APPEAL BY JANSSEN-CILAG LIMITED AGAINST THE FINAL APPRAISAL DETERMINATION BY THE NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE FOR BORTEZOMIB MONOTHERAPY FOR RELAPSED MULTIPLE MYELOMA

1. INTRODUCTION

Following consideration of NICE's draft determination with respect to bortezomib monotherapy for relapsed multiple myeloma, Janssen-Cilag Limited provides formal notification of its wish to appeal the Final Appraisal Determination (FAD). Janssen-Cilag requests an oral hearing before NICE's Appeal Panel for the determination of this appeal.

The appeal is brought under all of the three grounds permitted under NICE's appeal procedures, namely: Ground 1 (Procedural Unfairness); Ground 2 (Perversity); and Ground 3 (Excess of Powers).

The points of appeal raised under these three grounds are set out at Section 2 below. However, particular features of the particular disease under consideration, the technology under appraisal and the history of the appraisal process to date are fundamental to any consideration of the issues raised in this case and therefore, for completeness, we provide a brief summary by way of introduction to the appeal.

1.1 Bortezomib and the treatment of multiple myeloma

Janssen-Cilag assumes that members of the Appeal Panel will have varying experience of haematological malignancies and their treatment. A brief introduction is set out below, but does not replace the more detailed information contained in its original submission to the Institute for the purposes of this appraisal.

Multiple myeloma is a haematological malignancy, with an estimated annual incidence in England and Wales of 3,145 cases (5-6 cases per 100,000 persons per year) [1]. The average age at presentation is 68-70 years and, with modern treatments, median survival is

[1] Multiple myeloma statistics for the UK. http://info.cancerresearchuk.org/cancerstats/types/multiplemyeloma/?a=5441: Cancer Research UK.

approximately 4 years from diagnosis. The disease is approximately twice as common in black as white populations.

Multiple myeloma affects B lymphocytes (plasma cells) which are responsible for the production of immunoglobulins (antibodies). Affected patients develop excessive numbers of abnormal plasma cells in the bone marrow, reducing the amount of normal marrow available to produce normal white blood cells, red cells and platelets and resulting in over production of intact monoclonal immunoglobulins or immunoglobulin fragments (monoclonal kappa and gamma light chains, known as Bence-Jones proteins). Production of normal immunoglobulins is impaired, causing an increased susceptibility to bacterial infections and high levels of paraproteins in the blood and urine results in renal damage. The bone lesions produce pain, (typically affecting the spine, ribs, neck and pelvis) and hypercalcaemia; pathological fractures occur frequently and spinal cord compression develops in 20% of patients at some point during the course of their disease with associated back pain, numbness, weakness or paralysis in the legs. Other symptoms associated with multiple myeloma include fatigue due to anaemia, bleeding problems as a result of platelet dysfunction and hyperviscosity, caused by the accumulation of paraproteins in the blood, with the associated risk of complications, such as deep venous thrombosis and stroke.

The disease is heterogeneous and the course and response to treatment are affected by many disease and patient variables. While multiple myeloma is not generally curable, it responds to treatment with extended survival and reduced morbidity. However, all patients eventually relapse following treatment and the disease frequently becomes refractory to further courses of standard chemotherapeutic agents.

Janssen-Cilag is the holder of the marketing authorisation for bortezomib (Velcade), which was granted under the centralised procedure by the European Commission on 26 April 2004 and subsequently extended on 20 April 2005, following a favourable opinion by the Committee for Medicinal Products for Human Use (CHMP), issued on 16 March 2005.

Bortezomib is a novel antineoplastic agent that inhibits the proteasome enzymes which influence cell proliferation leading to apoptosis (programmed cell death). The current licensed indications provide that the product should be used

"*...as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation*".

In 2005, prior to the extension to the licensed indication, the UK Myeloma Forum, the Nordic Myeloma Study Group and the British Committee for Standards in Haematology (BCSH) issued joint guidelines on the diagnosis and management of multiple myeloma. The guidelines recommended, consistent with the marketing authorisation as it then was, *"bortezomib is appropriate for third line therapy in patients with reasonable performance status and organ function and reasonable life expectancy"*.

On 14 June 2005 following the licence extension allowing use of Bortezomib in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation, the UK Myeloma Forum and the Haematology Oncology Task Force of the BCSH issued a position statement on the use of bortezomib in multiple myeloma. The position paper referred to the promising results demonstrated in the Phase III APEX Clinical Trial of Bortezomib and stated *"given the strength of this data the UK Myeloma Forum and the British Committee for Standards in Haematology believe that bortezomib should be available for prescription by UK haematologists according to its licensed indication in patients with relapsed myeloma"*.

1.2 NICE'S appraisal of bortezomib: procedural history

In September 2005, NICE issued a press release indicating that it was proposing to develop a revised procedure for the rapid appraisal of important new drugs and health technologies. The Institute subsequently prepared a draft process for single technology appraisals (STAs), comprising a Draft "Interim" Guide to the Single Technology Appraisal Process and a Draft Specification for the Manufacturer/Sponsor Submission. These documents were subject to consultation between 11 November 2005 and 6 February 2006. Following the conclusion of the consultation process, NICE's Guide to the Single Technology Appraisal (STA) Process was issued in September 2006. There were significant differences between the draft, interim procedure, and the final version issued in September 2006, including:

- The absence of any scoping stage.

- The absence of a requirement for the Institute to consider the manufacturer's "decision-problem" prior to the submission of evidence.

- The lack of any express requirement for the Appraisal Committee to consider use of the technology in sub-groups of patients.

Bortezomib was referred by the Department of Health for appraisal in July 2005. It was therefore one of the first STA appraisals conducted by NICE and was carried out under the "Interim" STA Guide. Janssen-Cilag was advised by the Institute by letter dated 3 November 2005 that an evidence submission should be presented by 28 February 2006, using the draft specification which was then the subject of consultation. There was no scoping stage to the appraisal and the Interim Guide did not provide for any consideration by NICE of the "decision problem", identified by Janssen-Cilag, prior to the submission of evidence.

The Southampton Health Technology Assessments Centre (SHTAC) was commissioned by the NHS R&D HTA programme on behalf of NICE to prepare an Expert Review Group (ERG) Report. The company provided clarification of various issues raised by SHTAC, in correspondence dated 12 April 2006. This submission was considered by SHTAC, before their report was completed in April 2006.

The Appraisal Committee met for the first time to consider this appraisal on 4 July 2006. Following this meeting, an Appraisal Consultation Document (ACD) was issued in July 2006. The preliminary recommendations in the ACD provided:

> *"Bortezomib monotherapy, in its licensed indications, is not recommended for the treatment of patients with multiple myeloma except for use in well designed clinical studies that focus on the establishment of the position of bortezomib in the pathway of care for people with multiple myeloma in comparison with other agents that are currently used in clinical practice in England and Wales".*

The responses to consultation on the preliminary guidance in the ACD consistently expressed the view that the preliminary guidance was inappropriate.

The Appraisal Committee met for a second time to consider bortezomib on 6 September 2006 and following this meeting a Final Appraisal Determination (FAD) was issued in October 2006. The preliminary guidance contained within the FAD states:

"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".

2. GROUNDS OF APPEAL

2.1 Ground 1: Procedural Unfairness

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

As indicated above, the appraisal of bortezomib was one of the first STAs conducted by NICE and is one of the only technologies to have progressed through the NICE appraisal process (whether the MTA or STA procedure) without any scoping exercise having been undertaken.

The appraisal proceeded under the draft "Interim" Guide to the Single Technology Appraisal Process, which has since been revised. Two highly significant differences between the interim and final procedures are that the interim procedure did not include a scoping stage and included no requirement for NICE to consider and, if necessary, to assist in relation to the formulation of the "decision problem" for the appraisal, prior to the submission of evidence. The final version of the Guide to the Single Technology Appraisal process has been modified following consultation and now includes both these essential steps.

The scoping process now included in the Guide provides for a consultation with manufacturers/sponsors and the wider consultee community, to ensure that a scope is developed which is fit for purpose. The reason for the inclusion of a scoping stage is obvious; the scope defines the issues that will be encompassed by the appraisal including the clinical problem and the population(s) and any relevant subgroups for whom treatment with the technology is being appraised; the technology and the setting for its use; the relevant comparator technologies (and their treatment settings); the principal health outcome measures appropriate for analysis; the measures of costs to be assessed; the time horizon over which benefits and costs will be considered; and

special considerations and issues that are likely to affect the appraisal. In the absence of a properly considered scope, there is no plan to guide the company in formulating its submissions to the Institute, to direct the ERG in reviewing the evidence for use of the technology under consideration or to assist the Appraisal Committee in determining how it should assess the technology.

The final version of the Guide also introduces the requirement for the manufacturer to provide to the Institute, seven weeks prior to the full evidence submission its formulation of the "decision problem" for the appraisal. The decision problem summary will define the population, the intervention, the comparators and the outcomes relevant for the STA and it is used to ensure that the decision problem is appropriately specified in relation to the final scope issued by the Institute. It is also clearly an iterative process as the Guide states *"On request, the institute will provide help to ensure that the decision problem is specified appropriately"* and, in addition, reserves the right to request a further submission where it believes the decision problem has been inappropriately defined.

As recognised in the final version of the Guide, it is clear that the scope and definition of the decision-problem are critically important aspects of any appraisal. The Institute now takes steps to ensure that both scope and the decision problem are properly determined before the appraisal is commenced. Therefore, the fact that NICE's appraisal of bortezomib has proceeded under the Interim Guide, without the benefit of a scope or confirmation of the decision-problem, has resulted in an appraisal that is procedurally unfair. In particular, the absence of these steps has prejudiced this appraisal including in the following ways:

2.1.1.1 As indicated in its evidence submission to the Institute, Janssen-Cilag believes that this appraisal should have considered the clinical and cost effectiveness of bortezomib in combination with dexamethasone.

The combination of high dose dexamethasone and bortezomib is now established as a standard regimen by many clinicians treating myeloma patients in the UK. The BCSH in its 2005 position statement on the use of bortezomib in multiple

myeolma, recommended use of bortezomib in combination with dexamethasone stating:

"...as it has been established that responses with the combination of bortezomib and dexamethasone are approximately 20% greater than with single agent bortezomib, we would recommend that this combination should be used for all patients, unless there is a specific clinical reason to avoid dexamethasone".

In these circumstances, Janssen-Cilag did not doubt that NICE would consider the benefits associated with combination therapy, in appraising bortezomib.

While the licensed indications for bortezomib refer to the treatment of multiple myeloma as monotherapy, NICE's procedures would not preclude assessment of combination treatment, particularly if the Institute was advised to consider such regimens by the Secretary of State in the appraisal remit. (There is, of course, precedent for NICE issuing guidance in respect of use of a medicinal product beyond the terms of its marketing authorisation (see for example the approach of the Appraisal Committee to mycophenolate mofetil in TA85, NICE's appraisal of the use of immunosuppressive therapy for renal transplantation)).

Had a scope been formulated for the purposes of this appraisal, Janssen-Cilag would have been given an opportunity to consider with NICE whether the appraisal should properly consider combination treatment and, if appropriate, to make representations to the Secretary of State regarding whether an express direction should be given.

Furthermore, consistent with NICE's Interim Guide, Janssen-Cilag provided its formulation of the "decision problem" for this appraisal and included this in section 1.1 of its evidence

submission for the purposes of this appraisal. The decision problem formulated by the company under the heading "key issues" clearly assumed that the Appraisal Committee would consider the combination of high dose dexamethasone and bortezomib. The Interim Guide did not provide for any discussion of the decision problem between NICE and Janssen-Cilag and the Institute gave no indication to the company that it did not agree with the decision problem as formulated.

In the event, therefore, Janssen-Cilag only became aware for the first time that NICE would not consider combination treatment when the ACD was issued and was deprived of any opportunity to focus its evidence submission accordingly or to provide for alternative strategies to increase the cost effectiveness of bortezomib.

2.1.1.2 If, despite Janssen-Cilag's submissions, NICE and/or the Secretary of State had declined to include any consideration of combination treatment with high dose dexamethasone and bortezomib in the scope/remit for this appraisal, this would have become clear during the scoping stage. In those circumstances, the company would have sought to find an alternative way to increase the cost effectiveness of bortezomib.

In this context, it is important to note that Janssen-Cilag has now contacted Mr Andrew Dillon, the Chief Executive of NICE, in relation to the possibility of bortezomib being made available to NHS patients through a risk-sharing scheme. While Mr Dillon has indicated to Janssen-Cilag that he is unable to discuss the issue with the company at this stage and that the NICE process has to continue its full course based on the existing data, this disregards the fact that, had the appraisal been properly and fairly defined at the outset through a scope and agreed decision problem, Janssen-Cilag would have had the opportunity to propose a risk sharing scheme. Mr Dillon

has confirmed that, had such a scheme been proposed at an earlier stage, "*[NICE] might, subject to the DH's [Department of Health's] position on it, been able to adapt the process to take account of it*".

A proposal outlining the scheme is provided in Appendix 1 to this Notice of Appeal. In summary, Janssen-Cilag would offer replacement product or a credit note on the cost of bortezomib treatment for those patients who failed to respond, defined as less than a partial response to bortezomib therapy, with or without high dose dexamethasone after receiving up to four cycles, as determined by standard response criteria. The result of this approach reduces the cost of bortezomib to the NHS and produces a cost per QALY comfortably below the £30,000 threshold. The Company would be pleased to provide further details of these analyses on request.

2.1.1.3 The lack of scope and agreed decision problem have clearly resulted in other areas of confusion in relation to the assessment of bortezomib including:

- the place of bortezomib in the clinical pathway of care has resulted in confusion regarding the population of patients who would receive treatment with bortezomib and the appropriate comparator intervention(s). This confusion is a direct result of the lack of a scoping process.

- in the context of treatment for multiple myeloma, the lack of standardisation in the current management of the condition has resulted in confusion regarding the appropriate comparators including the role of unlicensed thalidomide. For example, the institute has consistently alluded to the fact that thalidomide should be considered an appropriate comparator in this appraisal, despite the fact that it has no marketing authorisation in the UK and that no

properly designed, randomised controlled trials have been conducted in patients with relapsed multiple myeloma. This misconception could and should have been dealt with during the scoping and decision-problem exercise.

2.1.1.4 The preparation of a scope for the appraisal and the formulation of the decision problem would have involved discussion between consultees, the Institute and the ERG, which would have allowed for proper consideration of factors established to enhance cost-effectiveness. The company should have had the opportunity to discuss issues such as multi-patient use of vials, stopping rules and risk sharing schemes during the scoping process. In this context, it is relevant to note that the decision problem component of the final submission template includes a section where "special considerations and other issues" may be included.

In summary, the fact that this appraisal has been run under draft interim procedures as a pilot, has resulted in a process that is unfair, has deprived all parties of a clear focussed consideration of bortezomib and prevented the potential inclusion in the appraisal process of a risk-sharing scheme to offer cost effective treatment to patients.

2.1.2 No explanation is provided for the conclusion that the dose intensity of high-dose dexamethasone in the APEX trial was lower than in other studies

At paragraph 4.3 of the FAD, the Appraisal Committee states that:

"It was also aware that the dose intensity of HDD in the APEX RCT was lower than in other studies ... "

No explanation or evidence for this conclusion is provided in the FAD and it does not reflect the ERG report or the pre-meeting briefing paper or the ACD. Furthermore, it is unclear from the FAD precisely what is intended by the term "dose intensity", how it is calculated and whether it is clinically meaningful. Therefore, while Janssen-Cilag's review of the evidence confirms that response rates for dexamethasone in the

APEX trial are consistent with other published data, it is unable fully to understand or respond to the unsupported statement in the FAD, without clarification.

Until very recently, the quality of studies evaluating the efficacy of dexamethasone administered alone, were of poor quality, out of date (conducted between 1986 and 1992), showed inconsistency in dosing schedules and were either single-centre, retrospective, case theories or small pilot studies[2]. Furthermore, the criteria for measuring response rates were often poorly defined and inconsistent between studies, making it difficult to compare results and to establish a credible baseline response rate for dexamethasone.

Following the publication of the APEX trial in 2005, clinical trial results have been reported from two new large-scale, prospective, randomised, multi-centre clinical trials (the US MM-009 and the European MM-010 trials) of lenalidomide plus dexamethasone versus dexamethasone in relapsed multiple myeloma patients[3]. In the lenalidomide studies, a 4-week dosing schedule for dexamethasone was used as opposed to a 5-week dosing schedule in APEX. Response rates were measured using the same rigorous European group for Blood and Marrow Transplant (EBMT) criteria as those used in the APEX trial and were independently validated by a panel of clinical experts in multiple myeloma. Despite the differences in dosing schedules between the lenalidomide trials and APEX the results showed that in relapsed patients, the dexamethasone response rates reported in these studies was between 18.4% and 22% in the European MM-010 study. Therefore, the response rates observed in the APEX trial for dexamethasone alone was consistent with that reported in the lenalidomide trials and demonstrates that there are no discernible differences between a 4-week and a 5-week cycle in terms of the magnitude of effect of dexamethasone.

While, therefore, Janssen-Cilag believes that the results of APEX confirm that the efficacy in terms of response rates for dexamethasone are consistent with other published data, the company is unable to provide a substantive response to the

[2] Alexanian et al (1986), Friedenberg et al (1991) and Alexanian et al (1992)
[3] Dimopoulos et al (2005), Dimopoulos et al (2005)

conclusions expressed in the FAD in the absence of further clarification as to the basis for the conclusions reached by the Appraisal Committee.

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

At paragraph 4.3 of the FAD, the Appraisal Committee expressed the view 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. No explanation for this conclusion is provided and, in circumstances where responsiveness to dexamethasone was one of the criteria for inclusion in the study, Janssen-Cilag does not understand the basis for the conclusion by the Committee.

While nearly all patients in the APEX trial had previously been treated with a corticosteroid (98% and 99% of the patients in the bortezomib and dexamethasone groups respectively), only 40% of patients had previously been treated with dexamethasone. The history of steroid usage reflected in the APEX participants is, in our view, an accurate reflection of clinical practice in that the majority of patients with myeloma will receive a first line corticosteroid, whether as part of a haematopoietic stem cell transplantation induction protocol or with conventional chemotherapy combination treatment. Significantly, patients who were resistant to dexamethasone were excluded from the APEX trial. Resistance to dexamethasone was defined as patients who had not fully or partially responded to a treatment containing high doses of dexamethasone or whose disease had progressed within six months of the last dose of dexamethasone. Finally, although 9% of patients were later found to be resistant to dexamethasone in a post-hoc retrospective analysis of the APEX data, when these patients were excluded from the analysis the results of the study did not change. Therefore, prior use of steroids did not alter the efficacy results of the study.

In these circumstances, Janssen-Cilag does not believe that the conclusion of the Appraisal Committee is correct. However, in the absence of proper explanation and disclosure of the evidence relied upon, a complete response to this conclusion cannot be provided.

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 QALY exceeds £20,000

At Section 4.5 of the FAD, the Appraisal Committee considers the cost-effectiveness of treatment with bortezomib in circumstances where patients who fail to respond to treatment after three cycles, do not receive further treatment with the drug. The Appraisal Committee noted that the ICER for bortezomib compared with high-dose dexamethasone in this context was £33,500 per QALY. However, the FAD states that:

> *"..., the Committee concluded that this scenario would not put bortezomib within the range of cost effectiveness that might be considered appropriate for the NHS."*

No explanation for this conclusion is provided and it is therefore unclear whether and if so how, NICE took into account the additional factors listed in its Guide to the Methods of Technology Appraisal as having particular application where the cost per QALY was greater than £20,000. Section 6.2.6.10 of the Guide states:

"Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use for NHS resources are more likely to make more explicit reference to factors including:

- *the degree of uncertainty surrounding the calculation of the ICER*
- *the innovative nature of the technology*
- *the particular features of the condition and population receiving the technology*
- *where appropriate, the wider societal costs and benefits."*

Therefore in reaching any judgement about whether or not it is appropriate to make a recommendation for use of a product in NHS patients, where the ICER is likely to exceed £20,000, NICE is required to take into account the listed factors. Without any explanation in the FAD as to whether and if so how such factors have been considered

by the Appraisal Committee in this case, it is impossible for Janssen-Cilag properly to assess the draft determination contained in the FAD.

The requirement for NICE to provide a reasoned explanation for its conclusions is particularly acute in view of the fact that, in general, bortezomib scores very highly in relation to all of the additional factors.

- NICE has accepted that the product is innovative (paragraph 4.2 of the FAD) as a first in class agent that acts in a way that is different to other myeloma treatments. It is also relevant to note that bortezomib is the first new licensed treatment for myeloma in the past 10 years.

- The clinical need of the patients with the disease under consideration is considerable. Myeloma is an incurable, terminal disease, associated with substantial morbidity for which the only licensed treatment is dexamethasone. In view of these facts, there is substantial need for further treatments with different modes of action. The benefits to patients of a new, tested and effective treatment are very high indeed.

- Inevitably, there is a degree of uncertainty with respect to experience with bortezomib outside the clinical trial context, in view of the fact that it has only recently been granted a marketing authorisation. However, the level of uncertainty seen in this case has not precluded a positive recommendation by NICE in other similar cases. As an example, the published guidance for imatinib for the treatment of chronic myeloid leukaemia, another haematological malignancy, shows that NICE was willing to make a recommendation in this case, despite the fact that uncertainty existed around the cost effectiveness estimate produced by the Assessment Group (£26,000 (CI £13,500 - £52,000).

2.1.5 NICE's approach to the evidence for bortezomib is inconsistent with that followed in other appraisals and is therefore unfair.

NICE repeatedly states that it is concerned to compare different products, including in different therapeutic areas, by reference to a cost per QALY approach. However, in those circumstances, there must be consistency in the approach followed and the

conclusions drawn in relation to different technologies, in circumstances where the evidence for efficacy is similar and the level of uncertainty comparable.

2.1.5.1 The Appraisal Committee has adopted different criteria with respect to the acceptability of uncertainty for cost effectiveness in this appraisal.

In this context, Janssen-Cilag has undertaken a systematic review of all published technology appraisals completed since 2002 to the present date, to examine the influence of decision uncertainty on the ultimate recommendation. We have especially focused our review on those technologies with a reported basecase cost per QALY in the range £25,000 to £35,000.

The results of this review clearly show that there is inconsistency in the approach followed by NICE and that a number of technologies associated with higher levels of decision uncertainty have been recommended for use in equally or arguably less deserving patient populations than bortezomib. In circumstances where NICE has repeatedly stated its intention to apply the same standards across different therapeutic areas, this inconsistency is unfair.

In our systematic review, a total of 79 appraisals were evaluated. Of these, 26 technologies were recommended with a cost per QALY in the range of £25,000 to £35,000. The results of this analysis are presented in Tables 1 and 2 below.

Table 1 shows that, in 12 out of the 26 recommended technologies where the cost per QALY was between £25,000 and £35,000, the reported range of cost-effectiveness is wider, indicating a higher level of decision uncertainty, than that reported for bortezomib in this appraisal (CE estimate

(monotherapy) £33,000 (£28,518 to £44,135). Specifically there is a greater difference between the upper and lower cost effectiveness estimates reported for these technologies as compared with the difference of £15,617 reported for bortezomib in our economic model.

1. TABLE 1

Publication year	Technology appraisal Number	Technology Appraisal title	Technology	Cost per QALY	Range
Mar-02	36	Rheumatoid arthritis - etanercept and infliximab	Etanercept	£31,000	£16,330 to £63,974
			Infliximab	£31,000	£23,936 to £99,373
Apr-02	40	Use of infliximab for Crohn's disease	Infliximab	£27,500	£6,700 to £165,000
Feb-03	57	Diabetes (Type 1) insulin pump	Continuous subcutaneous insulin infusion or insulin pump	£31,429	£8,400 to £500,000
Aug-03	64	Somatropin in adults with growth hormone deficiency	Human growth hormone	£35,000	£25,000 to £45,000
Sept-03	68	Use of photo-dynamic therapy for age-related macular degeneration	Verteprofin	£26,000	£10,000 to £57,000
Oct-03	70	Guidance on the use of imatinib for chronic myeloid leukaemia (chronic/accelerated/blast phase)	imatinib	£26,000	£13,500 to £52,000
Oct-04	86	Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours	imatinib (response to treatment within 12 weeks/patient with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GISTs)	£32,000	£14,000 to £59,000

May-05	90	Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events	clopidogrel	£33,500	£18,907 to £94,446
Aug-05	93	Irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer	oxaliplatin	£32,000	NR**
Jan-06	95	Implantable cardioverter defibrillators for arrythmias	Inplantable cardioverter defibrillator***	£28,000	£28,000 to £72,000
Apr-06	99	Immunosuppressive therapy for renal transplantation in children and adolescents	Tacrolimus	£34,000	£34,000 to £145,000
Jul-06	104	Etanercept and infliximab for the treatment of adults with psoriatic arthritis	Etanercept	£28,190	£17,200 to £65,590

Table 2 shows that, in 12 out of the 26 recommended technologies where the cost per QALY was between £25,000 and £35,000, the upper cost effectiveness estimate exceeded that reported in our economic model for bortezomib (£44,135). In a significant number of cases the upper range limit was well above this figure. For example the appraisal of Diabetes (Type 1) insulin pump reported an upper cost effectiveness estimate of £500,000, infliximab for crohn's disease reported an upper cost effectiveness estimate of £165,000 and, more recently, tacrolimus an immunosuppressive for renal transplantation reported an upper cost effectiveness estimate of £145,000.

2. TABLE 2

Publication year	Technology appraisal Number	Technology Appraisal title	Technology	Cost per QALY	Range
Mar-02	36	Rheumatoid arthritis - etanercept and infliximab	Etanercept	£31,000	£16,330 to £63,974
			Infliximab	£31,000	£23,936 to £99,373

Apr-02	40	Use of infliximab for Crohn's disease	Infliximab	£27,500	£6,700 to £165,000
Dec-02	53	Guidance on the use of long-acting insulin analogues for the treatment of diabetes-insulin glargine	Insulin glargine	£32,500	NR** to £71,978
Feb-03	57	Diabetes (Type 1) insulin pump	Continuous subcutaneous insulin infusion or insulin pump	£31,429	£8,400 to £500,000
Sept-03	68	Use of photo-dynamic therapy for age-related macular degeneration	Verteprofin	£26,000	£10,000 to £57,000
Oct-03	70	Guidance on the use of imatinib for chronic myeloid leukaemia (chronic/accelerated/ blast phase)	imatinib	£26,000	£13,500 to £52,000
Oct-04	86	Imatinib for the treatment of unresectable and/or metastatic gastrointestinal stromal tumours	imatinib (response to treatment within 12 weeks/patient with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GISTs)	£32,000	£14,000 to £59,000
May-05	90	Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events	clopidogrel	£33,500	£18,907 to £94,446
Jan-06	95	Implantable cardioverter defibrillators for arrythmias	Inplantable cardioverter defibrillator***	£28,000	£28,000 to £72,000
Apr-06	99	Immunosuppressive therapy for renal transplantation in children and adolescents	Tacrolimus	£34,000	£34,000 to £145,000
Jul-06	104	Etanercept and	Etanercept	£28,190	£17,200

		infliximab for the treatment of adults with psoriatic arthritis			to £65,590

***Secondary prevention of sudden death

****Primary prevention of sudden death

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.

While the FAD includes references to calculations based on the cost per life year gained associated with bortezomib therapy, this merely reflects Janssen-Cilag's submission and it is clear that NICE has based its conclusions with respect to the cost effectiveness of bortezomib, exclusively on the cost per QALY data (paragraphs 4.5 and 4.6 of the FAD).

It is generally accepted that NICE's standard approach, based upon quality adjusted life years (QALYs) is likely to discriminate against persons with a short life expectancy, such as those with terminal illnesses and that analyses using cost per life year gained (LYG) estimates may more accurately reflect the cost effectiveness of oncology treatments such as bortezomib.

Janssen-Cilag recognises that NICE prefers to assess all technologies using a standard QALY approach. However, we believe that a fair appraisal requires that the potential unfairness resulting from reliance upon QALYs, should be balanced by a proper consideration of the cost per LYG. There is no indication, that NICE has recognised the potential pessimism resulting from its reliance upon QALYs and has appropriately balanced this by reference to the cost per LYG calculations.

2.1.7 The Appraisal Committee's approach to license status is inconsistent

At paragraphs 4.4 and 4.6 of the FAD, the Appraisal Committee have referred to the fact that Janssen-Cilag did not consider comparators other than high dose dexamethasone in its cost effectiveness assessment of bortezomib, while recognising that there are inadequate data to assess the effectiveness of such products. The only

comparative product specifically identified by the Appraisal Committee is thalidomide. It is clear that the Appraisal Committee recognises that not including thalidomide in the economic model results in increased uncertainty and throughout the ACD and FAD, it is clear that the Committee feel that thalidomide is a valid comparator.

NICE has refused to consider the use of licensed bortezomib in combination with licensed dexamthasone, but has consistently been comfortable with considering an unlicensed drug (thalidomide) with no randomised evidence as a comparator in this appraisal. The failure by NICE to adopt a consistent approach to both bortezomib and thalidomide is patently unfair.

2.2 Ground 2: Perversity

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.

Bortezomib has proven efficacy against multiple myeloma as demonstrated in high quality, randomised controlled trials and is authorised within the EU for the treatment of patients at first relapse. The only alternative licensed therapy in relapsed disease is dexamethasone. The effect of NICE's draft determination, which states that bortezomib should not be used to treat NHS patients, is to require patients and clinicians to use unlicensed and experimental drug therapies, such as thalidomide, to treat relapsed myeloma in the absence of licensed alternatives. This is perverse.

The evidence base for the efficacy of therapies other than bortezomib and dexamethasone is very limited indeed. For example, no randomised controlled trials for thalidomide in relapsed myeloma have been reported. No consensus exists with respect to the appropriate dosing schedule for thalidomide, when used for the treatment of relapsed myeloma and the clinical and safety profile of thalidomide in this indication is uncertain, but in view of historical experience raises very serious concerns. Furthermore, thalidomide is not a cheap generic product but will cost the NHS between £5,000 - £15,000 per patient per year, depending on the dosage prescribed. Assuming that a marketing authorisation is not granted in respect of thalidomide, it will never undergo appraisal by NICE and will continue to benefit from

negative determinations by the Institute in respect of other licensed products with demonstrated benefit in high quality clinical trials.

The effect of NICE's preliminary recommendations are therefore that patients suffering from an incurable malignancy, associated with unpleasant symptomatology, will be deprived of the only medication which has been tested and authorised in this indication and will instead be limited to treatment with medicines (including those that are costly) that have not been subject to rigorous clinical trial evaluation and where the benefits and risks are uncertain. Such a strategy is wholly irrational and failure by the Appraisal Committee to consider the implications of its guidance in this context is perverse.

2.3 Ground 3: the Institute has exceeded its powers

2.3.1 NICE's proposed determination has the effect of acting as an unlawful restriction on the prescription of bortezomib

Directive 89/105/EEC (the Transparency Directive) requires governments of Member States to notify to the European Commission a series of criteria which are used, where the range of medicinal products covered by national health systems is to be restricted. The UK Government has notified a series of criteria to the Commission in accordance with these requirements, but these do not include clinical-effectiveness or cost-effectiveness.

NICE's determinations constitutes measures which are intended to restrict the range of medicinal products covered by the NHS and they therefore fall within the scope of the Transparency Directive. The fact that they are characterised as "Guidance" is irrelevant in this context, because their inevitable and intended effect is to lead to a de facto restriction on the prescription of medicinal products within the NHS in England and Wales. This is clearly demonstrated by the fact that measures have been put in place which provide penalties for any failure to adhere to the Institute's determinations. These measures are described at Section 5 of the FAD and in Guidance issued by the Healthcare Commission. Standards, set by the Department of Health together with NICE, and described in the publication "Standards for Better Health" issued in July 2004, provide that one of the core standards by which NHS organisations will be assessed is compliance with NICE's determinations. In addition, following the Department of Health Direction of December 2001, the

provision of funding for technologies recommended by NICE has been mandatory, with the implicit effect that, where a treatment such as bortezomib is not so recommended, funding will not be made available.

Therefore, a determination by NICE, that bortezomib should not be 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, is unlawful as a matter of Community Law, because it restricts the use of the product, based on criteria that have not been notified to the European Commission.

3. REQUESTED ACTIONS

In the context of the above concerns, Janssen-Cilag respectfully request the Appeal Panel to refer this appraisal back to the Appraisal Committee for further consideration with the following directions:

- Reconsider the scope of this appraisal.
- That consultees should have a further opportunity to make additional submissions in relation to this appraisal, including additional strategies for improving the cost effectiveness of bortezomib through a risk-sharing scheme.
- That the Committee should be required to provide detailed reasoning for its conclusions in the areas identified including in relation to the additional criteria laid out in NICE's procedures for the consideration of technologies where the cost per QALY exceeds £20,000.

Janssen-Cilag Limited

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