NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final Appraisal Determination

Bortezomib monotherapy for relapsed multiple myeloma

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

1.1 Bortezomib monotherapy is not recommended for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation.

1.2 People currently receiving bortezomib monotherapy should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 The technology

2.1 Bortezomib (Velcade, Janssen-Cilag Ltd) is an anticancer drug that belongs to a novel class of drugs known as proteasome inhibitors. Bortezomib has a UK marketing authorisation as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation. For further information about the drug, see the summary of product characteristics (SPC).

2.2 Bortezomib treatment is associated with peripheral neuropathy, thromobocytopenia and other side effects. For full details of side effects and contraindications, see the SPC.

2.3 The price of bortezomib is £762.38 for a 3.5-mg vial (excluding VAT; 'British national formulary', 51st edition). The cost per patient for a course of three cycles of treatment would be approximately £9000, and for eight cycles would be approximately £25,000. Costs may vary in different settings because of negotiated procurement discounts.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of bortezomib and a review of this submission by the evidence review group (ERG) (appendix B).

3.1 The manufacturer's submission approached the decision problem by comparing the clinical effectiveness of bortezomib with that of high-dose dexamethasone (HDD) based on the results of the APEX (Assessment of Proteasome Inhibition for Extending Remissions) randomised controlled trial (RCT). The population considered was people with multiple myeloma at first or subsequent relapse; however, the manufacturer's submission placed emphasis on patients at first relapse. The manufacturer considered HDD to be the most appropriate comparator because it is an effective monotherapy agent for the treatment of relapsed multiple myeloma that is commonly used in clinical practice in the UK, and its use at first relapse is within its licensed indications. In addition, HDD was the comparator agreed as the basis for regulatory approval of the APEX RCT.

3.2 In an interim analysis of the APEX trial (median follow-up of 8.3 months), it was found that people taking bortezomib had a significantly longer median time to disease progression compared

with people receiving HDD (6.2 months compared with 3.5 months, hazard ratio 0.55, 95% confidence interval 0.44 to 0.69; $p < 0.001$); significantly improved overall survival (hazard ratio 0.57, 95% confidence interval 0.40 to 0.81; $p = 0.001$); and a significantly higher overall (complete or partial) response rate (38% compared with 18%, $p < 0.001$). Following the predetermined interim analysis, 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. Updated analyses were performed at 15.8 months and 22 months of follow-up.

3.3 The manufacturer's submission provided cost-effectiveness evidence using a state-transition model described as 'semi-Markov' to compare bortezomib with HDD. The manufacturer did not include other comparators in the model because it contended that there is currently no UK consensus on best practice for the treatment of multiple myeloma at first relapse, because there are no other treatments available that hold a UK marketing authorisation for use at first relapse and because of limitations in the available evidence. Because a high percentage of patients in the HDD arm of the APEX RCT crossed over to receive bortezomib, the manufacturer argued that the true difference in overall survival between the bortezomib and HDD arms was greater than in the reported results. Data from the Mayo Observational Study of patients receiving a dexamethasone-containing regimen were therefore used in addition to data from the APEX RCT in the manufacturer's model. The base-case included people at first relapse only, resulting in a point estimate of the incremental cost-effectiveness ratio (ICER) of £31,000 per life year gained. One-way sensitivity analyses of the key parameters identified in the manufacturer's model resulted in a range of ICERs from £28,000 to £31,000 per life year gained and showed that the duration of treatment effect was the most influential parameter. Three scenario analyses were presented that

focused on a stopping rule for patients whose disease had not responded to treatment, the proportion of patients entering the model at first and second or subsequent relapse, and bortezomib in combination with HDD, resulting in ICERs ranging from £28,000 to £40,000 per life year gained.

3.4 In an additional analysis produced in response to questions raised in the evidence-review phase, the base-case cost per life year gained of £31,000 was estimated to translate to £38,000 per quality-adjusted life year (QALY). However, the manufacturer requested that due consideration be given to the assertion that it is more appropriate to measure cost effectiveness in terms of cost per life year gained in patients with multiple myeloma. The manufacturer argued that survival gain is the single most important outcome for people with relapsed multiple myeloma, that there is a lack of robust utility data to compute QALYs for people with relapsed multiple myeloma and that the EuroQoL-5D is not sensitive to some important facets of multiple myeloma.

3.5 The ERG raised a number of key issues concerning the manufacturer's submission.

- Concerns were raised over the generalisability to clinical practice in the NHS in England and Wales of the data, including data from the Mayo Observational Study, that were used to inform inputs into the economic model.
- The model submitted by the manufacturer may have overestimated the treatment effect shown in the APEX RCT.
- Adverse effects were not included in the economic model, in terms of either reduction in quality of life or increased resource use.
- The ERG's review of sensitivity analyses indicated a greater variability in cost-effectiveness estimates than was presented in the manufacturer's submission. The ERG found that the most

influential parameters were the hazard ratio for time to disease progression and the cost of bortezomib.

- The ERG stated that, if patients are treated at a later stage of multiple myeloma, the cost per life year gained increases significantly. The ERG found that when all patients were treated at second relapse, the ICER was £77,000 per life year gained; when all patients were treated at third relapse, the ICER was £107,000 per life year gained.

3.6 The manufacturer's response to the Appraisal Consultation Document (ACD) included clarification of issues related to the APEX study and a revised economic report that included additional scenarios involving vial sharing.

3.7 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/TAxxx

4 Consideration of the evidence

4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bortezomib, having considered evidence on the nature of the condition and the value placed on the benefits of bortezomib by people with multiple myeloma, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.2 The Committee discussed the position of bortezomib in the pathway of care for people with multiple myeloma. The Committee understood that the disease is incurable, and was aware that because of the heterogeneous nature of the disease and its clinical course, the treatment appropriate for each patient at any one time may differ. The Committee understood that there are defined treatment pathways for relapsed multiple myeloma and that choice of therapy for an individual patient is influenced by the initial

treatment and the response to it, the inherent characteristics of the disease and the patient's performance status and preferences. The Committee understood that bortezomib works through novel mechanisms and that the APEX trial has established bortezomib as an evidence-based treatment for relapsed multiple myeloma. It noted that the APEX RCT compared bortezomib with HDD, and accepted that HDD was an appropriate comparator. The Committee understood that many alternative treatments have a limited evidence base for relapsed multiple myeloma, may be costly, and may have been used for the initial treatment of multiple myeloma. It concluded that bortezomib is considered a clinically important treatment for patients with multiple myeloma at both first and subsequent relapse.

4.3 The Committee considered the evidence for the clinical effectiveness of bortezomib monotherapy at both first and subsequent relapse. It understood that the only RCT that included patients at first relapse was the APEX study, which compared bortezomib with HDD. The Committee noted that the APEX study was the largest published RCT of the treatment of relapsed multiple myeloma, and that patients in the bortezomib arm experienced statistically significant improvements in response rate, time to disease progression and overall survival. The Committee understood that there was a greater frequency of peripheral neuropathy and gastrointestinal adverse effects in the bortezomib arm, but that bortezomib was associated with less bone destruction and fewer infections than HDD. The Committee discussed the methods and results of the APEX study. It considered the issues raised, and the conclusions of the ERG report. It was also aware that the dose intensity of HDD in the APEX RCT was lower than in other studies, and that more than 98% of patients had received prior treatment with corticosteroids, which may have influenced the disease's response to HDD. The Committee concluded that despite

the issues raised, the APEX RCT constitutes clear evidence that bortezomib monotherapy is more clinically effective than HDD monotherapy.

4.4 The Committee considered the cost effectiveness of bortezomib compared with HDD. The Committee understood that it was difficult to include other comparators in the model because of lack of evidence. However, it acknowledged that this contributed greatly to the uncertainty in the assessment of cost effectiveness. The Committee discussed the base-case and the sensitivity and scenario analyses of the manufacturer's economic model. It noted that clinical experts in England and Wales have suggested several criteria for using bortezomib more cost effectively in the treatment of relapsed multiple myeloma, including definition of patient characteristics, use at first relapse only, applying a stopping rule and use in combination with HDD. The experts stated that mechanisms exist to ensure the use of bortezomib in this defined way. The Committee noted that for the base case, which included patients at first relapse only, the ICER was £31,000 per life year gained and £38,000 per QALY. It noted that for the scenarios in the ERG report in which treatment was limited to patients at second relapse only or third relapse only, the ICERs were markedly increased (to £77,000 and £107,000 per life year gained, respectively). The Committee accepted that bortezomib is more cost-effective when used at first rather than subsequent relapse.

4.5 The Committee considered the scenario in the economic model in which patients whose disease had not responded to bortezomib after three cycles did not receive further treatment with the drug, whereas those who had experienced a response received up to eight cycles of treatment. In this scenario, the ICER for bortezomib compared with HDD (presented in the manufacturer's comments on the ACD) was £33,500 per QALY. The Committee heard from clinical experts that this treatment approach is current practice in

the UK. The experts explained that with special arrangements the response to treatment can be assessed in an appropriate time frame to ensure implementation of this approach. The Committee accepted that overall bortezomib is more cost-effective if treatment is stopped if no response has occurred after three cycles. However, the Committee concluded that this scenario would not put bortezomib within the range of cost effectiveness that might be considered appropriate for the NHS.

4.6 The Committee considered further the ERG's evaluation of the manufacturer's economic model, including modelling of time to disease progression and overall survival, the assumptions used to quality adjust life years, and the modelling of the cost and health outcomes related to adverse events. The Committee agreed with the ERG that the cost-effectiveness results presented in the manufacturer's submission may underestimate the cost per life year gained of bortezomib compared with HDD. The Committee considered certain results submitted by the manufacturer to be particularly relevant to this appraisal. These were the base-case (first relapse, no stopping rule) ICER of £38,000 per QALY and the scenario of first relapse plus stopping rule, for which the ICER was £33,500 per QALY. The Committee was concerned that the utility assumption used for quality adjustment of life years during remission might be high considering the nature of the disease; that there was uncertainty about the impact of using data from the Mayo study in the model and that these data might not reflect the experience of patients in NHS practice; and that the exclusion of comparators other than HDD leads to additional uncertainty. Overall, the Committee was of the opinion that the manufacturer's results were likely to be underestimates of the true cost per QALY, and that in addition there was a high level of decision uncertainty.

4.7 The Committee discussed the scenario presented in the manufacturer's response to the ACD in which vial sharing was

adopted as a more cost-efficient use of bortezomib. The Committee was aware that the UK marketing authorisation for bortezomib specifies single use of these vials immediately after preparation. Additionally, the Committee had several concerns over the practice of vial sharing, including issues related to maintenance of best aseptic practice and the practical constraints of patient numbers and geographical locations of myeloma centres, which would limit the possibility of several patients being treated in the same session over several cycles, each of which requires four doses of bortezomib at least 72 hours apart. The Committee was not persuaded that vial sharing could be considered either safe or routinely achievable in practice across the NHS.

4.8 The Committee was informed that it is currently common practice in England and Wales to use bortezomib in combination with dexamethasone. The Committee was concerned that the possible enhanced clinical effectiveness of this combination over monotherapy had been accepted on the basis of the results of two trials in which patients were not randomised to combination use, but were allowed to receive dexamethasone in addition to bortezomib if they had progressive disease after two cycles or stable disease after four cycles. The two trials, SUMMIT and CREST, were the only clinical evidence given in the manufacturer's submission and by clinical specialists to support combination therapy. The Committee noted that the manufacturer had presented evidence of the potential additional cost effectiveness of this combination over bortezomib monotherapy in comparison with HDD. The Committee was, however, mindful that the current UK marketing authorisation for bortezomib is for monotherapy alone, and that therefore combination therapy using bortezomib and dexamethasone was not within the scope of this appraisal.

4.9 The Committee discussed at length the alternatives to the use of bortezomib monotherapy. It heard from experts that thalidomide is

considered an important treatment for multiple myeloma and that it is currently being used without a UK marketing authorisation, both as first-line therapy and for relapsed multiple myeloma. The Committee also heard that bortezomib is likely to have enhanced effectiveness in combination with HDD and/or with cytotoxic drugs, and that a number of trials are either in progress or planned to investigate this. The Committee concluded that this further research will be important to further establish the position of bortezomib in the pathway of care for multiple myeloma.

4.10 The Committee discussed ongoing research on the use of bortezomib for the treatment of patients with relapsed multiple myeloma. It noted from comments made during the consultation on the ACD that no further trials of bortezomib monotherapy are planned. Current research focuses on the use of bortezomib in combination with other treatments and as first-line treatment, and on identifying subgroups of patients with multiple myeloma for whom bortezomib may be particularly appropriate. The Committee also noted that fewer than 10% of patients with multiple myeloma are in a position to enter clinical trials because of strict entry criteria, the geographical location of the trial sites, or resource and funding restrictions.

Summary of the considerations

4.11 The Committee concluded that bortezomib monotherapy for the treatment of relapsed multiple myeloma is clinically effective compared with HDD, but that it has not been shown to be cost effective. Therefore, bortezomib monotherapy is not recommended for the treatment of patients with relapsed multiple myeloma. The Committee also considered people currently receiving bortezomib and concluded that they should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare Standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAxxx). *[Note: tools will be available when the final guidance is issued]*

6 Recommendations for further research

6.1 The Committee considered that further research into the effectiveness of bortezomib for the treatment of relapsed multiple myeloma is needed. Such studies should include:

- comparisons with other agents that are currently used in clinical practice in the NHS in England and Wales
- a robust design, adequate sample size and appropriate statistical analysis
- assessment of long-term prognosis, for which observational studies would be appropriate
- measurement of quality of life in patients with relapsed multiple myeloma, including the effect of treatment and adverse events
- a consideration of subgroups of patients in whom bortezomib might be particularly effective.

7 Related guidance

7.1 NICE is in the process of producing the following guidance.

Erythropoietin for anaemia induced by cancer treatment. NICE technology appraisal. (publication date to be confirmed).

8 Review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 The guidance on this technology will be considered for review in October 2007.

David Barnett
Chair, Appraisal Committee
October 2006

Appendix A. Appraisal Committee members and NICE project team

A. Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies, and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Darren Ashcroft
Senior Clinical Lecturer, School of Pharmacy and Pharmaceutical Sciences, University of Manchester

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Dr Peter Barry
Consultant in Paediatric Intensive Care, Leicester Royal Infirmary

Mr Brian Buckley
Vice Chairman, InContact

Professor John Cairns

Public Health and Policy, London School of Hygiene and Tropical Medicine

Professor Mike Campbell

Statistician, University of Sheffield

Dr Mark Chakravarty

Head of Government Affairs and NHS Policy, Procter and Gamble Pharmaceuticals (UK)

Dr Peter I Clark

Consultant Medical Oncologist, Clatterbridge Centre for Oncology NHS Trust, Merseyside

Dr Mike Davies

Consultant Physician, University Department of Medicine & Metabolism, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic

Professor Jack Dowie

Health Economist, London School of Hygiene and Tropical Medicine

Dr Fergus Gleeson

Consultant Radiologist, The Churchill Hospital, Oxford

Ms Sally Gooch

Former Director of Nursing & Workforce Development, Mid Essex Hospital Services NHS Trust

Mr Sanjay Gupta

Stroke Services Manager, Basildon and Thurrock University Hospitals NHS Trust

Professor Philip Home

Professor of Diabetes Medicine, University of Newcastle upon Tyne

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Professor of Statistics and Dean, Faculty of Natural Sciences, Keele University

Dr Mike Laker

Medical Director, Newcastle Hospitals NHS Trust

Dr George Levvy

Lay member

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Mr Terence Lewis

Mental Health Consultant, National Institute for Mental Health in England

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Ruairidh Milne

Senior Lecturer in Health Technology Assessment, National Coordinating Centre for Health Technology Assessment, University of Southampton

Dr Neil Milner

General Medical Practitioner, Sheffield

Dr Rubin Minhas

General Practitioner and CHD Clinical Lead, Medway PCT

Mr Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Professor Mark Sculpher

Professor of Health Economics, University of York

Dr Lindsay Smith

General Practitioner, East Somerset Research Consortium

Mr Roderick Smith

Finance Director, Adur, Arun and Worthing PCT

Dr Ken Stein

Senior Lecturer in Public Health, Peninsula Medical School, University of Exeter

Professor Andrew Stevens

Professor of Public Health, University of Birmingham

B. NICE project team

Each technology appraisal is assigned to a team consisting of one or more health technology analysts (who act as technical leads for the appraisal), a technical advisor and a project manager.

Helen Chung and **Ebenezer Tetteh**

Technical Leads

Elisabeth George

Technical Adviser

Emily Marschke

Project Manager

Appendix B. Sources of evidence considered by the Committee

A The following manufacturer provided a submission for this appraisal:

- Janssen-Cilag

B The evidence review group (ERG) report for this appraisal was prepared by Southampton Health Technology Assessment Centre:

- Green C, Bryant J, Takeda A, et al. (April 2006) *Bortezomib for the treatment of multiple myeloma patients*.

C The following individuals were selected from clinical specialist and patient advocate nominations from the professional/specialist and patient/carer groups. They gave their expert personal view on bortezomib for the treatment of multiple myeloma by providing written or oral evidence to the Committee.

- Professor Gareth Morgan, Professor of Haematology and Head of Clinical Unit, nominated by the International Myeloma Foundation and the Institute of Cancer Research – clinical specialist
- Dr Graham Jackson, Consultant Haematologist, nominated by the British Committee for Standards in Haematology – clinical specialist
- Dr Stephen A Schey, Chair, UK Myeloma Forum – clinical specialist (present at the Appraisal Committee meeting on behalf of Dr Graham Jackson, who was unable to attend)
- Mr Brian Jago, nominated by the International Myeloma Foundation – patient expert
- Mr Eric Low, Chief Executive, International Myeloma Foundation (UK) – patient expert
- Dr Jamie Cavenagh, Consultant Haematologist nominated by the British Society for Haematology – clinical specialist (present at FAD meeting)

Appendix C. List of organisations involved in this appraisal

The following organisations accepted the invitation to participate in this appraisal. They were also invited to comment on the Appraisal Consultation Document (ACD) and supporting evidence. Consultee organisations have the opportunity to appeal against the Final Appraisal Determination.

I Professional/specialist and patient/carer groups:

- Cancerbackup
- International Myeloma Foundation (UK)
- Leukaemia Care Society
- Long-Term Medical Conditions Alliance
- Macmillan Cancer Relief
- Marie Curie Cancer Care
- National Cancer Alliance
- National Council for Palliative Care
- Tenovus Cancer Information Centre
- Association of Cancer Physicians
- Association of Surgeons of Great Britain and Ireland
- British Association of Surgical Oncology
- British Oncological Association
- British Oncology Pharmacy Association (BOPA)
- British Psychosocial Oncology Society
- British Society for Haematology
- Cancer Research UK
- Community Practitioners' and Health Visitors' Association
- Royal College of General Practitioners
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians of Edinburgh

- Royal College of Physicians' Medical Oncology Joint Special Committee
- Royal College of Radiologists
- Royal College of Surgeons
- Royal Pharmaceutical Society
- UK Myeloma Forum
- Department of Health
- Sedgefield PCT
- Southend PCT
- Welsh Assembly Government

II Commentator organisations (without the right of appeal):

- Board of Community Health Councils in Wales
- British National Formulary
- Medicines and Healthcare products Regulatory Agency (MHRA)
- National Public Health Service for Wales
- National Coordinating Centre for Health Technology Assessment (NCCHTA)
- NHS Confederation
- NHS Purchasing and Supplies Agency
- NHS Quality
- Baxter Healthcare Ltd (cyclophosphamide)
- Bristol-Myers Squibb Pharmaceuticals (carmustine)
- Clonmel Healthcare Ltd (vincristine)
- GlaxoSmithKline (melphalan)
- Mayne Pharma (doxorubicin, vincristine)
- Medac (UK) (doxorubicin)
- Pfizer (cyclophosphamide, doxorubicin)
- Pharmion (thalidomide)
- Schering-Plough (interferon alfa-2b)
- Teva Pharmaceuticals (doxorubicin)
- National Collaborating Centre for Cancer
- Institute of Cancer Research

- Haemato-oncology Department, King's College Hospital
- Leukaemia Research Fund
- MRC Clinical Trials Unit
- National Cancer Research Institute
- Scottish Medicine Consortium