

## Bortezomib and Thalidomide for the first-line treatment of multiple myeloma

### Janssen-Cilag's response the Appraisal Consultation Document

These tabulated comments need to be read alongside our cover letter.

Preliminary recommendations page 3	Please refer to section 1 of our cover letter.
Overall comment	<p>Based on a communication from NICE on 18<sup>th</sup> 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.</p> <p>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.</p> <p>Janssen-Cilag would also welcome the opportunity to discuss the exact nature of the evidence deemed academic in confidence.</p>
Page 9, section 4.1.5	<p>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'.</p> <p>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.</p>

<p>Page 12, section 4.1.12</p>	<p>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.’</p> <p>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.</p> <p>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.</p> <p>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.</p>
<p>Page 13, section 4.1.13</p>	<p>It is stated: ‘it was not possible to estimate overall survival in the group receiving VMP’.</p> <p>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 are reported from survival analysis and relied on in the assessment.</p>

<p>Page 14-15, section 4.1.18</p>	<p>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’.</p> <p>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.</p>
<p>Page 23, section 4.2.21</p>	<p>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’.</p> <p>It is wrong to position this as a “scenario” and refer to ‘no loss of efficacy’. The 31.5 vials represent the actual 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.</p> <p>Throughout our modeling 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.</p>

<p>Page 23, section 4.2.20</p>	<p>It is stated that ‘In scenario A (no subsequent therapies) the ICERs for MPT, CTDa and VMP versus MP increased from £9174, <u>£29,837</u>, <u>£33,216</u> to £9738, £34,013 and £37,727 per QALY gained respectively.’</p> <p>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, <u>£33,216</u>, <u>£29,837</u> to £9738, £34,013 and £37,727 per QALY gained respectively.’</p>
<p>Page 23, section 4.2.22</p>	<p>It is stated that ‘the manufacturer of <u>thalidomide</u> conducted a mixed-treatment comparison for MPT versus MP with trials that included thalidomide maintenance’.</p> <p>The statement needs to be revised as underlined: ‘the manufacturer of <u>bortezomib</u> conducted a mixed-treatment comparison for MPT versus MP with trials that included thalidomide maintenance’.</p>
<p>Page 26, section 4.2.30</p>	<p>It is stated that ‘the ICER for VMP versus MP varied between £10,498 (manufacturer of bortezomib) and <u>£44,838</u> (calculated by the Assessment Group to allow a comparison between the manufacturers’ and Assessment Group’s economic models) per QALY gained.’</p> <p>In section 4.2.17 page 22, the ICER presented in the base case for VMP vs. MP is <u>£29,837</u>. 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 <u>£29,837</u> (calculated by the Assessment Group to allow a comparison between the manufacturers’ and Assessment Group’s economic models) per QALY gained.’</p> <p>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.</p>

<p>Page 28 section 4.3.3</p>	<p>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.’</p> <p>This statement is incorrect as only the ongoing MMIX study includes a randomization to maintenance thalidomide after patients received CTDA or MP.</p> <p>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.</p> <p>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.</p> <p>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.</p>
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<p>Page 29, section 4.3.3</p>	<p>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).’</p> <p>Please refer to sections 2.2 and 2.3.1 of our cover letter.</p>
<p>Page 29, section 4.3.3</p>	<p>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.’</p> <p>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.</p> <p>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.</p>
<p>Page 31, section 4.3.7</p>	<p>It is incorrectly stated that ‘This gave an ICER of 22,500 per QALY gained for VMP compared with MP’.</p> <p>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.</p> <p>The above statement needs to be revised as underlined: ‘This gave an ICER of <u>£18,996</u> per QALY gained for VMP compared with MP’.</p> <p>This revision also needs to be done in the tabulated summary of the Appraisal Committee’s key conclusions.</p>

Page 31-32, section 4.3.8	<p>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’:</p> <ol style="list-style-type: none"><li>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.</li><li>2. The cost of 2<sup>nd</sup> 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.’<ol style="list-style-type: none"><li>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.</li><li>b. In our submission (page 64) the inclusion of the cost of 2<sup>nd</sup> and 3<sup>rd</sup> line therapies leads to an increase in the cost of chemotherapy post-progression of approximately £8K in the MPT arm (vs. VMP arm).</li><li>c. Therefore the addition of the costs of 2<sup>nd</sup> and 3<sup>rd</sup> 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 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> line therapies is taken into account.</li><li>d. As the clinical effects of 2<sup>nd</sup> and 3<sup>rd</sup> 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.</li><li>e. In the base case scenario of our submission the cost of 2<sup>nd</sup> 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 2<sup>nd</sup> 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.</li></ol></li></ol>
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