NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Bortezomib for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation for the treatment of multiple myeloma

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Janssen	(*A summary is presented here - for the full manufacturer's response to the ACD, please refer to the Evaluation report*) Janssen welcomes the opportunity to comment on the preliminary recommendation made by the appraisal committee and to respond to the request for additional analyses detailed in the appraisal consultation document (ACD). We are disappointed that neither bortezomib in combination with thalidomide and dexamethasone (VTD) nor bortezomib in combination with dexamethasone (VD) is recommended for the induction treatment of adults with previously untreated multiple myeloma (MM) for whom high-dose chemotherapy with haematopoietic stem cell transplantation (SCT) is suitable. VTD and VD remain the only licensed regimens for MM in the induction setting. The most commonly used treatment in England and Wales, cyclophosphamide in combination with thalidomide and dexamethasone (CTD), is unlicensed and suffers from a limited evidence base as this regimen is not widely used outside of the UK. Moreover, as induction therapy occurs shortly after diagnosis at the early stage of the patient pathway, the RCT data to support this indication are somewhat immature due to the prolonged survival in this patient population. This combination of immature trial data and comparator issues cause some problems from an HTA perspective and we hope NICE can work with us to try to find a pragmatic solution that will enable MM patients to access this important treatment option. The license for VTD and VD was granted after the efficacy and safety of the bortezomib-based induction regimens was robustly demonstrated in multiple randomised clinical trials (RCTs) such as PETHEMA, GIMEMA and IFM-2005. The bortezomib-based regimens are now standard of care in many other European countries. The decision problem for this single technology appraisal (STA) rests upon whether the addition of bortezomib to induction regimens demonstrates value for money to the NHS. As demonstrated in the original submission, in the addendums and in this document, we maintain that bortezomib is highly cost-effective when added to thalidomide plus dexamethasone (i.e. the VTD regimen), or to dexamethasone alone (i.e. the TD regimen). Whilst the negative recommendation for VTD appears to be based on three key factors, we believe none of these factors are supported by evidence: • Use of the Alvares long-term OS data: The Alvares data are from a non-randomised, *retrospective review* covering a highly select group of patients who actually received a SCT. (On this point, please note that the final scope	Comments noted. The Committee considered the manufacturer's response to the appraisal consultation document that included changes to the economic models for all the bortezomib regimens. Taking into account its consideration that the uncertainty around stem cell transplant rates was not likely to have a substantial impact on the ICER (section 4.16 of the Final appraisal determination [FAD]) and taking into consideration ICERs based on survival data from the MRC VII and Alvares studies, the Committee concluded that, on balance, the ICERs for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, and for bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone and compared with vincristine, adriamycin and dexamethasone, were likely to be below £30,000 per QALY gained. Therefore both bortezomib regimens could be considered a cost-effective use of NHS resources. A summary of the Committee's conclusions relating to the manufacturer's response to ACD consultation is presented in the Final Appraisal Determination (sections 4.3, 4.16–4.20). In the FAD, the Committee has recommended bortezomib as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple

Consultee	Comment	Response
	for this STA specifies "adults with newly diagnosed multiple myeloma for whom induction therapy is considered appropriate prior to high dose chemotherapy and autologous stem cell transplantation" as the relevant population, not those who actually received a SCT.) In contrast, MRC VII is the most recent, UK-based prospective dataset in the relevant patient population for which long-term OS data by response category have been reported. Moreover, compared with the MRC VII data, the Alvares data are neither newer nor fit better to the PETHEMA Kaplan-Meier curve for patients with less than partial response (PR). (See Section 2.1.1 below for more details.) • Use of the post-transplant response rates: For those patients who never received a SCT, post-induction response rates are the most relevant response rates. It is not logical to apply the post-transplant response rates to patients without a SCT. Moreover, contrary to the ERG's assertion, the "maximal response" from MRC VII is in fact defined as the post-induction response, not the post-transplant response. Therefore, it is not appropriate to apply the post-transplant response rates to the economic model submitted in July 2013. (See Section 2.1.2 below.) • Incremental clinical efficacy of cyclophosphamide in addition to TD: The committee appears to believe that CTD is substantially more efficacious than TD when the most plausible ICER estimate was considered. This is not consistent with the opinion expressed by clinical experts; CTD and TD can be considered clinically equivalent and broadly similar. It is important to acknowledge, therefore, that TD should be considered a relevant comparator for this appraisal. The final scope clearly states that "chemotherapy regimens containing thalidomide" are relevant comparators. (See Section 2.1.4 below.)	myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
	Furthermore, the ERG exploratory analysis presented at the appraisal committee meeting was inappropriate, and we are concerned that an inordinate amount of discussion during the meeting was taken up with this analysis, which was based upon a comparison of single arms from heterogeneous trials taken from two different economic models. The conclusions drawn from this analysis are spurious, particularly the assertion that VTD is dominated by CTD. This is wholly inappropriate and we are concerned about the inclusion of this statement in the ACD (paragraph 4.12).	At the first meeting the Committee understood the limitations with the ERG's exploratory analyses because the data were drawn from a range of heterogeneous studies containing different comparators and different study designs and differences in trial design and baseline characteristics had not been taken into account (see section 4.15 of the FAD). The Committee fully acknowledged the debilitating nature of the disease and the

Consultee	Comment	Response
	It is also regrettable that, at the meeting which began a few hours behind schedule, clinical and patient experts were not given adequate time to explain the clinical need for VTD and VD as well as how these regimens would fit in to the patient pathway. The clinical discussions appeared to be rushed and, consequently, the ACD contains a number of important outstanding clinical questions. For example, the ACD seems to indicate that clinical need for VTD might be weaker than that for VD by stating: "there was no specific preference for bortezomib triple therapy also including thalidomide" (paragraph 4.12). Given the apparent misunderstanding around the clinical place in induction therapy of bortezomib, we would request that the clinicians and patient groups present at the first appraisal committee meeting be permitted to attend the second meeting in February 2014. In the following sections, we discuss the cost effectiveness of: • VTD compared with TD (Section 2), • VD compared with CTD (Section 3), and, • VD compared with an alternative comparator in circumstances when CTD is not suitable (Section 3). In the ACD, the ERG and the appraisal committee made a number of suggestions that would enhance the robustness and transparency of the economic analysis. We welcome such suggestions and have adopted them to amend the economic model. This is discussed in details in Section 2.2. In order to test the robustness of the ICER estimates, a number of different data sources, including the Kaplan-Meier curves from the PETHEMA and IFM-2005 studies, were used in the additional economic analysis undertaken for this response. The majority of the ICER estimates were below £30,000/QALY, and many of them were below £20,000/QALY. Along with the results already reported in our original submission and the addendums, the cost-effectiveness analyses in this document clearly indicate that both VTD and VD are cost-effective when compared to a relevant comparator.	importance of having a range of treatment options available (see section 4.1 and 4.2 of the FAD). However, prior to consultation, the Committee was not convinced that the right comparisons had been presented as it heard that current standard induction therapy in the UK was cyclophosphamide, thalidomide and dexamethasone, and also that vincristine, adriamycin and dexamethasone is no longer used and was also outside the scope. The threshold analysis presented by the manufacturer in response to the ACD persuaded the Committee that bortezomib, thalidomide and dexamethasone against thalidomide and dexamethasone was a reasonable basis for appraising bortezomib, thalidomide and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone. The manufacturer also presented comparisons for bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone, as requested in the appraisal consultation document and the results from these comparisons factored into Committee's decision making in the FAD.

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Myeloma UK	**Myeloma UK response to appraisal consultation document on bortezomib for induction therapy in myeloma before high-dose therapy and autologous stem cell transplantation** <u>Introduction</u> Myeloma UK welcomes the opportunity to comment on the NICE appraisal consultation document (ACD) covering bortezomib as an induction therapy for myeloma patients prior to high-dose therapy and autologous stem cell transplantation. We appreciate that this appraisal is not straight forward but nonetheless are disappointed by the draft decision. Our focus now is to work with stakeholders to find a way forward that will mitigate the concerns and uncertainties and to enable access to this important treatment for the appropriate group of patients eligible for high-dose therapy and stem cell transplantation. As myeloma is a heterogeneous cancer we are very supportive of opportunities that enable appropriate wider access to new treatments for patients and prescribing flexibility for clinicians. Myeloma UK has a good working relationship with NICE and we have absolute confidence in its appraisal methodology and processes. However, having read through the Velcade ACD, we are disappointed with the conclusions the Appraisal Committee has reached. As it currently stands, if the NICE guidance came into affect it would preclude any newly diagnosed myeloma patient from accessing Velcade on the NHS, which is unacceptable and would represent an abject failure on behalf of all the stakeholders involved. We therefore offer the following comments to assist NICE to take forward the appraisal and to hopefully overturn the 'minded' no NICE reached after the first Appraisal Committee meeting. <u>The clinical case and evidence for Velcade induction</u>	Comments noted.

Nominating organisation	Comment	Response
	Myeloma UK understands that the comparative data between cyclophosphamide, thalidomide and dexamethasone (CTD) and Velcade and dexamethasone (with or without thalidomide) is limited, particularly as the clinical trials conducted using Velcade induction were not designed for a UK setting or with a robust HTA appraisal in mind. However, as there is compelling clinical evidence to show that Velcade is a good therapeutic option for patients in the induction setting and that it improves progression free and overall survival, we firmly believe it is the responsibility of NICE and other stakeholders involved in the NICE appraisal to find a way to ensure that Velcade induction is made available on the NHS as a treatment option for myeloma patients who need it. We need to work together to make the best use of the clinical evidence available and to find a rationale and a form of words to approve Velcade for an appropriate group of patients who are eligible for high-dose therapy and stem cell transplantation.	Comment noted. The Committee acknowledged that bortezomib regimens had a clear advantage with respect to induction response and that a link between improved response and survival was plausible (see 4.20 of the FAD).
	<u>Further subgroup analysis</u> One opportunity that may be worth exploring in more depth is whether or not there are subgroups of myeloma patients that would be likely to benefit more than others if Velcade was approved for use as an induction therapy. Evidence suggests that patients who attain a complete response from their initial treatment have better long term outcomes[1]. This highlights the urgent need for clinicians and their patients to have access the best possible treatments at diagnosis and have the ability to choose between available treatments to pick the one that is best for any given patient depending on the clinical situation at hand. For example, as in the NICE MTA guidance covering thalidomide and Velcade in newly diagnosed patients who are not candidates for intensive therapy, it was deemed important for patients who are contraindicated or intolerant to thalidomide to be able to access an alternative but similarly	Comment noted. In the FAD, the Committee has recommended bortezomib as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

[1] Harousseau et al (2009), Blood Vol 114 no 15 3139-3146

Nominating organisation	Comment	Response
	effective treatment. In addition, as we highlighted in our initial response to the appraisal there is also evidence to suggest that bortezomib is better and can improve outcomes in myeloma patients with kidney impairment. <u>Appraisal Committee meeting</u> Since 2006 and the first NICE appraisal of Velcade monotherapy, Myeloma UK has been involved in a wide range of NICE appraisals of novel myeloma treatments and have always felt that they are held in a very professional manner. However, we were very disappointed with how the NICE Appraisal Committee was conducted on 17 October and do not think that it reached the high standards that we have come to expect. Prior to the Committee's discussion of Velcade induction there was a lengthy and difficult appraisal that had already taken place and proceedings were running over an hour and half later than anticipated. Understandably, when we were called into the meeting the members of the Appraisal Committee appeared not in the right frame of mind to conduct another complex and lengthy appraisal. We felt that on arrival the topic was rushed through, the details and discussion were not of the depth and quality that we have experienced at previous appraisal meetings and we do not think that we were given the appropriate amount of time to discuss the complex issues associated with the data on bortezomib induction. It is difficult to see how the NICE committee could have reached any other decision, apart from a negative one, given the circumstances and frame of mind the Committee was in during the proceedings. We therefore very much look forward to the further opportunity to discuss the Velcade induction appraisal and the associated uncertainty at the next Committee meeting. <u>Conclusions</u> As outlined above, Myeloma UK is disappointed with the negative recommendations made by NICE in the ACD on bortezomib as an induction	Comments noted. Comment noted.

Nominating organisation	Comment	Response
	therapy. However, we are confident that with the additional data supplied by the pharmaceutical company, further collaboration and with further consideration of how we can overcome the uncertainty associated with the data, we can find a way of making bortezomib available to myeloma patients in the UK to patients who need it.	
UK Myeloma Forum (endorsed by the Royal College of Pathologists and the British Society for Haematology)	We write in response to the above document, on behalf of the UK Myeloma Forum, and the Royal College of Pathologists. <u>The analysis by the ERG</u> 1. We understand that the results of the mixed treatment comparisons (MTC) initially carried out by the manufacturer were noted to be subject to substantial uncertainty, hence were not used for the economic modeling. We were therefore surprised to find that, at the meeting, the ERG presented results of comparisons across different trials, without adjusting for trial design or study populations! We also noted that in such comparisons (Tables 16, 17and 18 in the Pre-meeting briefing document), the costs for CTD consistently came out *lower* than those for TD. This was pointed out during the meeting, and no explanation was forthcoming. We conclude that any exploratory ICERs using CTD as the base case based on these calculations must be intrinsically flawed. 2. We are concerned that the committee have elected to uphold the conclusions from the ERG's scenario analysis using data from Alvares et al to inform long term survival. We are surprised that the report from the meeting failed to mention our comment on the use of the Alvares data to model long term survival. We pointed out that the Alvares study, being a retrospective study, analysed survival by CR and less than CR rates only *in those patients who were evaluable at 3 months post-transplant (n=260).* The whole study population was 383 (median age of 54 years), of whom only 282 proceeded to a stem cell transplant (and 260 survived to be evauable at 3 months). The group of patients who received a transplant and survived to be analysed for response at 3 months	Comment noted. The reason for costs being lower for CTD than for TD was because the cycle lengths were different between the two interventions (CTD was 21 days, TD was 28 days). The Committee understood the limitations with the ERG's exploratory analyses because the data were drawn from a range of heterogeneous studies containing different comparators and different study designs and differences in trial design and baseline characteristics had not been taken into account (see section 4.15 of the FAD). Comment noted. Section 4.13 of the ACD stated that the clinical specialists raised concerns that the Alvares study was retrospective in design and also quite old and therefore a more recent study would be more appropriate. Section 4.18 of the FAD outlines further discussion by the Committee after consultation, concluding that that using data from the NMSG 5/94 study would represent a pessimistic scenario and that the ICERs based on survival data from the MRC Myeloma VII and Alvares studies were appropriate for its

Nominating organisation	Comment	Response
	post-transplant are therefore a highly selected group, with obviously a better prognosis. They are not representative of the group of patient who, at the time of starting induction therapy, are considered candidates for intensive therapy (stem cell transplantation). We know from the recent MRC Myeloma IX study that only 67% of such patients eventually go on to receive a transplant. Furthermore, the patients included in the Alvares study were diagnosed between 1985 and 2004, which seems contemporaneous with the Myeloma VII study, which the ERG considered to be too old! <u>Comment on the Appraisal meeting 15th October</u> We were disappointed that a considerable proportion of the meeting was devoted to a discussion of process, and of the appropriateness of the modeling assumptions, with consequently less opportunity to discuss the clinical need and effectiveness of bortezomib-containing regimens in general in this patient group. We were also disappointed to note that our point regarding the un-suitability of the Alvares data for modeling survival was not minuted, and have re-iterated that point above, in our comment on the ACD. We are pleased however, to note that the committee has understood that we, as physicians, feel that bortezomib-containing regimens are a valuable treatment option for this patient group, although there is no specific preference for a triplet regimen incorporating thalidomide (see below). <u>Comment on the Scope</u> We were disappointed and surprised to learn that the scope of the health economic analysis (and hence of the Appraisal) had been altered since the scoping workshop that we had attended, such that only VTD was being assessed for cost-effectiveness. We feel that restricting the appraisal of cost effectiveness to the VTD regimen and excluding the VD regimen from the base case analysis is at odds with clinical practice. The majority of physicians using a bortezomib regimen in this setting would use it in	decision making. Comments noted. The Committee considered the manufacturer's response to the appraisal consultation document that included changes to the economic models for all the bortezomib regimens. Taking into account its consideration that the uncertainty around stem cell transplant rates was not likely to have a substantial impact on the ICER (section 4.16 of the FAD) and taking into consideration ICERs based on survival data from the MRC VII and Alvares studies, the Committee concluded that, on balance, the ICERs for bortezomib, thalidomide and dexamethasone compared with thalidomide and dexamethasone, and for bortezomib and dexamethasone compared with cyclophosphamide, thalidomide and dexamethasone and compared with vincristine, adriamycin and dexamethasone, were likely to be below £30,000 per QALY gained. Therefore both bortezomib regimens could be considered a cost-effective use of NHS resources (see section 4.20 of the FAD). A summary of the Committee's conclusions relating to the manufacturer's response to ACD consultation is presented in the Final Appraisal Determination (sections 4.16–4.20).

Nominating organisation	Comment	Response
	combination with Dexamethasone, and sometimes, a third agent, but this would not necessarily be thalidomide. In particular, for patients not suitable for thalidomide, we may use a combination with cyclophosphamide. The meeting Chair indeed commented that such a combination would be regarded favourably from the financial point of view. Restricting the base case analysis to the VTD regimen not only increases the cost and makes the treatment less competitive, it will force physicians into using a regimen that may be more intensive and/or toxic than other bortezomib regimens with which we have far more experience. <u>Clinical Practice in the UK</u> The most widely used regimen for treating patients with newly diagnosed multiple myeloma in the UK is CTD, which is an oral regimen that produces disease free survival that is comparable to the traditional VAD-type protocols (Myeloma IX study, Morgan et al, 2011). With the recent licensing of bortezomib, we have a real opportunity to improve on the results of frontline treatment for this group of patients; the progression free survival of patients on the bortezomib arms in the GIMEMA, PETHEMA and IFM studies (36 months – not reached) is superior to that reported for patients receiving CTD (Myeloma IX, 27 months), albeit with the limitations of comparing across studies. As we pointed out at the meeting, the real benefit may lie in getting more of these patients to a stem cell transplant. The availability of bortezomib for frontline therapy will be a significant advance in the therapy of these patients. <u>Request for further analyses</u> We realize that the Committee has requested the manufacturer to carry out further analyses including an indirect comparison between bortezomib in combination with dexamethasone compared with CTD, and compared with another comparator, in situations where a thalidomide containing regimen is not suitable. We welcome this request, as we believe it reflects the Committee's intention to more fully understand the real clinical benefit of the technology in this patient setting. Hence we wish to point out that there are two groups of patients for whom we feel it is vital to have access to a	The VD regimen was included in the scope and was appraised by the Committee). The comparator in the manufacturer's original analysis, vincristine, adriamycin and dexamethasone, was however outside the NICE scope and the Committee also heard that it was no longer used in clinical practice. Please see section 4.19 of the FAD for the Committee's discussion on the updated comparison provided by the manufacturer. Comments noted. In the FAD, the Committee recommended bortezomib as an option within its marketing authorisation, that is, in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adults with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Nominating organisation	Comment	Response
	bortezomib containing regimen for induction therapy prior to stem cell transplantation. Firstly, there is a group of patients for whom thalidomide is clinically unsuitable, eg with a high risk of VTE despite thromboprophylaxis, those intolerant of thalidomide, and those unable to comply with the pregnancy prevention programme. Secondly, there is a group of patients for whom bortezomib would be preferred on clinical grounds, because its relatively fast activity would help prevent irreversible organ damage. Examples of patients in this second group would be those at risk of renal failure from light chain kidney disease, and patients who require rapid tumour reduction because of the risks of hyperviscosity in association with coronary or cerebral vascular disease, or because of impending cord compression from an extradural tumour in the spine (where surgery or radiotherapy is not the preferred treatment because of multi-level disease). These patients may be those whose chances of getting to a stem cell transplant have previously been low, and for whom the availability of a bortezomib containing regimen may make all the difference. They would certainly not feature in the patient group reported by Alvares and co-workers. We wish to conclude with 3 main points: 1. The analysis of the health economic benefits of the VTD regimen is flawed due to the use of the survival data form the Alvares study. We feel that the Alvares study is inappropriate for modeling survival because it reports a highly selected patient group from a single tertiary referral centre whose excellent survival outcomes are unlikely to be representative of the UK patient population with newly diagnosed multiple myeloma who would benefit from a stem cell transplant. 2. The clinical benefit of bortezomib as part of induction therapy in this group of patients is supported by a wealth of clinical trial data, as well as the recent advances in subcutaneous administration and successful prevention and management of treatment–emergent neuropathy. It would be an immense retrograde step for the	

Nominating organisation	Comment	Response
	management of multiple myeloma in the UK if the technology were to be unavailable for these patients, because of uncertainties in health economic modeling that arise from of lack of clinical trial data comparing with CTD, and the current choice of alternative studies. 3. Finally, investing in providing a choice of effective frontline treatments in this incurable disease is crucial because it will impact on the first disease free interval (and hence wellbeing and quality of life). The treatments available differ not only in their mode of action on tumour cells, but also importantly in route of administration, toxicities and likely side effects. Having a choice of active agents around which to base an informed discussion between patient and physician is important for joint decision making, and will ensure that myeloma patients in the UK are able to benefit from the latest therapeutic advances in this disease.	

Comments received from commentators

None received

Comments received from members of the public

None received

Summary of comments received from members of the public

Not applicable