NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Bortezomib and thalidomide for the first-line 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
Celgene	Celgene UK is of the view that all relevant evidence has been taken into account and the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. Whilst we broadly agree with the provisional recommendations, we'd like to reiterate that any final NICE recommendation regarding the first line treatment of multiple myeloma should leave enough room for clinicians and patients to use the treatment which suits them best.	Comment noted
Janssen-Cilag	1.1. Janssen-Cilag welcomes the fact that the committee has recognised that both thalidomide and bortezomib based combinations are more clinically effective and cost-effective than MP alone.	Comment noted
Janssen-Cilag	1.2. We note that the committee's draft recommendation is to restrict the use of bortezomib in combination with an alkylating agent and a corticosteroid to those people who are unable to tolerate or have contraindications to thalidomide. It is on this issue that we would like to focus our response. We will contend that this restriction is inappropriate because it has relied heavily on an assessment report, which is flawed by the omission of key data relevant to and within the scope of this appraisal.	Comment noted
Janssen-Cilag	1.3. Before expanding on our main point, we would first like to comment briefly on the wording in section 1 of the ACD. Our interpretation is that the committee's intention was to make bortezomib containing regimens available as an option for patients who are not appropriate for thalidomide, which is consistent with the language that was used in NICE's press release in which Dr Longson states '....for those people who are unable to take thalidomide, bortezomib was considered an appropriate and cost effective treatment option'[1] (http://www.nice.org.uk/newsroom/pressreleases/DraftGuidanceBortezomibThalidomideMultipleMyeloma.jsp). In our view, the current ACD wording, which defines the group in terms of 'intolerant or contraindicated', does not adequately convey this intention. Our concern is that unless physicians could prove that the patient has a definitive contraindication or clear evidence of intolerance, people will fall into a significant 'third' group. As a consequence they will be disadvantaged as they will only have the option of receiving MP. This is inequitable and would not be an optimal use of NHS resources. We appreciate that this 'third' group is somewhat heterogeneous but would include, for example, people who are unsuitable for thalidomide because of co-morbidities e.g. thromboembolic risk, specific disease features such as high risk cytogenetics or patient characteristics. A better terminology would be to define them as 'not considered appropriate for thalidomide'. We note a similar form of wording was used in section 1 of the recent Topotecan NICE guidance (TA 184), where the committee recommended it as an option where retreatment with a first line agent was 'not considered appropriate'.	Comment noted. The Committee heard different opinions for and against restricting the wording of the guidance around the contraindications to thalidomide and agreed that the SPC for thalidomide covered the safety risks adequately (FAD section 4.3.11)
Janssen-Cilag	2.1. The above comments are only relevant considerations if the committee were to accept that SHTAC's analyses were robust and constituted a sound basis for decision making. Our contention is that this is not the case and in our response below, we will demonstrate that the evidence synthesis developed by the SHTAC was flawed. This is because of the omission of key clinical trial data, which were within the scope of the appraisal and which provided data that is crucial in informing an unbiased evaluation of comparative	Comment noted

Consultee	Comment	Response
	effectiveness. We will demonstrate that the decision to restrict the use of bortezomib regimens to this aforementioned sub population is not supported by the clinical and cost-effectiveness results when all the available evidence is taken into account. Analyses which include all the relevant evidence clearly show that bortezomib is a cost-effective option for front-line patients who are unsuitable for high dose chemotherapy and a stem cell transplant as defined by the product license.	
Janssen-Cilag	2.2. The relative cost-effectiveness of bortezomib and thalidomide is highly sensitive to the relative efficacy of the products in improving overall survival. These estimates of efficacy are properly derived from a full systematic review of the evidence and meta-analysis as specified in the NICE methods guide. One large registration study comparing VMP with MP was identified and both Janssen-Cilag and the SHTAC also identified one study comparing CTDa with MP and five studies comparing MPT with MP. However, Janssen-Cilag and the SHTAC differed in which evidence from these MPT studies was included in the assessment of efficacy. This difference in study inclusion is pivotal, as it results in estimates of relative cost-effectiveness varying from dominance of thalidomide (based on the SHTAC's approach) to both treatments being similarly cost-effective (based on Janssen-Cilag's approach). For clarity we set out the differences in study inclusion below, as studies may be referred to differently by different parties. (Table not replicated here).	Comment noted
Janssen-Cilag	2.3. With this in mind, we would be grateful if the committee would consider the following two major issues that we believe require their attention. 2.3.1. The approach to the evidence synthesis undertaken by the SHTAC was not systematic. The NICE methods guide states that 'The analysis of clinical effectiveness should be based on data from all relevant studies of the best available quality…..' and that 'The process of assembling evidence for health technology assessment needs to be systematic. That is, evidence must be identified, quality assessed and, when appropriate, pooled using explicit criteria and justifiable and reproducible methods'. We contend that the SHTAC's evidence synthesis was not conducted in accordance with these principles. As described above Janssen-Cilag and the SHTAC identified the same five studies assessing the efficacy of MPT, however the SHTAC's approach to study inclusion for evidence synthesis was neither systematic nor justifiable. It is not scientifically valid to exclude critically important studies simply because they have only been published in abstract form, especially when it seems that no attempt has been made to obtain further details (Wijermans 2009 and Gulbrandsen 2008). As we indicated in our response to the assessment report, the investigators of both studies were willing to share further details on these studies, which have both now been published online in peer reviewed journals (Wijermans, 2010; Waage, 2010). In addition, there was an inconsistency in their approach in that the reviewers did seek and obtain additional information for another study that was also published in abstract form only (the MRC Myeloma IX trial). In accordance with NICE's principles therefore, failure to include the full relevant evidence base means that the evidence synthesis is open to selection bias and is not fit for purpose. Furthermore, our results presented below demonstrate that the inclusion of the relevant studies results in a significantly improved estimate of the cost-effectiveness of VMP compared to MPT.	Comment noted. The Assessment Group adhered to the methods outlined in the research protocol when producing the systematic review. The MMIX data were not derived from an abstract publication but from the MMIX study investigators since they were invited to make a submission by NICE. The Committee noted that maintenance with thalidomide monotherapy after first-line treatment

Consultee	Comment	Response
		with a combination regimen did not fall within the appraisal scope. It also noted that, where possible (that is, when available for first-line treatment without maintenance), outcome data (for example, complete response) had been included in the Assessment Group's systematic review of clinical effectiveness see FAD section 4.3.4).
Janssen-Cilag	2.3.2. Exclusion of overall survival from studies including a 'maintenance' phase is inappropriate The evidence base for MPT includes some studies that were designed such that thalidomide was administered to progression up to a maximum dosage period, whilst others were designed such that thalidomide was dosed to progression for a shorter period (induction), and then continued only in those reaching some defined indicator of benefit, normally without a maximum duration. Studies of this latter design have been termed 'maintenance' studies and have been excluded from consideration for overall survival in the ACD. There appears to be two justifications for this exclusion, which we address in turn below: • Overall survival data from studies including a maintenance phase with thalidomide is not considered relevant to the decision problem, as these studies presumably do not reflect clinical practice or the licensed indication for thalidomide. However, we contend that the distinction of 'maintenance' and 'non-maintenance' studies is a false dichotomy given the length of maximum treatment that was allowed in the 'non-maintenance' studies. To illustrate this we can compare the Facon 2007 study, which allowed for treatment to progression of all patients up to a maximum of 72 weeks, with the Palumbo 2008 study which allowed for 24 weeks of treatment followed by maintenance. The reported median doses (217mg in the Facon study, not reported in the Palumbo study but the protocol dose was 100mg daily) and median durations of treatment (11 months in the Facon study and 8 months in the Palumbo study) are consistent with those specified by the SMPC (up to 200mg per day for a maximum number of 12 cycles of 6 weeks (or approximately 18 months)) and therefore relevant to the decision problem. A similar conclusion holds for the other excluded studies.	Comment noted. The Committee noted that the Assessment Group had excluded in which participants received maintenance with thalidomide after first-line treatment. The Committee noted that maintenance with thalidomide monotherapy after first-line treatment with a combination regimen did not fall within the appraisal scope. It also noted

Consultee	Comment	Response
		that, where possible (that is, when available for first-line treatment without maintenance), outcome data (for example, complete response) had been included in the Assessment Group's systematic review of clinical effectiveness (FAD section 4.3.4).
Janssen-Cilag	During the open session of the first appraisal committee meeting it was suggested to the committee that 'maintenance' treatment may worsen overall survival outcomes and that this could explain the heterogeneity of results between those studies that included a maintenance phase and those which did not. Hence this would justify the exclusion of this data from the decision making process. If this was the case we would expect an increase in the heterogeneity between the 'maintenance' and 'non-maintenance' studies over the follow-up period as the maintenance treatment lengthened and its effect became more pronounced on overall survival outcomes. The data does not support this conclusion; in fact the greatest heterogeneity between the 'non-maintenance' and 'maintenance' studies in terms of overall survival is evident early in follow-up before initiation of the maintenance phase (see figure 1 below and Appendix 1) (Not replicated here). Each point on the above graph represents the hazard ratio when the analysis is restricted to a shorter follow up time. That is to say the hazard ratio is derived using all deaths up to that point but excluding further follow up. It can be seen that in all studies excepting the Facon study (Facon 2007) the hazard ratio improves as follow up increases - this pattern is evident regardless of whether the studies included a maintenance phase or not. In the four studies including a maintenance phase, out of the six studies considered, an excess of deaths is seen in the thalidomide arm early in treatment, rather than later in follow up as would be expected if the poor outcome in these studies was due to resistance to subsequent treatments caused by prolonged use of thalidomide as stated in the ACD. Therefore the evidence does not suggest that continued maintenance treatment worsen survival outcomes, but that there is heterogeneity between studies in survival during the induction period. The assumption that these studies should be excluded from the appraisal is therefore scientifically flawed.	Comment noted. A description of Figure 1 has been included in the Evidence Section of the FAD (4.1.20) and considered by the Committee. The Committee concluded (see section 4.3.10) that to afford studies (published and ongoing) in which the results were confounded by treatment outside the appraisal scope equivalent weight to the two key studies without maintenance treatment was not justified (see FAD section 4.3.4).
Janssen-Cilag	2.4. Unfortunately the SHTAC's report does not present estimates of cost-effectiveness including all	Comment noted. The

Consultee	Comment	Response
	survival data whilst also correcting for their error regarding the number of bortezomib vials used in the VISTA trial. Therefore to provide the committee with cost-effectiveness estimates for this scenario we have adjusted our model to include the assumptions used by SHTAC for other parameters (see footnote of Table 1b). We have replicated the SHTAC's cost-effectiveness estimates for their base case and the alternative scenarios as well as providing an ICER for this new scenario (table 1b, column entitled Scenario 4). The close agreement between the two models is demonstrated by comparing the results of Scenario 1 in the SHTAC and Janssen models in tables 1a and b. As reported in column 'Scenario 4' of table 1b, when all the available evidence is used and the correct number of doses is used, the cost-effectiveness ratio for VMP vs. MP is similar to that for MPT vs. MP, and the ratio between VMP and MPT (£14,426) is within the conventionally acceptable range. When the distribution of second line therapies is as observed in the VISTA trial, the ICER for VMP vs. MPT (£21,565) remains within the conventionally acceptable threshold (Scenario 5, Table 1b) (Not replicated here). Table 1. Comparison of the ICERs estimated using the SHTAC's model and Janssen-Cilag's model To ease the comparison of estimates between Tables 1a and b, we have numbered each scenario in Tables 1a and b. 1a. ICERs estimated by the SHTAC (as provided in the SHTAC's report or as presented at the 1st appraisal committee meeting) (Tables not replicated here).	additional cost-effectiveness estimates have been included in the Evidence Section of the FAD (4.2.30) and considered by the Committee. The Committee did not accept the manufacturer of bortezomib's assertion that the bortezomib regimen (VMP) was cost-effective compared with the thalidomide regimen (MPT) (see FAD section 4.3.10).
Janssen-Cilag	2.5. Below we provide the committee with further reassurance that a worsening effect of maintenance treatment is not responsible for improved outcomes and cost-effectiveness of bortezomib vs. thalidomide when all studies are included. We have conducted additional analyses based on the same model as in Table 1b, where we have repeated our evidence synthesis whilst attempting to exclude any effect of maintenance on survival. To achieve this we have based our hazard ratio estimates for survival only on the early phases of these 'maintenance' studies, before maintenance could have any effect on outcomes. The results, based on the most conservative assumptions (see footnote # in Table 2), are presented in table 2 (NB/ as the length of 'induction' in the Gulbrandsen study was not available, two alternative plausible scenarios (24 and 32 weeks) are presented. These are based on the duration of the 'induction' period in the studies by Palumbo (24 weeks) and Wijermans (32 weeks)). These analyses show that the estimates of overall survival are insensitive to the inclusion (base case scenario) or exclusion (alternatives 1 and 2) of the maintenance phases of the three MPT studies (Wijermans 2009, Gulbrandsen 2008, Palumbo 2008). In each of the three scenarios the point estimate for the HR overall survival of MPT vs. MP is between 0.83 and 0.84 and the upper bound of the 95% CI MPT vs. MP is either close to or crossing 1. Details of these analyses are presented in Appendix 1.	Comment noted
Janssen-Cilag	2.6. We also note that the ACD concludes clinical equivalence of CTDa and MPT and therefore the outcomes of the Myeloma IX study are also relevant to the overall assessment of efficacy of thalidomide. Further comment on the handling of survival from this study is provided in the tabulated comments.	Comment noted
Janssen-Cilag	2.7. The ACD also rejects the cost-effectiveness of bortezomib vs. thalidomide due to the inclusion of	Comment noted. The

Consultee	Comment	Response
	differential second line therapy costs in the estimation of cost-effectiveness. These arguments are not justified. A lifetime time horizon has been adopted based on the NICE's methods guide to 'reflect all important differences in costs or outcomes between the technologies being compared'. As the effect of second line therapies on outcomes are already incorporated into the overall survival estimates the cost of these second line therapies should be captured in the modelling. These costs are based on the differential use of second line therapies in the VISTA trial which was supported by clinical experts' opinion and NICE guidance for bortezomib (TA127) in the absence of published data. In addition the effect of these assumptions on estimates of cost-effectiveness supported by scenario analyses presented by both ourselves and SHTAC did not alter the conclusions. We discuss this issue further in the comment template. It may be argued that the extent of differential use should be limited to that seen in the study as it is this use which generated the observed effects. For that reason we have provided scenario 5 in table 2 which is based on the distribution of use of second line therapies observed in the VISTA trial.	Committee agreed that some accounting for second-line treatments was plausible, but not such that the cost of thalidomide in effect carried the cost of bortezomib, and certainly no more than the distribution of second-line treatments noted in the VISTA trial (FAD section 4.3.9).
Janssen-Cilag	3. In summary, Janssen-Cilag believes that when the appropriate clinical evidence base is considered, both bortezomib and thalidomide containing regimens are clinically effective and superior to MP, and are similarly cost-effective to each other. We therefore believe that it would be appropriate to recommend 1) both treatments as options for patients with front line multiple myeloma within the licensed indication and 2) for clinicians to have the ability to chose the treatment which best meets the needs of the individual.	Comment noted
Janssen-Cilag	Appendix 1: Meta-analyses and indirect comparison – additional analyses Additional analyses were performed to assess the impact of the inclusion/exclusion of the maintenance phase on the hazard ratio for overall survival of MPT vs. MP and VMP vs. MPT. Two types of analyses were performed: 1. Cumulative hazard ratio for each individual study in order to identify the maintenance phase on the plots 2. Cumulative HR after meta-analysing the five MPT studies. As the length of 'induction' in the abstract by Gulbrandsen study is not clear, two alternative scenarios are presented in addition to our base case scenarios. These are based on the duration of the 'induction' period in the studies by Palumbo and Wijermans. • Alternative scenario 1: Hulin and Facon: whole duration of the studies; Palumbo = first 24 weeks; Wijermans = first 32 weeks; Gulbrandsen first 24 weeks • Alternative scenario 2: Hulin and Facon: whole duration of the studies; Palumbo = first 24 weeks; Wijermans = first 32 weeks; Gulbrandsen first 32 weeks; The results are embedded in the attached spreadsheet (Not replicated here) and presented as cumulative	Comment noted

Consultee	Comment	Response
	hazard ratios for overall survival for up to 48 months.	
Janssen-Cilag	(Referring to preliminary recommendations page 3) Please refer to section 1 of our cover letter.	Comments noted
Janssen-Cilag	Based on a communication from NICE on 18th June we understand that the assessment group's economic model cannot be released to consultees and commentators because it contains information designated as confidential, and cannot be redacted without producing severe limitations on the functionality of the model. We request that every effort be made to lift the restrictions for the release of the economic model so that all stakeholders can review the disaggregated costs and effectiveness results as these are missing in the SHTAC's report. In the absence of the disaggregated outcomes, we feel that we haven't been able to fully understand the SHTAC modelling in any level of detail during this consultation process. Janssen-Cilag would also welcome the opportunity to discuss the exact nature of the evidence deemed academic in confidence.	Comment noted. The MTA process guide (section 3.4.7) states: 'If the Assessment Group has produced an economic model in support of the assessment report, NICE offers to send it (in its executable form) to consultees and commentators during consultation on the assessment report. This offer is made if the economic model does not contain confidential information.
Janssen-Cilag	(Referring to page 9, section 4.1.5) It is stated that 'The GIMEMA study included maintenance therapy with thalidomide after first-line treatment and therefore overall survival, which was a secondary outcome in this study, was not eligible for inclusion in the Assessment Group's systematic review'. Please refer to sections 2.3.2 and 2.5 of our cover letter demonstrating that the exclusion from the appraisal of studies including a maintenance phase, such as the GIMEMA study, is scientifically flawed.	Comment noted. The Committee noted that the Assessment Group had excluded in which participants received maintenance with thalidomide after first-line treatment. The Committee noted that maintenance with thalidomide monotherapy after

Consultee	Comment	Response
		first-line treatment with a combination regimen did not fall within the appraisal scope. It also noted that, where possible (that is, when available for first-line treatment without maintenance), outcome data (for example, complete response) had been included in the Assessment Group's systematic review of clinical effectiveness (FAD section 4.3.4).
Janssen-Cilag	(Referring to page 12, section 4.1.12) With regard to the VISTA trial it is stated that 'The quality of the RCT was difficult to determine because details needed for quality assessment were incompletely reported. Risk of allocation bias and of unbalanced confounding factors could not be judged because details on these aspects were not reported. Most, but not all analyses had followed the intention-to-treat but the methods used to account for any missing data were not described.' Our submission provided details of how missing data were imputed (page 29) and a quality assessment of the study. Detailed explanation and information on the quality of the VISTA trial is also included in the clinical study report provided in appendix of our submission. The VISTA trial was designed as a registration trial and as such it has been conducted according to the highest standards of Good Clinical Practice, with frequent assessment of clinical outcomes (please refer to Table 5 in our submission page 20) and safety evaluations. The information was therefore readily available to the Assessment group and in accordance with SHTAC's protocol, this information should have been extracted and quality assessed in the same way as the published literature. We request that the statement is amended and the quality of the VISTA study reflected in light of the evidence that was provided to the SHTAC.	Comment noted and section 4.1.12 has been amended.
Janssen-Cilag	(Referring to page 13, section 4.1.13) It is stated: 'it was not possible to estimate overall survival in the group receiving VMP'. We believe that this statement refers to the fact that median overall survival had not been reached for VMP after a median follow-up of 36.7months, and should be amended to reflect this as outcomes for overall survival	Comment noted and section 4.1.13 has been reworded

Consultee	Comment	Response
	are reported from survival analysis and relied on in the assessment.	
Janssen-Cilag	(Referring to page 14-15, section 4.1.18) It is stated that 'data from MMIX trial on overall survival and progression free survival from the study comparing CTDa with MP were not eligible for inclusion in the systematic review undertaken by the Assessment Group because participants were randomised to maintenance therapy with thalidomide after first line treatment'. Please refer to sections 2.3.2 and 2.5 of our cover letter and below in our comments regarding Page 28 section 4.3.3 demonstrating that the exclusion from the appraisal of studies including a maintenance phase, such as the MMIX trial, is scientifically flawed and specifically that data from the MMIX study for those randomised to not receive maintenance is relevant to the assessment of efficacy of thalidomide even if the use of maintenance is not.	Comment noted. The Committee noted that the Assessment Group had excluded studies in which participants received maintenance with thalidomide after first-line treatment. The Committee noted that maintenance with thalidomide monotherapy after first-line treatment with a combination regimen did not fall within the appraisal scope. It also noted that, where possible (that is, when available for first-line treatment without maintenance), outcome data (for example, complete response) had been included in the Assessment Group's systematic review of clinical effectiveness (FAD section 4.3.4).
Janssen-Cilag	(Referring to page 23, section 4.2.21) It is stated that 'the Assessment Group undertook an additional analysis in which it was assumed that four cycles or 31 vials of bortezomib was used, with no loss of efficacy'. It is wrong to position this as a "scenario" and refer to 'no loss of efficacy'. The 31.5 vials represent the actual	Comment noted

Consultee	Comment	Response
	average number of vials used in the VISTA trial to achieve the clinical effect observed. It is methodologically incorrect to assume a cost for the per-protocol number of vials as the number of vials, and hence cost, should reflect the efficacy demonstrated in the study. To do so would result in a different base case to that used for thalidomide in this appraisal and to the way in which drug costs are calculated in all other appraisals. Throughout our modelling we do not provide any cost adjustments for vial sharing, but we do know that it happens increasingly in many centres. We note that assumptions around vial sharing have been acknowledged in other cancer appraisals and that there is a need for consistency of approach. Whilst we have not provided a specific analysis of vial sharing in our appraisal, we would be happy to do so if it would be useful. In the meantime, we request that the word "scenario" is removed throughout the ACD when the use of 31.5 vials is referred to, as this is the appropriate base case. We would also request at least qualitative consideration of the fact that with vial sharing, which could reasonably be 30% or higher in some units, will occur, reducing the ICERs further. Using 31.5 vials is therefore a conservative estimate of the true costs in clinical practice.	
Janssen-Cilag	(Referring to page 23, section 4.2.20) It is stated that 'In scenario A (no subsequent therapies) the ICERs for MPT, CTDa and VMP versus MP increased from £9174, £29,837, £33,216 to £9738, £34,013 and £37,727 per QALY gained respectively.' We believe the underlined figures have been transposed and therefore request the amendment of the statement as underlined: 'In scenario A (no subsequent therapies) the ICERs for MPT, CTDa and VMP versus MP increased from £9174, £33,216, £29,837 to £9738, £34,013 and £37,727 per QALY gained respectively.'	Commented noted and text has been amended.
Janssen-Cilag	(Referring to page 23, section 4.2.22) It is stated that 'the manufacturer of thalidomide conducted a mixed-treatment comparison for MPT versus MP with trials that included thalidomide maintenance'. The statement needs to be revised as underlined: 'the manufacturer of bortezomib conducted a mixed-treatment comparison for MPT versus MP with trials that included thalidomide maintenance'.	Commented noted and text has been amended
Janssen-Cilag	(Referring to page 26, section 4.2.30) It is stated that 'the ICER for VMP versus MP varied between £10,498 (manufacturer of bortezomib) and £44,838 (calculated by the Assessment Group to allow a comparison between the manufacturers' and Assessment Group's economic models) per QALY gained.' In section 4.2.17 page 22, the ICER presented in the base case for VMP vs. MP is £29,837. Therefore we believe that the statement in section 4.2. 30 should be revised as underlined: 'the ICER for VMP versus MP varied between £10,498 (manufacturer of bortezomib) and £29,837 (calculated by the Assessment Group to allow a comparison between the manufacturers' and Assessment Group's economic models) per QALY gained.' In addition, in order to appropriately compare our ICER for VMP vs. MP with their ICER, the SHTAC should use 31.5 vials of bortezomib and not 52.	Comment noted. As Celegene did not provide an ICER for VMP versus MP, the Assessment Group calculated the ICER (£44,838) to allow comparison between the manufacturer and Assessment Group models. Section 4.2.35 has been amended for

Consultee	Comment	Response
		clarity.
Janssen-Cilag	(Referring to page 28 section 4.3.3) It is stated that 'data from the GIMEMA and ongoing MMIX studies had been excluded because participants in the studies had been randomized to receive maintenance with thalidomide or no therapy after they had completed first-line treatment.' This statement is incorrect as only the ongoing MMIX study includes a randomization to maintenance thalidomide after patients received CTDa or MP. The fact that 'maintenance is randomized' means that data for patients who did not receive maintenance therapy is available and this is relevant to the overall efficacy estimates for thalidomide given the committee's acceptance of clinical equivalence between MPT and CTDa. Please refer to section 2.6 of our cover letter. Furthermore the ACD states that data from this study for overall survival is available for patients not randomized to maintenance and that this data was carefully considered by the committee. This data clearly forms part of the evidence base for the effect of thalidomide on overall survival, even if committee persisted with excluding maintenance treatment. Whilst we appreciate the concerns regarding the small number available for analysis, this is not a scientific justification for exclusion of this data. The correct approach would be to allow the uncertainty implicit in these small numbers to be accounted for appropriately through meta-analysis. If the patient level data were available then patients could be justifiably censored at the point of entering maintenance given this decision was based on randomization and therefore not associated with subsequent mortality risk or a time-dependent covariate for maintenance included. In the GIMEMA study by Palumbo et al, thalidomide was administered at 100 mg per day continuously during the six MPT cycles, and then at 100 mg per day, as maintenance therapy, until confirmed evidence of relapse or refractory disease.	Comment noted
Janssen-Cilag	(Referring to page 29, section 4.3.3) It is incorrectly stated that 'the two studies without maintenance treatment were the only two complete studies matching the decision problem (which did not include maintenance).' Please refer to sections 2.2 and 2.3.1 of our cover letter.	Comment noted. The Committee noted that the Assessment Group had excluded studies in which participants received maintenance with thalidomide after first-line treatment. The Committee noted that maintenance with thalidomide monotherapy after

Consultee	Comment	Response
		first-line treatment with a combination regimen did not fall within the appraisal scope (FAD section 4.3.4).
Janssen-Cilag	(referring to page 29, section 4.3.3) It is stated that 'The Committee was mindful that maintenance therapy data was not included in the Assessment Group's systematic review but it considered very carefully data from the small number of patients who were randomized to receive no treatment therapy in the MMIX trial.' Please refer to sections 2.3.2, 2.5 and 2.6 of our cover letter as well as our comment above regarding Page 28 section 4.3.3. In addition the protocol of the SHTAC does not specify the presence of a maintenance phase as an exclusion criterion of their systematic review. The three MPT studies including a maintenance phase were conducted in the appropriate population and included the relevant regimen, ie. MPT and MP.	Comment noted. The Committee noted that the Assessment Group had excluded studies in which participants received maintenance with thalidomide after first-line treatment. The Committee noted that maintenance with thalidomide monotherapy after first-line treatment with a combination regimen did not fall within the appraisal scope. It also noted that, where possible (that is, when available for first-line treatment without maintenance), outcome data (for example, complete response) had been included in the Assessment Group's systematic review of clinical effectiveness (FAD section 4.3.4).

Consultee	Comment	Response
Janssen-Cilag	(Referring to page 31, section 4.3.7) It is incorrectly stated that 'This gave an ICER of 22,500 per QALY gained for VMP compared with MP'. According to the slide 15 presented by Peter Jackson at the first appraisal committee meeting, the ICER for VMP vs. MP is £18,996 per QALY gained assuming 31.5 vials of bortezomib. The above statement needs to be revised as underlined: 'This gave an ICER of £18,996 per QALY gained for VMP compared with MP'. This revision also needs to be done in the tabulated summary of the Appraisal Committee's key conclusions.	Comment noted and has been addressed in section 4.3.8 of the FAD
Janssen-Cilag	(Referring to page 31-32, section 4.3.8) It is stated that 'the Committee did not accept the manufacturer of bortezomib's assertion that the bortezomib regimen (VMP) was cost-effective compared with the thalidomide regimen (MPT) for two reasons': 1. The inclusion of maintenance thalidomide trials in the meta-analysis. We have already commented on this point. Please refer to sections 2.3.2 and 2.5 of our cover letter and above. 2. The cost of 2nd line therapy. It is stated: 'this included adding the cost of thalidomide to the bortezomib regimen, and of bortezomib to the thalidomide regimen, neutralizing the approximately four-fold cost advantage of thalidomide, and greatly increasing the cost of MP.' a. In our submission (page 64) the cost of bortezomib (£24K) is approximately twice the cost of thalidomide (£10K in MPT) based on the average number of vials (n=31.5) actually used in the VISTA trial. We believe that the statement 'the four-fold cost advantage of thalidomide' is based on the number of vials as per protocol (n=52) which the appraisal committee has acknowledged as incorrect. b. In our submission (page 64) the inclusion of the cost of 2nd and 3rd line therapies leads to an increase in the cost of chemotherapy post-progression of approximately £8K in the MPT arm (vs. VMP arm). c. Therefore the addition of the costs of 2nd and 3rd line therapies does not neutralize the total cost difference between thalidomide and bortezomib. Instead the total cost for VMP is 6K higher than the total cost for MPT when the drug cost for 1st, 2nd and 3rd line therapies is taken into account. d. As the clinical effects of 2nd and 3rd line therapies are intrinsic to overall survival estimates, the cost of these second line therapies should be captured in the economic analysis. Please refer to section 2.7 of our cover letter. e. In the base case scenario of our submission the cost of 2nd line therapies is based on the differential use of second line therapies in the VISTA trial which was supported by clinical experts' opinion and NICE guidance for Bortezomib (TA127). Both we and the Assessment Group undertook sensitivity analyses to investigate the effect of the frequency of use of 2nd line therapies. Scenarios were: no subsequent therapy and subsequent therapies as per the VISTA trial. Whilst the ICERs were increased the effect did not change the conclusions. Please refer to section 2.7 and Table 1b of our cover letter.	Comment noted.
DOH	No comments.	

Consultee	Comment	Response
WAG	No comments.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal College of Pathologists and British Society for Haematology	The Royal College of Pathologists and the British Society for Haematology welcome the Appraisal Committee's preliminary recommendations and believe that if implemented the guidance would ensure that patients would receive therapy that gives the best chance of prolonged survival and improved quality of life.	Comment noted
Royal College of Pathologists and British Society for Haematology	We agree that relevant evidence has been taken into account and particularly appreciate the fact that the Committee has taken into consideration data from the MRC Myeloma IX trial, which in addition to related evidence from clinical experts, has been used in formulating provisional guidance. One consequence of this is that clinicians are able to select the alkylating agent (either Melphalan or Cyclophosphamide) which most appropriately meets the clinical needs of an individual patient. It is a matter of regret that because of the design of some otherwise relevant trials it was not possible to include all their data. We therefore welcome initiatives which encourage NICE's closer involvement in trial design in future.	Comment noted
Royal College of Pathologists and British Society for Haematology	We note the wide variation in the results of economic analyses provided by both the manufacturers and the assessment group and recognise the difficulty this creates in determining the clinical and cost effectiveness of the technologies under consideration, but believe that the committee has taken into account all the variables and produced a fair and reasonable interpretation of the evidence. We particularly welcome the re-evaluation of the ICER of Bortezomib at £22,500 per QALY gained for VMP compared with MP as a result of accepting that four cycles (31 vials) was more likely to reflect clinical practice than the 40 vials used in initial calculations. We confirm that 31 vials agree more closely with clinical practice than the higher figure of 40.	Comment noted. Following consultation comments from the Assessment Group and on further discussion with both the manufacturer and the Assessment Group at the second meeting, the Committee considered that the costs of delayed doses might still reflect clinical practice and need to be considered. It therefore agreed that

Nominating organisation	Comment	Response
		the manufacturer's preference for modelling 31.5 vials had to be considered the most optimistic estimate for clinical practice (FAD section 4.3.8).
Royal College of Pathologists and British Society for Haematology	We agree that the recommendations are sound and a suitable basis for guidance to the NHS and if implemented will permit clinicians to select in the context of the MDT process, the most suitable regimen for an individual patient. We believe that this flexibility in itself will lead to greater cost effectiveness, maximising as it will the chance to improve renal function, to avoid serious thrombotic problems and minimise the costs associated with treating these myeloma or treatment related problems. Furthermore and most importantly the consequence of the recommendations will also be that patients will have the greatest chance of best response and improved quality of life.	Comment noted
Royal College of Pathologists and British Society for Haematology	We do however have some reservations about the wording of the guidance and are concerned that the use of the word 'contraindications' in para 1.2 of the guidance 'the person is unable to tolerate or has contraindications to thalidomide' may be open to misinterpretation. We believe that the intention of the Committee is to recommend that clinicians, whilst using a thalidomide regimen in the majority of patients, should be able to select a bortezomib regimen for those patients who would be disadvantaged by treatment with thalidomide. These patients would include those at high risk of thrombosis, or with impaired renal function. In such patients, the use of 'bortezomib in combination with an alkylating agent and a steroid is likely to be a cost-effective option…' because it is the only option that is as clinically effective in treating the cancer.	Comment noted. The Committee heard different opinions for and against restricting the wording of the guidance around the contraindications to thalidomide and agreed that the SPC for thalidomide covered the safety risks adequately (FAD section 4.3.11)
Royal College of Pathologists and British Society for Haematology	We are anxious lest the term 'contraindications' is interpreted in the pharmacological sense to mean the contraindications which are listed in the SPC for thalidomide which are as follows: - Hypersensitivity to thalidomide or to any of the recipients. - Pregnant women (see section 4.6). - Women of childbearing potential unless all the conditions of the Thalidomide Celgene Pregnancy Prevention Programme are met. - Patients unable to follow or comply with the required contraceptive measures.	Comment noted. The Committee heard different opinions for and against restricting the wording of the guidance around the contraindications to

Nominating organisation	Comment	Response
	These do not cover the clinical situations in which thalidomide would be considered to be clinically inappropriate, as stated above and in section 4.3.2 of the ACD. We would like to avoid any such opportunities for misinterpretation which may lead to conflict between clinicians and PCT's, resulting in delays to patients receiving effective treatment, and in 'post-code prescribing'. We would therefore respectfully suggest that the Committee consider replacing the term 'contraindicated' by 'clinically inappropriate' or using the form of words as in para 4.3.2 of the ACD to qualify 'contraindicated' by saying 'such as those with clotting disorders and impaired renal function'.	thalidomide and agreed that the SPC for thalidomide covered the safety risks adequately (FAD section 4.3.11)
Royal College of Pathologists and British Society for Haematology	In summary the provisional recommendations of the Appraisal Committee are welcomed by RCPath and BSH as we believe they will ensure patients will receive effective therapy to have the best chance of prolonged survival and improved quality of life. To avoid misinterpretation of the Committee's intentions we suggest a change of wording of para 1.2 of the provisional recommendations.	Comment noted
Myeloma UK	Myeloma UK is pleased to submit this response to the Appraisal Committee's provisional recommendations on the above technologies. Myeloma UK welcomes the provisional recommendations and considers them to be a sound and suitable basis for guidance to the NHS and of significant benefit to patients. We have made one suggested change to paragraph 1.2 – details of this change you will find under Q2 below.	Comment noted
Myeloma UK	Myeloma UK is not aware of any evidence that has been missed which would have had an impact on the draft recommendations.	Comment noted
Myeloma UK	We consider that the Appraisal Committee has reached a fair and reasonable interpretation on the evidence in its summaries of clinical and cost effectiveness. We are satisfied that the Appraisal Committee has made valid assumptions in its modeling and produced an appropriate economic analysis. Myeloma UK accepts the ERG's conclusion that the two thalidomide-containing regimens (MPT and CTDa) are clinically and cost effective compared with melphalan and prednisolone (MP) alone. We also accept the conclusion that the bortezomib-containing regimen (VMP) is clinically and cost effective compared with MP. We accept that on the basis of the data reviewed that VMP appears less cost effective than MPT when both are compared with MP. We also accept the analysis showing that when directly compared with MPT, VMP is not cost effective; however, we consider the VMP vs. MPT comparison may be unnecessary in the context of this guidance.	Comment noted

Nominating organisation	Comment	Response
Myeloma UK	Myeloma UK considers that the provisional recommendations make a sound and suitable basis for guidance to the NHS, however we suggest a small change to the wording in paragraph 1.2 from its current form: *Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for first-line treatment of multiple myeloma in people for whom:* • *high-dose chemotherapy with stem cell transplantation is considered inappropriate* ***and*** • *the person is unable to tolerate or has contraindications to thalidomide* to read: *Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for first-line treatment of multiple myeloma in people for whom:* • *high-dose chemotherapy with stem cell transplantation is considered inappropriate* ***and*** • *a thalidomide-containing regimen is considered inappropriate* We believe that this would better reflect the Appraisal Committee's findings that (a) both thalidomide and bortezomib-containing regimens are clinically and cost effective; (b) thalidomide offers a more cost-effective option compared to melphalan and prednisolone than the bortezomib regimen offers; and (c) thalidomide is the preferred choice of clinicians for this patient group, unless considered clinically inappropriate. We believe that the Appraisal Committee's intention is to reflect their findings that while thalidomide is generally the preferred treatment, various factors may mean it is inappropriate for individual patients, and bortezomib would offer a preferable alternative. We are concerned that the current wording in paragraph 1.2. that "*the person is unable to tolerate or has contraindications to thalidomide*" does not accurately or fully reflect the possible reasons why thalidomide may not be considered to be appropriate. In 4.3.2 the Committee accepted that *"the choice of treatment for an individual patient will depend on the co-morbidities present and the different mechanisms of action and side effect profiles of the treatments".* However, there may also be other important patient factors which would influence choice of treatment, such as ability to comply with taking tablets or other issues which occasionally arise. Referring uniquely to intolerance and to the stated contraindications for thalidomide may place an unhelpful limit on clinicians' flexibility to use their judgment about what is appropriate, and could potentially cause difficulties in prescribing locally. Myeloma UK believes a change to the wording as per our suggestion above would avoid any potential	Comment noted. The Committee heard different opinions for and against restricting the wording of the guidance around the contraindications to thalidomide and agreed that the SPC for thalidomide covered the safety risks adequately (FAD section 4.3.11)

Nominating organisation	Comment	Response
	difficulties and better reflect the findings of the Appraisal Committee.	
Macmillan Cancer Support	Macmillan would like to support all the points put forward in the attached statement from Myeloma UK.	Comment noted
Royal College of Physicians	We welcome the Appraisal Committee's preliminary recommendations. Give the currents state of knowledge, we believe that this guidance offers therapy for patients with myeloma that provides the best opportunity to prolong survival and to improve quality of life.	Comment noted
Royal College of Physicians	We recognise the flaws in some clinical trial designs that make it difficult to generalise the results and therefore to utilise the data in coming to meaningful recommendations in relation to optimal patient management. However, we agree that every effort has been made to include all relevant evidence in reaching this provisional guidance. By making these recommendations the Committee have shown that they are cognisant of the need for clinicians to select therapy that most appropriately meets individual patient circumstances and hence maximising disease response whilst minimising toxicity and side-effects.	Comment noted
Royal College of Physicians	We believe that the committee's summaries of the clinical and cost effectiveness have taken into account the wide variation in the results of economic analyses provided by the manufacturers and the assessment group. It is important to note that the group accepted the expert clinical advice relating to the fact that in clinical practice less vials were utilised than in the initial assessment. This has clearly impacted on the ICER for bortezomib.	Comment noted
Royal College of Physicians	It is important that the final guidance provided by the assessment group is clear and leaves no room for conflict between clinicians and providers. Such conflict, could lead to treatment delays or the delivery of inappropriate treatment. The word 'contraindications' as applied in para 1.2 of the guidance suggests that bortezomib is a default position from thalidomide and may disadvantage individuals at high risk of toxicity from using either thalidomide (eg if they have a past history of thrombosis or renal failure) or bortezomib (eg if there is a history of neurological damage). We would suggest that in order to accommodate clinical decision making, the term 'contraindicated' should be replaced by the term 'clinically inappropriate'. We do, however, agree that the provisional recommendations provide a sound and suitable basis for guidance to the NHS. We believe that it offers clinicians the opportunity to use clinical judgement on an individual basis to maximise and improve outcomes for patients with this life-threatening disease whilst optimising the cost to the NHS.	Comment noted. The Committee heard different opinions for and against restricting the wording of the guidance around the contraindications to thalidomide and agreed that the SPC for thalidomide covered the safety risks adequately (FAD section 4.3.11)
Royal College of Physicians	The recommendations have taken into consideration the available data from what is a rapidly developing field. They recognise the fact that the disease and patients are heterogeneous requiring a degree of risk adjusted therapy in order to maximise responses whilst optimising the toxicity profile of treatment combinations to enhance quality of life.	Comment noted

Nominating organisation	Comment	Response
Royal College of Nursing	*(Has the relevant evidence has been taken into account?)* The evidence considered seems comprehensive.	Comment noted
Royal College of Nursing	*(Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?)* This seems appropriate.	Comment noted
Royal College of Nursing	*(Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?)* Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted
Royal College of Nursing	*(Are there any equality related issues that need special consideration that are not covered in the ACD?)* None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	Comment noted
Leukaemia CARE	With reference to the above ACD – Leukemia CARE fully endorses the response sent in by Myeloma UK. We also welcome the provisional recommendations made by NICE and, like Myeloma UK, we consider them to be a sound and suitable basis for guidance in the NHS, and to be of significant benefit to myeloma patients.	Comment noted
UK Myeloma Forum	The UKMF welcomes the Appraisal Committee's preliminary recommendations and believe that if implemented the guidance would ensure that patients would receive therapy that gives the best chance of prolonged survival and improved quality of life.	Comment noted
UK Myeloma Forum	*(Has all the relevant evidence been taken into account?)* We agree that relevant evidence has been taken into account and particularly appreciate the fact that the Committee has taken into consideration data from the MRC Myeloma IX trial, which in addition to related evidence from clinical experts, has been used in formulating provisional guidance. One consequence of this is that clinicians are able to select the alkylating agent (either Melphalan or Cyclophosphamide) which most appropriately meets the clinical needs of an individual patient. It is a matter of regret that because of the design of some otherwise relevant trials it was not possible to include all their data. We therefore welcome initiatives which encourage NICE's closer involvement in	Comment noted

Nominating organisation	Comment	Response
	trial design in future.	
UK Myeloma Forum	*(Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?)* We note the wide variation in the results of economic analyses provided by both the manufacturers and the assessment group and recognise the difficulty this creates in determining the clinical and cost effectiveness of the technologies under consideration, but believe that the committee has taken into account all the variables and produced a fair and reasonable interpretation of the evidence. We particularly welcome the re-evaluation of the ICER of Bortezomib at £22,500 per QALY gained for VMP compared with MP as a result of accepting that four cycles (31 vials) was more likely to reflect clinical practice than the 40 vials used in initial calculations. We confirm that 31 vials does accord more closely with clinical practice than the higher figure of 40.	Comment noted. Following consultation comments from the Assessment Group and on further discussion with both the manufacturer and the Assessment Group at the second meeting, the Committee considered that the costs of delayed doses might still reflect clinical practice and need to be considered. It therefore agreed that the manufacturer's preference for modelling 31 vials had to be considered the most optimistic estimate for clinical practice (FAD section 4.3.8).
UK Myeloma Forum	*(Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?)* We agree that the recommendations are sound and a suitable basis for guidance to the NHS and if implemented will permit clinicians to select in the context of the MDT process, the most suitable regimen for an individual patient. We believe that this flexibility in itself will lead to greater cost effectiveness, maximising as it will the chance to improve renal function, to avoid serious thrombotic problems and minimise the costs associated with treating these myeloma or treatment related problems. Furthermore and most importantly the consequence of the recommendations will also be that patients will have the greatest chance of best response and improved quality of life.	Comment noted

Nominating organisation	Comment	Response
UK Myeloma Forum	We do however have some reservations about the wording of the guidance and are concerned that the use of the word 'contraindications' in para 1.2 of the guidance 'the person is unable to tolerate or has contraindications to thalidomide' may be open to misinterpretation. We believe that the intention of the Committee is to recommend that clinicians, whilst using a thalidomide regimen in the majority of patients, should be able to select a Bortezomib regimen for those patients who would be disadvantaged by treatment with thalidomide. These patients would include those at high risk of thrombosis, or with impaired renal function. We are anxious that the term 'contraindications' may be interpreted in the pharmacological sense to mean the contraindications which are listed in the SPC for thalidomide which are as follows: - Hypersensitivity to thalidomide or to any of the excipients. - Pregnant women - Women of childbearing potential unless all the conditions of the Thalidomide Celgene Pregnancy Prevention Programme are met - Patients unable to follow or comply with the required contraceptive measures These do not cover the clinical situations in which thalidomide would be considered to be clinically inappropriate, as stated above and in section 4.3.2 of the ACD. We would like to avoid any such opportunities for misinterpretation which may lead to conflict between clinicians and PCT's, resulting in delays to patients receiving effective treatment, and in 'post-code prescribing'. We would therefore respectfully suggest that the Committee consider replacing the term 'contraindicated' by 'clinically inappropriate' or using the form of words as in para 4.3.2 of the ACD to qualify 'contraindicated' by saying 'such as those with clotting disorders and impaired renal function'.	Comment noted. The Committee heard different opinions for and against restricting the wording of the guidance around the contraindications to thalidomide and agreed that the SPC for thalidomide covered the safety risks adequately (FAD section 4.3.11)
UK Myeloma Forum	In summary the provisional recommendations of the Appraisal Committee are welcomed by UKMF as we believe they will ensure patients will receive effective therapy to have the best chance of prolonged survival and improved quality of life. To avoid misinterpretation of the Committee's intentions we suggest a change of wording of para 1.2 of the provisional recommendations.	Comment noted

Comments received from commentators

Commentator	Comment	Response
Southampton	*(Referring to 4.1.4 IFM 01/01 study reported median progression-free survival of 24.1 months (95% confidence intervals [CI] 19.4 to 29.0) for the MPT group compared with 18.5 months (95% CI 0.39 to 0.66) for the MP*	Comment noted and

Commentator	Comment	Response
Health Technology Assessments Centre (SHTAC)	*group after a median follow up of 47.5 months. [….].)* The 95% CI values reported are those for the 99/06 PFS hazard ratio. The 95% CI that should have been reported is 95% CI 14.6 to 23.1	addressed in FAD section 4.1.4
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.5 […] The hazard ratio (HR) for overall survival from the meta-analysis was 0.62 (95% CI 0.50 to 0.77) and showed that there was little or no heterogeneity between the three trials for this outcome.)* Only two trials included in this meta-analysis.	Comment noted and addressed in FAD section 4.1.5
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.6 ….] Complete response outcomes from the three studies were combined by meta-analysis, and this confirmed that MPT was superior to MP in terms of the proportion of patients achieving a complete response (relative risk [RR] 5.49, 95% CI 2.55 to 11.38).* Value should be 11.83. The incorrect value of 11.38 came from the text of the Assessment Group report, which has now been amended. Value in the accompanying Figure 3 is correct.	Comment noted and addressed in FAD section 4.1.6
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.7 ….] For thrombosis or embolism, somnolence, constipation and infections, the results were inconsistent between IFM 99/06 and IFM 01/01, with no significant difference in incidence in the IFM 01/01 study and statistically significantly more of these events in the MPT group in the IFM 99/06 study. This inconsistency may be a result of the different methods of reporting adverse events.)* The statement on incidence is not true with regard to infections. There was no statistically significant difference in the number of patients with infections of grade 3 and 4 (p=0.32) in the IFM 99/06 study. There was no detailed reporting on infections for the IFM 01/01 study.	Comment noted and addressed in FAD section 4.1.7
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.9 The Assessment Group identified one ongoing RCT, the UK Multiple Myeloma IX (MMIX) trial, which compared CTDa with MP. ….])* More than one ongoing RCT was identified by the Assessment Group – although the Assessment Group only had sufficient information on one, MMIX, enabling its inclusion in the report. Suggest text is changed to 'The Assessment Group identified an ongoing RCT, the UK Multiple Myeloma IX (MMIX) trial, which compared CTDa with MP.'	Comment noted and addressed in FAD 4.1.9
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.12 ….] Most, but not all analyses had followed the intention-to-treat but the methods used to account for any missing data were not described.)* Suggest alter wording; Most, but not all analyses had followed intention-to-treat principles but the methods used to account for any missing data were not described.	Comment noted and addressed in FAD section 4.1.12

Commentator	Comment	Response
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.13 [….] More recently reported 3-year survival rates after a median follow-up of 36.7 months are 68.5% versus 54% respectively. A median overall survival of 43.1 months for participants receiving MP; it was not possible to estimate overall survival in the group receiving VMP.[….])* Rather confused sentence, needs amending.	Comment noted and addressed in FAD section 4.1.13
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.13 [….] Median progression-free survival was 21.7 months for the VMP group compared with 15.2 months for the group receiving MP (HR 0.56, p < 0.001). [….])* For clarity, we suggest text is added to indicate this was after a median follow up of 16.3 months.	Comment noted and addressed in FAD section 4.1.13
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.17 […] Three studies (IFM 99/06, IFM 01/01 and GIMEMA) provided evidence of a complete response in a statistically significantly greater proportion of participants receiving MPT (RR 5.49, 95% CI 2.155 to 11.38). [….])* Errors in the values provided: (RR 5.49, 95% CI 2.55 to 11.83) As noted before 11.38 was an error in the Assessment Group report.	Comment noted and addressed in FAD section 4.1.17
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.1.19)* Omits time to disease progression which was the primary outcome of the VISTA trial.	Comment noted and addressed in FAD sections 4.1.13 and 4.1.19
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.2.8, 4.2.26, 4.3.7, 31.5 vials)* This is CIC data and should be blacked out.	Comment noted. The CIC status of this information has been checked and it is no longer CIC
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.2.18 VMP compared with MPT associated with ICER of £28,907 per QALY gained.)* This should read: VMP compared with CTDa associated with ICER of £28,907 per QALY gained.	Comment noted and addressed in FAD section 4.2.18
Southampton Health Technology Assessments Centre (SHTAC)	*(Referring to 4.2.22 The manufacturer of thalidomide conducted a mixed-treatment comparison for MPT versus MP with trials that included thalidomide maintenance.)* This is incorrect and should be the manufacturer of bortezomib.	Comment noted. and addressed in FAD section 4.2.22
Southampton	*(Referring to 4.3.8 The Committee noted the differences in the ICERs presented by the Assessment Group and*	Comment noted

Commentator	Comment	Response
Health Technology Assessments Centre (SHTAC)	*the manufacturer of bortezomib for VMP compared with MP. Apart from the fewer vials of bortezomib assumed by the manufacturer, which the Committee accepted, the manufacturer of bortezomib model also included costs for second-and third-line treatments. This included adding the cost of thalidomide to the bortezomib regimen, and of bortezomib to the thalidomide regimen, neutralising the approximately four-fold cost advantage of thalidomide, and greatly increasing the cost of MP.)* As paragraph 4.3.8 currently reads it could be misinterpreted – the reader might believe that the Assessment Group omitted costs of second- and third-line treatment. In fact, the assessment group included costs for second-line therapy. Only the manufacturer of thalidomide did not include costs for second- and third-line treatments.	
Clinical Trials Research Unit, University of Leeds	The Myeloma IX Trial Management Group welcomed the opportunity to submit the results of the MRC Myeloma IX Trial for consideration in this appraisal, and thank NICE and the Assessment Group for respecting the confidential nature of these data. We were disappointed that only the response data from the Myeloma IX Trial was included in the systematic review, and that the overall survival, progression-free survival, adverse events and health-related quality of life data were considered not eligible for inclusion because of the maintenance randomisation component of the trial. We note that the additional data we submitted from the small number of patients who were randomised to receive no maintenance therapy, were considered, but not included in the review, as the data were considered too immature and for a small number of patients. There is no mention in the consultation document about the additional modelling data that we submitted which included larger patient numbers (patients excluded from the maintenance randomisation plus patients randomised to receive no maintenance therapy). Despite these concerns, we support the Committee's recommendation that 'Thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate.' We would be delighted to continue to cooperate with NICE in their consideration of the Myeloma IX data and share the results of our further analyses when the guidance is reviewed. The proposed timeline of August2013 would tie in very well with our next planned analysis.	Comment noted and the document has been revised (see FAD section 4.1.10).
NHS Quality Improvement Scotland (QIS)	*(Has the relevant evidence has been taken into account?)* 1) Yes all relevant evidence had been taken into account. 2) Vial sharing for patients receiving bortezomib is common practice (4.2.16 not correct assumption, but addressed in committee's comments). Need to define what is meant by 'contra-indication to thalidomide'. The clinical contra-indications are much broader, I think, than on the SPC or in the BNF. They include neuropathy, recent ischaemic or thromboembolic event, contra-indication to anticoagulation etc. *3)* Yes.	Comments noted. The Committee heard different opinions for and against restricting the wording of the guidance around the

Commentator	Comment	Response
		contraindications to thalidomide and agreed that the SPC for thalidomide covered the safety risks adequately (FAD section 4.3.11)
NHS Quality Improvement Scotland (QIS)	*(Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?)* 1) Yes the summaries are reasonable intepretations of evidence. *2)* See section 4.2.16- the costs will be greater if use CTDa (or MPT) first-line as most clinicians will use bortezomib/dexamethasone based regimen second line. *3)* Yes.	Comments noted
NHS Quality Improvement Scotland (QIS)	*(Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?)* 1) In practice the recommendation that bortezomib can be used as first line therapy in patients for whom thalidomide is contraindicated will only apply to a very small minority of patients. The recommendation that intolerance to thalidomide would allow use of bortezomib is superfluous as this essentially would be second line therapy for which bortezomib is currently already approved. 2) Yes. *3)* Yes.	Comments noted
NHS Quality Improvement Scotland (QIS)	*(Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?)* Statement in 4.2.9 not correct – lenalidomide/dexamethasone is still not approved by most health boards in Scotland for 3rd line use. Also, if VMP used first-line, with long remission, it is not unreasonable to use bortezomib again third-line, although most would not use it second line in this instance.	Comment noted. The modelling reflected current NICE guidance
NHS Quality Improvement Scotland (QIS)	*(Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment.)* Very helpful Appraisal/Health Economic Assessment for determining first-line treatment of multiple myeloma for	Comment noted

Commentator	Comment	Response
	patients not suitable for stem cell transplantation.	

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	There is growing evidence that Bortezumib is most effective in the first-line setting and the option to use it is welcomed. However I would question whether its use should be limited to patients unsuitable for transplant as it is an excellent "cyto-reducer" of tumour load prior to transplant and may help to give a cleaner harvest of stem-cells. I would also question whether its use should always be exclusive of Thalidomide, unless you are going to allow its use with Lenolidamide where there appears to be considerable synergy between the drugs - unfortunately at considerable financial cost.	Comment noted
NHS Professional	2	Recent European studies presented last week at EHA show responses equivalent to HDT & transplant with the combination of Bortezumib, Lenolidamide & Dexamethasone. In a condition like Myeloma the quality of life is paramount & the avoidance of skeletal damage is crucial in avoiding pain.	Comment noted
NHS Professional	3	The neuropathy of Bortezumib is worse if there is a pre-existing neuropathy from Thalidomide. Some EU workers have used reduced dosages in combination with no significant deterioration of response or side-effects. Lenolidamide doesn't share the neuropathy profile & is becoming the favoured partner for Bortezumib in countries where cost doesn't limit drug-use. The diarrhoea associated with Bortezumib can be very troublesome in a few individuals.	Comment noted
NHS Professional	4	Very difficult to be certain you are comparing like with like in terms of patient selection. The studies used have reputable sources and reasonable length of follow-up given the pressures of assessing new technology. The newer studies I mentioned earlier are even less mature.	Comment noted
NHS Professional	5	No comment.	
NHS Professional	6	No comment.	
NHS Professional	7	No comment.	
NHS Professional	8	No comment.	

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
NHS Professional	Summary of Appraisal Committees key conclusions	A fair summary which highlights the difficulties of comparing large trials where the selection criteria are not identical. This has to be an improvement on the previous position but will need a close "watch this space" as newer regimes gather more data and perhaps these will also need to costed against the cost per qualy for transplantation. In Myeloma, the overall survival may have more relevance to the patient than the disease-free survival and it is possible that some of the more recent combinations will give as good a result as transplantation.	Comment noted