007 to consider an appeal against the Institute's Final Appraisal Determination (FAD), to the NHS, on the use of bortezomib for the treatment of relapsed multiple myeloma.

The Appeal Panel consisted of Professor Sir Michael Rawlins (chair of the panel and chair of the Institute), Mrs Mary McClarey (non-executive directors of the Institute), Dr Peter Brock (industry representative), Ms Alison Hawdale (patient representative), and Professor Robin Ferner (NHS member).

The Panel considered appeals submitted by:

- Myeloma UK, Cancerbackup and Leukaemia CARE (jointly)
- Royal College of Pathologists, British Society for Haematology, and UK Myeloma Forum (jointly)
- Janssen-Cilag (Ortho Biotech)

In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Professor David Barnett (chair of the appraisal committee), Dr Meindert Boysen, Mrs Helen Chung, Professor Peter Littlejohns, Dr Carole Longson (Director, Centre for Health Technology Evaluation), Dr Rubin Minhas, and Professor Mark Sculpher.

The Institute's legal advisor (Mr Stephen Hocking, Beachcroft LLP) was also present.

Under the Institute's appeal procedures members of the public are admitted to appeal hearings and a number of members of the public were present at this appeal.

There are three grounds on which a panel can hear an appeal:
Ground 1: The Institute has failed to act fairly and in accordance with its procedures;
Ground 2: The Institute has prepared guidance which is perverse in light of the evidence submitted;
Ground 3: The Institute has exceeded its legal powers.

The Appellants were invited to make introductory remarks before each of the grounds of appeal was considered separately. Having heard the opening comments from the Appellants, the Panel considered each of the grounds for appeal in turn.

2. Ground 1: The Institute has failed to act fairly and in accordance with its procedures

2.1 Janssen-Cilag (2.1.1): The fact that this appraisal was not defined by a scope and included no requirement for the Institute to consider the manufacturer's definition of the "decision-problem" prior to the submission of evidence has precluded a fair consideration of bortezomib

2.2 Royal College of Pathologists, British Society for Haematology, and UK Myeloma Forum (jointly): 1 It is a failure of process not to have an appraisal scope

2.3 Myeloma UK, Cancerbackup and Leukaemia CARE (jointly): (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 considered the appeal under these points together. Dr Longson, for the Appraisal Committee, explained that there had been no scope, but that the assessment had been made under an interim procedure which did not provide for a scope. That had been agreed by the board of the Institute, as had been done in the case of the introduction of the process for multiple technology assessment. The interim procedure had also been used as the basis for the consultation that led to the current definitive procedure on the single technology appraisal process. The definitive procedure includes a scoping stage. Professor Barnett explained that the Appraisal Committee had considered subgroups of patients who might benefit from bortezomib, and had established that the appropriate comparator was high dose dexamethasone. It had not considered the possibility of an "Outcomes Guaranteed Scheme" and would not have expected to do so. The Appraisal Committee had agreed with the market authorization holder what costs should be included.

All the clinical haematologists present (Professor Morris, Dr Behrens, Dr Cavenagh, Dr Jackson, Dr Mehta, and Dr Richardson) stated that, when they used bortezomib, they used it in combination with dexamethasone rather than as monotherapy as appraised. Professor Morris explained that 26 of his 29 patients in Northern Ireland were receiving the combination, with the remaining three being unable to take dexamethasone for clinical reasons.

Dr Longson reported that the regulatory authority held to the view that, where clinical practice was moving ahead of the licensed indication, the manufacturer should apply for an extension to the marketing authorization. Dr Williams, on behalf of Janssen-Cilag, stated that the company had seen no written affirmation of this view.

Professor Barnett reminded the Appeal Panel that the marketing authorization referred only to bortezomib monotherapy, not to the use of bortezomib in combination with dexamethasone. The Appraisal Committee had anyway considered the combination in great depth. He agreed that, whatever the licensing arrangements, the Institute wished to do the best for all patients.

Dr Cavenagh stated that the scope had already been widely discussed. In his view, there had been a failure of due process when the scoping stage had been omitted. He alluded to a French trial of bortezomib+ dexamethasone as initial therapy {IFM 2005-01: Velcade®/Dexamethasone versus Vincristine/Adriamycin® (Doxorubicin)/ Dexamethasone (VAD) for the Treatment of Patients With Multiple Myeloma} that reinforced the argument for combining these two treatments.

Mr Low, representing Myeloma UK, Cancerbackup and Leukaemia CARE, reinforced the views of the appellants who had already spoken. In his view, it was wrong not to have a scope.

The Appeal Panel accepted that the Board of the Institute had agreed the interim arrangements for single technology assessment. The process described in these arrangements was not intrinsically unfair, but had proved to be unfair in its application to this particular case. In a case where the standard clinical practice, which is to use bortezomib with dexamethasone, diverged so much from the use envisaged in the marketing authorization, it was unfair that that the company did not have the opportunity to argue that “off label” use should have been appraised. The appeal panel expresses no view, under this heading, as to whether “off label” use should or should not have been appraised; merely that fairness required that consultees should have had the opportunity to argue for it if they wished.

The Appeal Panel found that the operation of the interim procedure was on this occasion unfair.

The Appeal Panel therefore upheld the appeal by the three Appellants on these points to the extent that the operation of the interim procedure was on this occasion unfair.

2.4 Janssen-Cilag (2.1.2): No explanation is provided for the conclusion in paragraph 4.3 of the FAD that the dose intensity of high-dose dexamethasone in the APEX trial was lower than in other studies

Professor Barnett stated that the Appraisal Committee had considered the possible influences on the trial result. The trial compared bortezomib with dexamethasone, and

the Appraisal Committee wanted to be sure that the dose of dexamethasone was likely to have been effective. The dose used was lower than in a trial published by Friedenberg {Am J Hematol 1991; 36: 171-175}.

Dr Richardson, who had been principal investigator in the APEX and SUMMIT trials, explained on behalf of Janssen-Cilag that the dose of dexamethasone used in APEX had been chosen precisely because it was likely to be effective, but not to cause the serious adverse effects seen with the (even) higher dose used by Friedenberg.

Professor Barnett and Dr Richardson both stressed that the dexamethasone treatment used in APEX was a suitable comparator.

Dr Williams suggested that what was intended in paragraph 4.3 of the Final Appraisal Determination was 'some other studies,' not 'other studies.' Professor Barnett accepted that this would make the Appraisal Committee's view clearer.

The Appeal Panel decided that as it stood, the statement appeared to present a negative conclusion without reasoning and at odds with the facts of the appraisal and was therefore unfair. The Panel therefore upheld the appeal on this point.

The Appeal Panel asked that paragraph 4.3 be reworded to make it clear that, while some other studies had used higher doses of dexamethasone, the Appraisal Committee found the dose used in APEX to be entirely appropriate.

2.5 Janssen-Cilag (2.1.5): NICE's approach to the evidence for bortezomib is inconsistent with that followed in other appraisals and is therefore unfair

Professor Barnett agreed that the Appraisal Committee used quality-adjusted life years as the main measure of cost-effectiveness. However, the average value of the cost per quality-adjusted life year was not the only determinant of the Appraisal Committee's decision. If it were, there would be no need for any discussion, and the decision could be made on the numerical value alone.

Professor Barnett also stated that the range of estimates around the average value encompassed different sources of variability in different appraisals. It could, for example, represent the range of results from different trials, or the possible outcomes of mathematical models that examined different ways in which the drug would be used.

Professor Rawlins asked whether the cost of bortezomib treatment was £33 500 per quality-adjusted life year, confining treatment to patients at first relapse, and allowing for cessation of treatment after three cycles if patients failed to respond. Professor Barnett accepted that, while the base-case cost was £38 000 per quality-adjusted life year, the cost was £33 500 under the assumptions suggested by Professor Rawlins.

Professor Barnett agreed that on average bortezomib prolongs life by at least six months.

Professor Barnett assured the Appeal Panel that the Appraisal Committee would not inevitably find a treatment unacceptable if it cost more than £30 000 per quality-adjusted life year. There was no such cut-off value above which a treatment would necessarily be deemed unacceptable.

Professor Barnett listed a number of factors that the Appraisal Committee had considered in this case, in addition to the uncertainty in the estimate of the additional cost per quality-adjusted life year (the incremental cost effectiveness ratio). These included the innovative nature of the treatment, the availability of other treatments for the condition, and the use of the treatment at the end of life. Dr Boysen added that section 4.2 of the Final Appraisal Determination might have been unclear about the nature of the patients considered in the Appraisal.

Professor Barnett declined to speculate what the consensus finding of the Appraisal Committee would have been in the hypothetical case where the treatment in question had cost £28 000 per quality-adjusted life year.

Dr Berhens explained that one factor determining the cost-effectiveness of bortezomib was the ability to stop treatment if it was unsuccessful. She reassured the Panel that in

multiple myeloma there was a marker of tumour activity [paraprotein concentration] that clinical haematologists could use to ensure compliance with a rule that required treatment to cease if bortezomib had proved ineffective after three cycles of chemotherapy.

Professor Barnett explained that the Appraisal Committee had discussed the feasibility of such a rule, and considered the laboratory testing in some detail.

Professor Barnett said that the Appraisal Committee had not considered a scheme in which the company paid for treatments in patients who failed to respond. He stated that this was equivalent to setting a new price for the drug, and that was a matter for the Company and the Department of Health to discuss.

Mr Low expressed the view of the patients' organizations that the value obtained for the cost per quality-adjusted life year in the case of bortezomib was close to what was acceptable, and the Appraisal Committee had heaped uncertainty on uncertainty.

The Appeal Panel noted that the components that contributed to the range of values around the most plausible incremental cost-effectiveness ratio differed in different appraisals. Furthermore the extent to which it is possible to generalise from one technology and disease to another quite different circumstance must be limited, and fairness does not require guidance to go into such detail as to make such detailed comparisons possible. Therefore, as a general rule, the panel felt that it was not reasonable to impose too high an expectation as to substantive consistency across different appraisals.

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However, the Institute has published certain factors that illustrate the sorts of issues that will be considered in a technology where the cost effectiveness is towards the upper end of the range that has been recommended in the past. In some appraisals,, consideration of the particular features of the disease and technology in question, informed by truly relevant past appraisals, might reasonably lead a consultee to suppose that those published factors would support a recommendation to use. In such a case, fairness would require the committee to explain why, notwithstanding the

published factors, it was not recommending use. The panel felt that this was the case here.

This explanation need not take any particular form (or indeed necessarily be included in the guidance itself), or expressly deal with all of the factors listed in the Institute's guide to the methods of technology appraisal, or be limited only to those factors. But where consultees might, viewed objectively, reasonably have been expecting a positive recommendation (in the light of the overall findings on clinical and cost effectiveness in the Appraisal Consultation Document/Final Appraisal Determination and relevant past practice,) an explanation for a negative recommendation is required. The Appeal Panel concluded that the special circumstances considered in deciding whether to accept a cost per quality-adjusted life year above £20 000 had not been made sufficiently clear on this occasion, and that this was not fair.

The Appeal Panel therefore upheld the appeal on this point.

2.6 Janssen-Cilag (2.1.6) The Appraisal Committee's failure to take into account cost effectiveness of bortezomib, by reference to the cost per life year gained, is unfair

Professor Barnett stated that the Committee had considered life-years gained, but did not accept that this was the most relevant measure. The Committee had heard evidence from patient representatives who stated that quality of life was important. Dr Richardson agreed with this view; although Dr Price thought that it was difficult to capture quality of life in myeloma patients. Mr Ross-Goobey, for Myeloma UK, Cancerbackup and Leukaemia CARE, also agreed with the importance of quality of life to patients.

Dr Longson explained that there were standard methods, described in paragraph 6.2.6.12 of the Guide to Methods of Technology Appraisal, that allowed translation from life-years gained to quality-adjusted life years. The cost of a quality-adjusted life year always exceeded the cost of a life-year gained.

Professor Sculpher commented that quality-adjusted life years do reflect differences in survival, which is what is measured by life-years gained, but also allow for the fact that survivors may not be 100% fit. Quality-adjusted life years allow comparisons to be made between treatments that are life saving and others that improve quality of life without extending it.

Dr Williams raised a concern that in assessing the cost of bortezomib, the Appraisal Committee might have been prejudiced by the fact that the economic submission was made by the company. In multiple technology appraisals, an independent research group constructs the economic model. Professor Barnett stated that the Appraisal Committee reviewed evidence critically whether it came from the company or from an independent source, and refuted any suggestion of bias in assessing the economic model merely because it had been developed by the manufacturer.

The Appeal Panel understood that patients valued quality of life. They accepted that the Appraisal Committee had considered whether life-years gained should be preferred to quality-adjusted life years, but had properly reached the view that they should not.

The Appeal Panel therefore dismissed the appeal on this point.

2.7 Janssen-Cilag (2.1.7): The Appraisal Committee's approach to licence status is inconsistent

Professor Barnett accepted that thalidomide is recommended for treatment of multiple myeloma in the guidelines of the British Society for Haematology, and is licensed for use in multiple myeloma in other countries but has no marketing authorization for any indication in the United Kingdom. He made it clear that the Appraisal Committee had not used thalidomide as a comparator, and had not been influenced by the cost of thalidomide when assessing the value of bortezomib.

The Appeal Panel noted that bortezomib + dexamethasone was widely used in the United Kingdom, that bortezomib held a marketing authorization for use in multiple myeloma, and that the marketing authorization provided for use in monotherapy.

The Appeal Panel therefore dismissed the appeal on this point..

3. Ground 2: NICE has prepared guidance that is perverse in the light of the evidence submitted

3.1 Janssen-Cilag (2.1.3) No explanation is provided for the conclusion that prior treatment with corticosteroids may have influenced the response of patients in the APEX trial to high-dose dexamethasone

Professor Barnett explained why the Appraisal Committee had considered that prior treatment with corticosteroids might have influenced the response of patients in the APEX trial to high dose dexamethasone. He stated that the Committee were aware of the phenomenon of pharmacological tachyphylaxis, in which repeated doses of a drug elicit a diminishing response.

Dr Richardson explained that APEX was a large multi-centred trial, and it had been set up with the intention of recruiting only patients who would be expected to respond to dexamethasone. A few patients in whom previous dexamethasone treatment had failed had in fact entered the trial. To allow for this, a sensitivity analysis was undertaken showing that the exclusion of patients shown previously to be resistant to dexamethasone made no difference to the overall conclusion.

Professor Barnett agreed that it was right to exclude patients whose multiple myeloma was resistant to the corticosteroid drug dexamethasone, and pointed out the theoretical possibility that prior treatment with other corticosteroids might also attenuate the response to dexamethasone. This did not diminish from the Appraisal Committee's overall verdict that bortezomib prolongs survival in multiple myeloma.

The Appeal Panel accepted that the Appraisal Committee had been reasonable to consider the possibility that the response to dexamethasone might be altered in patients who had previously received other corticosteroids. The Appeal Panel was concerned, however, about the statement in paragraph 4.3 of the Final Appraisal Determination that 'the fact that 98% of patients in the APEX trial had received prior

treatment with corticosteroids, might have influenced the disease response to dexamethasone'. This could be interpreted as an unreasonable criticism of the trial.

The Appeal Panel upheld the appeal on this point. The panel was concerned that the wording of para 4.3 of the Final Appraisal Determination suggested that the committee had perversely considered the results of the trial to have over-estimated the effects of bortezomib.

3.2 Janssen-Cilag (2.1.4): NICE has not explained how it has considered the relevant additional factors provided in its procedures for cases where the cost per quality adjusted life year exceeds £20,000

Professor Barnett stated that the Appraisal Committee had considered all the relevant factors. One of these was the uncertainties in the estimate of the incremental cost-effectiveness ratio. The Appraisal Committee had been concerned that, as a result of patients crossing-over from dexamethasone to bortezomib, the APEX trial might underestimate the efficacy of bortezomib. The company had used a mathematical model to allow for this underestimate, and the Appraisal Committee had examined the results from the model and accepted them.

There were also, Professor Barnett explained, uncertainties in establishing the efficacy of dexamethasone, and the Appraisal Committee had considered observational data from the Mayo Clinic study {Mayo Clin Proc. 1975; 50: 29-40} that allowed an estimate of this

Other uncertainties had previously been discussed. Professor Barnett said that the Appraisal Committee was concerned, in discussing the scheme where treatment was stopped in patients who failed to respond to bortezomib after three cycles, that some patients would be denied treatment. About 15% of all those who would have responded to a full course of treatment would not have responded after three cycles. Professor Barnett also explained that the Appraisal Committee was obliged to state the reasons for recommending treatments that cost more than £20 000 per quality-adjusted life year, but was not obliged to state reasons if such treatments were not

recommended. As noted under ground one above, the appeal panel did not agree with this as an absolute rule. Under some circumstances, which applied in this case, fairness required that reasons should be given.

With one exception the reasons given by the committee at the appeal hearing seemed reasonable and the overall recommendation was not perverse (although this is without prejudice to the finding above that it was unfair not to state reasons in or alongside the Appraisal Consultation Document/Final Appraisal Determination). However, the Appeal Panel considered the position of the Appraisal Committee with regard to the stopping rule that might allow 85% of all those who could benefit from bortezomib to do so in a manner that was cost-effective. The Appraisal Committee had seemingly declined to recommend the adoption of treatment under this rule because 15% of patients who might benefit would not do so. The Appeal Panel found that this position was perverse.

The Appeal Panel therefore upheld the appeal on this point and considered the Appraisal Committee's reason for rejecting the stopping rule was perverse.

3.3 Janssen-Cilag (2.2.1) The effect of NICE's proposed recommendations, which is to limit NHS treatment for multiple myeloma to products which are untested and unlicensed for this indication, is perverse

Dr Price stated that bortezomib was licensed treatment for multiple myeloma, and had been subject to a large randomised controlled trial. Alternative treatments are untested and of unknown clinical effectiveness.

The Appeal Panel noted that the Appraisal Committee had undertaken the task it had been set by the Department of Health, and appraised the relevant information on bortezomib. There also appeared to be an inconsistency in the appellant's position and evidence, in that the appellant suggested that the correct use of bortezomib to have assessed was in combination therapy, which was an unlicensed use in the UK. If so, it could hardly be said to be perverse to issue recommendations with the effect claimed, since that is presumably what the appellant will be hoping to persuade the Institute to do when the appraisal is re-scoped.

The Appeal Panel dismissed the appeal on this point.

3.4 Royal College of Pathologists, British Society for Haematology, and UK Myeloma Forum (jointly). It is perverse to have failed to consider the increased efficacy of the combination of bortezomib and dexamethasone in its cost-effectiveness calculations

Professor Barnett said that the Appraisal Committee had examined data, though possibly not all available data, on the combination of bortezomib + dexamethasone. He reiterated that high dose dexamethasone works, and was a suitable comparator. Furthermore, the combination of bortezomib + dexamethasone had been used in the SUMMIT and CREST trials in patients who had already received bortezomib alone.

Dr Cavenagh explained that in the SUMMIT and CREST trials dexamethasone had been added if bortezomib had failed. There was a wealth of evidence that the combination was effective. He accepted that this did not come from randomised controlled trials, and that randomised controlled trials were the best evidence. He also agreed that the combination warranted further study. A French trial of bortezomib + dexamethasone in patients with previously untreated multiple myeloma had given promising results, but had not yet been published as a scientific paper. Dr Richardson confirmed that there was no evidence from randomised controlled trials of the effectiveness of bortezomib + dexamethasone in comparison to bortezomib alone.

The Appeal Panel accepted that the Appraisal Committee had examined the available evidence for the combination of bortezomib + dexamethasone, and had not reached a perverse decision within the remit of the appraisal as conducted. The appeal on this point was therefore dismissed.

The Appeal Panel noted, however, its finding under Ground 1 that the interim arrangements had in this case resulted in unfairness; and the finding under this heading is without prejudice to the need to reconsider with an open mind whether or not combination therapy should be appraised.

3.5 Myeloma UK, Cancerbackup and Leukaemia CARE (2.1) The Final Appraisal Determination has given undue weight to cost effectiveness in contradiction to paragraph 6.2.6.4 of the 'Guide to the Methods of Technology Appraisal'

Dr Mehta, for Myeloma UK, Cancerbackup and Leukaemia CARE (jointly), stated that cost-effectiveness was not the only consideration, and that the Appraisal Committee should have taken into account access to treatment and equity in treatment.

Sir Michael Rawlins explained that the Appraisal Committee was obliged to consider cost-effectiveness.

The Appeal Panel was satisfied that the Appraisal Committee had a duty to examine cost-effectiveness, and had done so appropriately and without giving it unreasonable weight. The Appeal Panel therefore dismissed the appeal on this point.

3.6 Myeloma UK, Cancerbackup and Leukaemia CARE (2.2) 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

Dr Mehta also stated that the Appraisal Committee should have considered the extent to which APEX exaggerated the cost of bortezomib because of cross-over from the dexamethasone to bortezomib.

The Appeal Panel decided that this point had been adequately answered in the previous discussion (see paragraph 3.2). The Appraisal Committee had attempted to make allowances for the effects of cross-over.

The Appeal Panel therefore dismissed the appeal on this point.

3.7 Myeloma UK, Cancerbackup and Leukaemia CARE (2.3) The fact that the Rule of Rescue was not applied to this treatment is perverse

Mr Low accepted that the Rule of Rescue was a difficult concept. However, if the Appraisal Committee's determination is put into practice, patients will die earlier; they will be treated with drugs whose efficacy is not established; and future medical developments may be inhibited.

Mrs de Winter, for Myeloma UK, Cancerbackup and Leukaemia CARE, explained that the marginal cost of her receiving bortezomib was £3 500, the difference between the figure of £30 000 per quality-adjusted life year and the likely additional cost of bortezomib. She asked what patients denied bortezomib were recommended to do.

Mr Ross-Goobey explained that even though new drugs such as bortezomib did not represent a cure for multiple myeloma, advances in treatment were rapid. A treatment such as bortezomib that prolonged life provided a 'bridge' to carry patients along to the next advance. Without this, patients would die before the next advance was made.

The Appeal Panel understood the anxieties of patients, and the desire to provide them with the opportunity to benefit from promising new treatments. However, the Rule of Rescue was not an accepted part of the Institute's policy, and the Appraisal Committee could not be perverse in failing to apply it.

The Appeal Panel therefore dismissed the appeal on this point.

4. Ground 3: The Institute has exceeded its legal powers.

None of the Appellants wished to pursue an appeal point under this ground.

5. Conclusion and effect of the Appeal Panel's decision

The Appeal Panel has upheld the appeal under ground one by Janssen-Cilag (point 2.1.1), Royal College of Pathologists and others, and Myeloma UK and others, to the extent that the operation of the interim procedure was on this occasion unfair. It also upheld the appeal by Janssen-Cilag point 2.1.2, 2.1.5, and 2.1.7 with regard to bortezomib + dexamethasone.

The Panel upheld the appeal under ground two by Janssen-Cilag point 2.1.3, with regard to the effect of prior treatment with dexamethasone, and 2.1.4 with regard to the Committee's assessment of a rule to stop treatment in patients who had not responded after the third cycle of bortezomib treatment.

The Appeal Panel's decision is that the guidance must be remitted back to the appraisal committee for further consideration. In carrying out that further consideration, consultees must be given the opportunity to argue that combination therapy should be assessed, regardless of the fact that this is an unlicensed use in the UK.

The appeal panel suggests that the Appraisal Committee reassess the evidence for the cost-effectiveness of bortezomib in the following circumstances:

1) when used only for patients after first relapse;
2) when used only for patients after first relapse, and when treatment ceases after three cycles if patients fail to respond;
3) when used only for patients after first relapse, and when treatment ceases after three cycles if patients fail to respond, and when the company pays for treatment in patients who fail to respond; and
4) when used only for patients after first relapse, and when treatment ceases after three cycles if patients fail to respond, and when the company pays for treatment in patients who fail to respond, and where bortezumib is used in combination with dexamethasone.,

Additionally, the Appeal Panel has requested:

1) paragraph 4.3 be reworded to make it clear that, while some other studies had used higher doses of dexamethasone, the Appraisal Committee found the dose used in APEX to be entirely appropriate;

2) paragraph 4.3 of the Final Appraisal Determination be reworded to avoid any misinterpretation of the statement regarding prior treatment with corticosteroids;

3) the Appraisal Committee, if it should decline to recommend bortezomib treatment for use in the NHS, must explain more fully its reasons for failing to recommend such treatment with the first of a new class of agents that Committee accepted would prolong, significantly, the life of patients with an incurable disease; and whose incremental cost effectiveness ratios were within the same ranges as the cost of some treatments it had previously considered to be an effective use of NHS resources.. The factors listed above give guidance as to the issues which should be addressed when considering this.

There is no possibility of further appeal within the Institute against this decision of the Appeal Panel. However, the decision of the Appeal Panel and the Institute's decision to issue the Guidance may be challenged by an interested party through an application to the High Court for permission to apply for judicial review. Any such application must be made promptly and in any event within three months of this Decision or the issuing of the Guidance.