

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE
Health Technology Appraisal
Appeal Hearing

Advice on bortezomib and thalidomide for the first-line treatment of multiple myeloma

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 15th November 2010 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the use of bortezomib and thalidomide for the first-line treatment of multiple myeloma.
2. The Appeal Panel consisted of Dr Peter Brock (industry representative), Mrs Gill Donovan (lay representative), Professor Robin Ferner (NHS representative), Dr Margaret Helliwell (vice-chair of the Institute), and Mr Jonathan Tross (non executive of the Institute and chair of the Panel).
3. None of the members of the Appeal Panel had any competing interest to declare.
4. The Panel considered appeals submitted by Janssen-Cilag Limited ("the Company"/"Appellant").
5. The Company was represented by Dr Jamie Cavanagh (consultant haematologist), Ms Sabine Gaugris (health economist), Mr Rod Murphy (medical lead), Mr Mike Spencer (health economist), and Dr Adela Williams (legal representative).
6. In addition, the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel: Mr Meindert Boysen (Programme Director at the Institute), Dr Sally Doss (technical lead),

Dr Nicola Hay (technical advisor), Miss Carina Righetti (technical lead), Professor Andrew Stevens (chair of the Appraisal Committee), and Dr Frances Sutcliffe (Associate Director).

7. The Institute's legal advisor (Stephen Hocking, Beachcroft LLP) was also present.
8. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal.
9. There are three grounds on which an appeal can be lodged:
 - The Institute has failed to act fairly;
 - The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted;
 - The Institute has exceeded its legal powers.
10. The Chair of the Appeals Committee (Dr Maggie Helliwell), in preliminary correspondence, had confirmed that the appellant Janssen-Cilag Ltd had potentially valid grounds of appeal as follows: Grounds 1 and 2.
11. Bortezomib is an anticancer drug that causes apoptosis (cell death) in tumours, and inhibits tumour growth. This effect is seen in patients with the malignant bone marrow disorder called multiple myeloma. Bortezomib has to be given by injection. An alternative treatment for multiple myeloma is the drug thalidomide, which can be given orally.
12. The appraisal that is the subject of the current appeal provided advice to the NHS on the use of thalidomide and bortezomib in first line treatment for multiple myeloma.

13. Before the Appeal Panel inquired into the detailed complaints, Mr Murphy for Janssen-Cilag Ltd and Professor Stevens for the Appraisal Committee made preliminary statements.

Appeal by Janssen-Cilag Ltd Appeal Ground 1: The Institute has failed to act fairly

Appeal Ground 1.1: NICE's failure to disclose to consultees the economic model upon which its guidance is based, lacks transparency and is unfair

14. Dr Williams, for Janssen-Cilag Ltd, stated that fairness required disclosure of the economic model in an executable form. The requirement for this had been clearly established in previous judicial reviews. In this instance the model had been withheld on the basis that it included academic-in-confidence material that the Appellant supposed to come from the Medical Research Council (MRC) Multiple Myeloma IX trial. Further the reported incremental cost-effectiveness ratios (ratios of costs to benefits) were not broken down into costs and benefits. In consequence, there was unfairness.

15. Mr Boysen, for the Institute, said that it had learnt lessons from the judicial reviews regarding disclosure. On this occasion, there were 41 pages of e-mail correspondence within the Institute and between the Institute and the MRC Clinical Trials Unit about the status of the confidential material.

16. Mr Boysen regretted that the Institute had failed to keep consultees informed of the negotiations with the MRC Clinical Trials Unit, and considered that while there was not an obligation to do so, it would be desirable to do so in future.

17. Dr Sutcliffe, for the Institute, explained that this very large, very interesting trial would soon be published. It had been expected that the data should have been published in the first half of the year but was successively delayed beyond the publication of the Appraisal Consultation Document, the Final Appraisal Determination, and the Appeal. The Institute had repeatedly contacted the MRC Clinical Trials Unit about release of data. She counted

twenty five interactions between the Institute and the MRC Clinical Trials Unit regarding this. There had been discussion of providing a possible reduced model that did not contain the MRC data, but the Assessment Group had advised that this would not be helpful.

18. Professor Stevens, for the Institute, highlighted the importance of including data from the MRC trial, which was a large trial of treatments currently used in the United Kingdom. He stated that the Appraisal Committee had used the outputs from the Assessment Group's processes, and were also able to compare these with the two companies' models.
19. Mr Boysen offered to make available 41 pages of documents listing the e-mail exchanges suitably redacted. The Chair of the Panel proposed that the information be provided both to the Panel and the Appellant. He proposed giving them four days to comment on the documents, and the Panel would then consider the documents and the comments in reaching its conclusion.
20. Dr Williams accepted that it was reasonable to proceed on this basis.
21. The redacted documents were provided to the Appeal Panel and to the Appellant after the hearing and a written submission on them was received from the Appellants. The Appeal Panel considered the documents and the comments of the Appellants.
22. The Appeal Panel concluded as follows. The requirements imposed on the Institute when it receives an economic model containing confidential information are clear, and were not in dispute. For the purposes of this appeal the Appeal Panel felt it sufficient simply to quote the more relevant passages of the *Servier* judgement.

NICE is always under a duty and imperative of transparency and fairness which normally requires full disclosure of its fully executable economic model and the data upon which it is based. It should not, therefore, normally give (or permit its assessment groups to give) undertakings as to confidentiality. Exceptionally, it may do so if the

importance of the material to the quality and robustness of the appraisal is sufficiently great; and if it has tried sufficiently hard to obtain permission to disclose, but has failed. Further, the ambit of any confidentiality undertaking should be as restricted as possible.
[Paragraph 115]

Even after a confidentiality undertaking has been justifiably given, NICE remains under a positive duty, at appropriate stages in the process, to take all reasonable steps to obtain permission to disclose the information. In deciding what are reasonable steps it must keep firmly in mind the high importance of fairness and transparency, and the importance of the respective information to understanding the appraisal. Having regard to the decision of the Court of Appeal in Eisai v NICE, it must particularly strive to seek permission to disclose the economic model and /or the data contained therein. [Paragraph 123]

23. The Committee had explained the relevance and significance of the confidential data in this case, and the Panel found that “*the importance of the material to the quality and robustness of the appraisal is sufficiently great;*” so that it was reasonable initially to accept the data in confidence.

24. However, there remained the duty to take reasonable steps to secure permission to release the information thereafter. The Appeal Panel reviewed the email traffic and was not satisfied that all reasonable steps had been taken. Although the necessary steps must be a question for the Committee's judgement in each appraisal, at least initially, the Panel was not persuaded that the Institute had clearly explained to the MRC Clinical Trials Unit the strong reasons for disclosing the data. Nor did the emails show that the Institute had suggested possible alternatives to full disclosure to every consultee; for example, limited disclosure to a "confidentiality club". Again the Panel considered it was necessary to make this suggestion, or at the least to invite dialogue. (For the avoidance of doubt, the Appeal Panel considered that not every proposal for limited disclosure need be agreed to. Some may themselves be unfair, or unduly onerous, or add little to transparency. But the issue must be raised, where necessary with all interested parties.) Furthermore, the Appeal Panel found no evidence that the data owner had been made aware that consultees were themselves bound by obligations of confidentiality. What dialogue there was appeared to deal mainly with the

anticipated timeline for the lifting of the obligation of confidentiality generally. While this is clearly a relevant issue, the Appeal Panel considered that it could not be sufficient to discharge the duty imposed by *Servier*.

25. The Panel had regard to the written submissions from the Appellant, which were consistent with its own conclusion.

26. In consequence, the Appeal Panel concluded that the Appellant was deprived of the opportunity to view the full economic model without the necessary steps having been taken to try to secure its disclosure, and that this was unfair.

27. The Appeal Panel therefore upheld the appeal on this point.

Appeal Ground 1.2: The Appraisal Committee's reasons for limiting use of bortezomib to patients who have contraindications to thalidomide, rather than those for whom thalidomide is clinically inappropriate are unexplained.

28. Mr Murphy, for Janssen-Cilag Limited, stated that the current wording in the Final Appraisal Determination was very restrictive, limiting the first-line use of bortezomib to patients who had been treated with thalidomide and were intolerant of it, or patients who had contra-indications to thalidomide. This was on the basis of clinical opinion, but the only clinical opinion the Company had seen was in favour of replacing the term 'contra-indications to thalidomide' with the term 'in whom thalidomide was clinically inappropriate.'

29. Professor Stevens explained that the Appraisal Committee had explicitly discussed whether the NHS should permit the use of bortezomib when the patient had a 'sub-contra-indication,' that is, a condition that the Summary of Product Characteristics did not regard as an absolute bar to prescription of thalidomide. For these conditions, the Summary of Product Characteristics states, essentially, 'use and monitor.' When discussing whether the rules should be more relaxed, the Appraisal Committee was conscious of the very large difference in incremental costs between thalidomide and bortezomib when compared to MP, which was of the order of £24,500. Professor Stevens

reminded the Appeal Panel that bortezomib has already been approved for second-line therapy in patients with multiple myeloma.

30. Dr Jamie Cavanagh, for Janssen-Cilag Ltd, put forward the view that a significant history of thrombo-embolism would currently be taken as a reason for prescribing bortezomib rather than thalidomide.
31. Professor Stevens reiterated that such use was not cost-effective. Paragraph 4.3.3 of the Final Appraisal Determination contained the phrase 'contra-indications (e.g. clotting disorders).' Clotting disorders were not listed as a contra-indication to thalidomide in the Summary of Product Characteristics, but that paragraph recorded what the Committee had been told by the clinical experts.
32. Dr Williams explained that this was not clear from the Final Appraisal Determination.
33. Mr Murphy insisted that he had been present at a meeting where the wording was discussed, and had heard no advice to the Appraisal Committee to use the current wording.
34. Professor Stevens stated again that the Appraisal Committee were clear that bortezomib was not cost-effective when compared with thalidomide.
35. The Appeal Panel considered whether there had been any unfairness in the Appraisal Committee's assessment of the restriction of bortezomib. The Committee's discussions had clearly been informed by expert opinion and by considerations of costs and benefits. The essential reason to prefer thalidomide to bortezomib, in a patient able in principle to take either, was cost effectiveness. That reason was clearly given in the guidance. The appeal point as formulated therefore had to fail, as the reason for restricting use of bortezomib was clear. In identifying those patients for whom thalidomide should not be tried at all, it was clear that the Committee meant something more precise than the term 'clinically inappropriate' suggested by

consultees, and again, the reason was the desire to limit cost ineffective use of resources. The Appeal Panel therefore dismissed the appeal on the grounds of unfairness.

36. However, the Appeal Panel noted that the wording in the Final Appraisal Determination might be confusing, because "contra-indication" was sometimes used in its technical sense, for example in paragraphs 1.2 and 4.3.11; and sometimes in a looser sense, for example, in paragraph 4.3.3. It would be helpful if the Appraisal Committee, in conjunction with the Guidance Executive, could find a form of words that removed this confusion.

Appeal Ground 1. 3: In deciding to place less weight on thalidomide studies which included a maintenance phase, the appraisal committee relied on evidence from the assessment group which has not been disclosed to consultees

37. Mr Spencer, for Janssen-Cilag Ltd, identified that six studies of regimens including thalidomide in the treatment of multiple myeloma existed, but the Appraisal Committee had used data from only two of these studies in assessing overall survival. Four studies, accounting for three-quarters of all trial patients, had been left out of the analysis. The Appraisal Committee had been informed that the difference in apparent overall survival between the included and excluded studies was the result of harm occurring during the extended maintenance phase in the excluded trials. The Company's view was that this explanation was wrong, but it was still mentioned in the Final Appraisal Determination.

38. Dr Sutcliffe, for the Appraisal Committee, confirmed that Janssen-Cilag Ltd was present during the relevant discussions, saw the relevant documents, and were party to the discussions.

39. Mr Spencer accepted that the Company had been able to put forward its views prior to the publication of the Appraisal Consultation Document, and in response to the Appraisal Consultation Document. He agreed that the Final Appraisal Determination explicitly acknowledged at paragraph 4.3.10 that 'The

Committee heard a strong case from the manufacturer of bortezomib that the maintenance studies should be included in the economic analysis...'

40. Dr Williams contended that the Company had not had the opportunity to consider views in opposition to the inclusion of maintenance treatment which appeared to have been conveyed in private during the second meeting of the Appraisal Committee.

41. The Appeal Panel considered the submissions from Janssen-Cilag Ltd and the Appraisal Committee. It was evident that the Appraisal Committee had heard and considered the views on maintenance treatment, and that the Company had had ample opportunity to make informed comment at the time of the Appraisal Consultation Document, and had done so. The Company's comments had not persuaded the Committee but there was no unfairness.

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

Appeal Ground 2: The Institute has formulated guidance which cannot reasonably be justified in the light of the evidence submitted

Appeal Ground 2.1: The exclusion of critical evidence from thalidomide trials has resulted in a fundamentally flawed evidence synthesis that is not a sound basis for decision-making

43. Ms Gaugris, for Janssen-Cilag Limited, reiterated that there were six studies of regimens of thalidomide with alkylating agent and a corticosteroid, but the Appraisal Committee had ignored four of them, which contributed three-quarters of the patients.

44. Professor Stevens suggested that there might be confusion between the work of the Appraisal Committee and of the Assessment Group. The Appraisal Committee's decisions depended on expert advice, the manufacturers' submissions, the assessment report, and the views of the members of the Committee. There were two opposing views on maintenance regimens, which were part of the design of all four excluded studies. If the studies with

maintenance regimens were included at full value, the cost of bortezomib per quality-adjusted life year was of the order of £20,000, and if they were entirely excluded, as in the Assessment Group's work, then the cost was of the order of £320,000. The Committee's view was that the most plausible position lay between the two extremes. The Appraisal Committee considered that the approach of the company in effect loaded the higher costs of bortezomib used as a second-line agent onto the cost of thalidomide used first line. The Committee formed the view that, even allowing that every assumption made by Janssen-Cilag Ltd was correct, (which was not the Committee's eventual position) there was still no reason to prefer bortezomib to thalidomide.

45. Mr Spencer accepted that the Company had had to make a series of assumptions in interpreting data from maintenance trials, because details were unavailable. He also accepted that the absolute cost of bortezomib added to an alkylating agent and a corticosteroid was higher than the equivalent cost of thalidomide.
46. The Appeal Panel discussed the proposition that the evidence synthesis relied on by the Appraisal Committee was fundamentally flawed. They noted that the Committee had considered variants on the modelling, including one incorporating maintenance data. The Panel decided that the Appraisal Committee had acted reasonably in declining to accept unreservedly the synthesis proposed by the Company.
47. The Appeal Panel therefore dismissed the appeal on this ground.

Appeal Ground 2.2: The Appraisal Committee have demonstrated a lack of consistency in considering clinical experts' opinion to inform its decision

48. Mr Murphy described how the Appraisal Committee had accepted the view of clinical experts with regard to the equivalence of the two regimens CTDa (cyclophosphamide, thalidomide and attenuated dexamethasone) and MPT (melphalan, prednisolone and thalidomide). The Appraisal Committee had not, however, accepted the view of clinical experts with regard to those

patients who should receive bortezomib in preference to thalidomide. This was unreasonable.

49. Professor Stevens did not see that the Appraisal Committee should take a uniform approach to expert advice in two different matters. One dealt with the probable equivalence of two chemotherapy regimens, and the second dealt with the entirely different question of whether the contra-indications listed in the Summary of Product Characteristics for thalidomide should be used as a basis for deciding which patients should be eligible to receive bortezomib. The Appraisal Committee had, in that instance, to take into account both the clinical advice and the data on cost-effectiveness that demonstrated that bortezomib was much more expensive than thalidomide.

50. Mr Murphy accepted that the Appraisal Committee need not accept all clinical advice proffered. However, in the absence of clinical data from a direct comparison of bortezomib and thalidomide, the Appraisal Committee should have considered the clinical advice it received.

51. The Appeal Panel viewed as self-evident Professor Stevens's assertion that the Appraisal Committee need not give equal weight to all clinical expert advice it received. The Appraisal Committee had been reasonable in making separate decisions that one piece of advice was valuable when assessing the therapeutic equivalence of CTDA and MPT; and that another was less helpful in deciding whether bortezomib should be limited by prior adverse effects.

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

Appeal Ground 2.4: Failure to consider vial sharing of bortezomib is inconsistent with the available evidence and with the approach followed in other appraisals

53. Ms Gaugris described how vial sharing had been considered in other appraisals, but had not been considered in this appraisal. This was unreasonable.

54. Professor Stevens noted that vial sharing differed from vial minimization. Janssen-Cilag Ltd had not suggested vial sharing when they made their submission. The submission relied on the results of the VISTA trial. [San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *New England Journal of Medicine* 2008;359:906-17.] The protocol for that trial specified 52 vials of bortezomib per patient, but in practice, dose reduction and delayed administration of doses resulted in an average dosage of 31.5 vials per patient.
55. Mr Murphy accepted that bortezomib was unstable once opened, and vials were packed under nitrogen. Vial sharing did, however, take place.
56. Dr Cavanagh confirmed that in his Trust vial sharing did take place.
57. The Appeal Panel found the reference to other appraisals unhelpful. The possibility and extent of vial sharing depended on the characteristics of the product, its indications, and the arrangements made for treating patients. A relatively stable product available only in large vials for a relatively common condition treated at large treatment centres lent itself to vial sharing. An unstable product available in small vials and used for rarer conditions in small centres did not lend itself to vial sharing. The importance of vial sharing would therefore differ from one appraisal to another.
58. The Appeal Panel noted that the Summary of Product Characteristics for Velcade™ bortezomib stated expressly that ‘The reconstituted solution should be used immediately after preparation. If the reconstituted solution is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user...’ The Appeal Panel also accepted that the dosage of bortezomib envisaged in the protocol for the VISTA trial was substantially higher than the dosage used as a basis for the Appraisal Committee’s decision. There had been some initial confusion as to whether this was because of vial sharing, but it had been clarified that this was not the case. The protocol for the VISTA trial explicitly excluded vial-sharing. There was no

evidence that vial sharing, if it occurred at all, could reduce usage below the 31 vials which had been used in sensitivity testing of the model. The Appraisal Committee had not been unreasonable in not considering this issue further.

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

Conclusion and effect of the Appeal Panel's decision

60. The Appeal Panel therefore upholds the appeal on the ground that insufficient efforts were made to obtain permission to release the executable model to consultees. The appeal is dismissed on all other grounds.

61. The appraisal is remitted to the Appraisal Committee, which must now take all reasonable steps to explore the possibility of releasing the model to consultees. If this remains impossible it should re-consider whether there is any information relating to the economic model, not yet released, which can be released and which might allow consultees a materially fuller understanding of the modelling in this appraisal. (The Appeal Panel notes that the Committee has discussed this issue with the Assessment Group, but advises the Committee to reconsider the issue, and if it remains of the view that this is not possible, to have a robust justification.)

62. If it is possible either to release the model or to release additional information, this must be done and consultees must be given a chance to comment on it before guidance is finalised. If the Committee is satisfied having made all reasonable efforts that it is not possible to release the model or any further information, it may notify the Appellant of that fact, and pass the guidance as it currently stands to the Guidance Executive for publication, subject to consideration of the Panel's observations at appeal point 1.2 above.

63. There is no possibility of further appeal against the decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.