

SHTAC response to Consultee comments on the assessment report “The clinical and cost-effectiveness of bortezomib and thalidomide for the first-line treatment of multiple myeloma: a systematic review and economic evaluation.”

SHTAC have considered all comments on the assessment report submitted by Consultees. We grouped comments into key themes and have provided responses for each of these themes.

#### 1. Study inclusion in the systematic review

Several Consultees commented on the small number of trials that met the inclusion criteria and one indicated that bias may have been introduced by the exclusion of a large amount of information. SHTAC would argue that systematic reviews use explicit and reproducible methods to provide a reliable and unbiased report about the effects of an intervention. We followed the general principles outlined in ‘Systematic Reviews: CRD’s guidance for undertaking reviews in health care’ and the *a priori* methods for systematically reviewing the evidence of clinical- and cost-effectiveness were described in our research protocol. Specifying the methods in advance in this way reduces the risk of introducing bias into the review.

One Consultee misinterpreted the information regarding study selection. Of 1436 records which were independently screened by 2 reviewers, 40 records (not 40 studies) were retrieved; these comprised 5 full papers, 31 abstracts, 2 clintrials.gov records, 2 other records. From the 40 records retrieved, 5 studies were identified and included (described by 25 records: 5 full papers and 20 abstracts), 4 ongoing studies were identified (described by 9 records: 7 abstracts and 2 clintrials.gov records), and the remaining 6 records (4 abstracts and 2 other records) were excluded.

Abstracts or conference presentations of studies were eligible for inclusion in the systematic review, but only if sufficient details were presented to allow an appraisal of the methodology and an assessment of the results to be undertaken. Four ongoing studies were identified described only by abstracts and clintrials.gov records. It is not clear whether any of the ongoing trials, all of which compare MPT with MP, meet the inclusion criteria of the review. For three of the ongoing trials, including the Hovon 49 trial and the Nordic trial which were specifically mentioned in comments from Janssen Cilag, the uncertainty about eligibility is because the trials include maintenance therapy with thalidomide. Maintenance therapy with a single agent following initial treatment with a combination chemotherapy regimen did not fall within the NICE scope and therefore outcomes reported for participants who have received maintenance therapy are not eligible for inclusion in the review. However as section 4.3 of our report indicates, if outcome data are available for participants at a time point prior to the start of maintenance therapy then these data could be considered for inclusion if sufficient information to judge the methodology and results of the trials were available.

Janssen Cilag comment that SHTAC were inconsistent in their approach to the inclusion of abstracts because SHTAC contacted the MRC Myeloma IX (MMIX) study investigators in order to obtain more information about the MMIX study which has been reported in conference abstracts. SHTAC can clarify that they did not initiate contact with any study investigators, including those of the MMIX study. The MMIX study investigators were invited to make a submission to NICE. SHTAC were encouraged by NICE to liaise with NICE and the MMIX investigators in identifying the data required and were asked to assess the MMIX submission. In doing so, SHTAC were able to include the information provided on outcomes from participants who did not receive maintenance therapy with thalidomide in the systematic review. The MMIX trial data enabled the MTA to include an assessment of CTDA as well as VMP and MPT.

## 2. MMIX Trial

Some Consultees expressed concern that data from the MMIX trial had not been taken into account in the systematic review. As noted above the systematic review was conducted in accordance with the review protocol which was informed by and adhered to the scope developed by NICE for the appraisal. Maintenance therapy with a single agent following initial treatment did not fall within NICE's scope. Where possible outcome data from the UK MRC Myeloma IX study has been included in the systematic review of clinical effectiveness and data from the study has also contributed to the economic model.

In addition some Consultees felt that SHTAC should have sought to obtain data on the subgroup of participants who did not receive maintenance therapy as this would meet the inclusion criteria for the review. When it was known that data could be provided by the MMIX investigators, SHTAC raised on several occasions the importance of obtaining separate data on the "no maintenance" patients with NICE and MMIX investigators. Unfortunately when outcome data were received, most were for the MMIX trial population as a whole. Although this limited the outcomes that could be included in the review of clinical effectiveness, data were reported if these met the scope of the NICE appraisal. Given the limited data available for the assessment of cost-effectiveness, a more pragmatic approach was taken. With no other data available for the evaluation of CTDA, SHTAC included data from the MMIX study to provide an exploratory analysis with some caution over the evident uncertainty.

## 3. Other comments on, misunderstandings arising from, and errors identified in the systematic review

Janssen Cilag indicate that their submission contains a paragraph on page 29 on how missing data were imputed and state that detailed explanation is also included in the clinical study report provided in appendix of their submission. Table 5 will be amended to show that information was available in the manufacturer's submission.

Table 6 will be corrected to show the HR for overall survival and p-value after a median follow-up of 36.7 months as reported in the abstract by Mateos (reference 60): HR=0.653, p= 0.0008.

Janssen Cilag state that the median progression free survival (PFS) stated on page 59 and in the Table 10 page 60 is incorrect and indicate that the PFS values should be [REDACTED] taken from the J&J Velcade CSR1 page 145. SHTAC intend to add the PFS data from the manufacturer's submission to Table 10 along side the data reported in the supplementary appendix to the published paper on the VISTA trial. SHTAC will indicate in a table footnote that the two values differ and that we have been informed that the value published is incorrect but that the reasons why this value is incorrect have not been provided. It will be for others to decide which is the most appropriate value.

Table 11 will be corrected to provide the correct reference (Dhawan and colleagues abstract) as the source of the VISTA quality of life data.

## 4) SHTAC review of manufacturers submissions

The Estimation of Costs summary, within section 1.13 contains contradictory information regarding the inclusion of outpatient costs in the Celgene model. The final sentence of this summary will be deleted to make it clear that outpatient costs were included.

Janssen Cilag indicated as soon as they received the assessment report that SHTAC had misinterpreted data on the average number of vials used in the VISTA trial. The assessment group assume costs of approximately 47 vials per person, based on the SPC recommendations

with some adjustment. With limited evidence to indicate high levels of withdrawal or discontinuation of treatment with VMP and no indication of such by clinical experts, the assessment group had assumed the different number of vials [REDACTED] used by Janssen-Cilag was due to vial sharing. The reason for the difference between the vial usage in the Janssen-Cilag model (from the VISTA trial) and that recommended by the SPC remains unclear. All statements made in the assessment report regarding our incorrect assumption of vial sharing in the VISTA trial have already been removed.

5) SHTAC economic model: data sources – Hazard ratios

Celgene commented on several aspects of the SHTAC model in regard to hazard ratios. It was not possible for SHTAC to derive the hazard ratio for each six-monthly period for each of the treatments versus MP from patient level data because SHTAC did not have access to patient level data from any of the trials that contributed outcome data to the cost-effectiveness model.

Celgene were also surprised that the SHTAC model did not consider or adjust for cross-over therapy (i.e. second-line and subsequent treatments received). Second-line and other subsequent treatments received by participants in each of the included studies were variable and their effects are uncertain. SHTAC acknowledge that it most likely leads to an underestimate of intervention benefit in comparison to MP. SHTAC have therefore used a conservative assumption in not attempting to adjust for the uncertain impacts of second-line and subsequent treatments. In order to extrapolate beyond the trial period it was necessary to make an assumption on the likely survival. In the absence of other data, the assumption was made to use the average hazard rate and hazard ratios during the trial period as per standard practice.

6) SHTAC economic model: data sources – Drug doses and vial sharing

As already noted above, Janssen Cilag indicated as soon as they received the assessment report that SHTAC had misinterpreted the reason for the average number of vials used in the VISTA trial being lower than would be expected from the bortezomib SPC. In addition, other Consultees indicated that in practice patients usually receive fewer cycles of therapy with bortezomib than the nine cycles indicated in the bortezomib SPC.

The base case analysis presented in the assessment report uses the number of cycles of treatment with bortezomib, as per the protocol for the VISTA study, i.e. 9 cycles. After discontinuation of treatment for some patients due to deaths or disease progression, this equates to about 48 vials per individual. SHTAC have undertaken an additional scenario analysis to investigate the cost effectiveness of treatment for a shorter number of treatment cycles (i.e. 4 cycles), with no loss of efficacy. A figure of 4 cycles has been selected as the lowest estimate provided within Consultee comments which suggest the number of treatment cycles given to patients in the UK usually ranges between 4 to 6 cycles. A reduced number of treatment cycles equates to about 31 vials of bortezomib used per patient. In this scenario, bortezomib becomes more cost effective, with ICER of £18,996 per QALY gained versus MP and £319,923 per QALY gained versus MPT.

	VMP vs MP		VMP vs MPT	
	Base case	Scenario	Base case	Scenario
<b>Incremental QALY</b>	1.20	1.26	-0.02	0.04
<b>Incremental Cost, £</b>	£35,749	£23,947	£24,542	£12,490
<b>ICER, £/QALY</b>	£29,837	£18,996	-£1 million	£319,923

Consultees also indicated that in practice vial sharing would occur in a large proportion of cases and that the cost-effectiveness analysis should take this into account. In an earlier NICE

appraisal for second line therapy with bortezomib, NICE stated that cost analyses should be conducted assuming no vial sharing. Therefore, in the base case SHTAC have assumed no vial sharing. However, we did acknowledge in our assessment report that vial sharing might occur in practice and therefore we included vial sharing as a scenario analysis (Scenario B, Table 49).

#### 7) SHTAC economic model: data sources – Adverse events

Some Consultees noted the view of one of our clinical experts that the incidence of adverse events may be underestimated by clinical trials, but Consultees felt that comprehensive guidance is now available to manage adverse events such as peripheral neuropathy and thrombosis. SHTAC acknowledges that such adverse events may not necessarily limit duration of treatment and therefore the text of the 6<sup>th</sup> bullet point in section 1.17 (p145) will be amended to read “This may be managed by dose modification or may limit the duration of treatment with thalidomide or with bortezomib for some patients and there can be a need for long term treatment of neuropathic pain with gabapentin.”

#### 8) SHTAC economic model: data sources – HRQoL/Utilities

Celgene commented that SHTAC did not differentiate across different types of adverse event. SHTAC acknowledge that this is the case, however there is much uncertainty in the reporting of adverse events and the disutility associated with these events. Therefore it is difficult to differentiate between the treatments in terms of adverse events.

Janssen Cilag note that it is unclear in the report what the utility estimate is for the post-progression period. SHTAC agree and this will be clarified in the report. SHTAC use a utility of 0.68 for the post-progression period.

The MRC MMIX Trial Management Group believes that none of the data they supplied were included in our assessment report. These data were not included in the systematic review of QoL (section 1.11) because they did not meet the inclusion criteria. However, SHTAC did analyse the MMIX QoL data as reported within section 1.14.3.4 Health-related HRQoL on p123. These data were used for the utility for complete response. [REDACTED]

[REDACTED]. As the data from MMIX are academic in confidence data, in the interests of transparency, SHTAC have used the data values from the other published reports.

#### 9) SHTAC economic model: data sources – Second-line treatments

Celgene comment that the SHTAC model includes second-line treatment and that as very little data exist to inform efficacy or HRQoL the model only includes second-line treatment as a cost. SHTAC acknowledge this point, however as advised by our clinical experts, bortezomib is the recommended second line treatment. So including second line therapy gives a more realistic cost-effectiveness estimate of the treatments. SHTAC have included a scenario analysis which shows the results without the inclusion of second-line therapy (Scenario A, Table 49).

Janssen Cilag identified that the title of Table 39 does not reflect the content. SHTAC acknowledge this error and will change the title of the table.

#### 10) SHTAC economic model: Results

Two consultees highlighted the high cost effectiveness estimate for the CTDA regimen in comparison to the MPT regimen. SHTAC indicated in the assessment report that the result for CTDA should be treated with caution [REDACTED]

[REDACTED] and included data for patients who received thalidomide maintenance therapy. Additional data from the MMIX trial for the subgroup of participants who

did not receive maintenance therapy with thalidomide have recently been made available to SHTAC. These data do not substantially alter the outcomes from the SHTAC economic model.

#### 11) SHTAC economic model: Sensitivity analysis

The range of numbers of cycles of bortezomib used in the sensitivity analyses was queried by one Consultee. As a consequence of other comments regarding the number of cycles of bortezomib used in the base case, a scenario analysis has been conducted using a lower number of cycles of VMP treatment. The results are reported in the table at the end of the text of point 6) above.

A Consultee noted that the use and duration of thromboprophylaxis was variable. SHTAC used a treatment duration of 5 months for low molecular weight (LMW) heparin. Sensitivity analyses for the duration of treatment with LMW heparin, varying treatment duration between 3 and 12 months, had little impact on the cost-effectiveness results.

Janssen-Cilag commented that the economic model used the number of cycles for thalidomide, as per usual clinical practice, rather than that used in the clinical trials. Furthermore, they commented that it is difficult to assess the impact of MPT on OS when prescribed according to UK clinical practice. SHTAC has conducted a scenario analysis to investigate the cost effectiveness through treatment for a longer number of treatment cycles as used in the MPT IFM trials, ie 12 cycles. In this scenario, MPT becomes slightly less cost effective than in the base case compared to MP, with an ICER of £13,728 per QALY gained (base case: £9,174).

#### 12) SHTAC summaries and conclusions

Janssen Cilag state that on page 140 no statement is made with regard the higher complete response rate observed with VMP vs. MP, while a statement is made for MPT vs. MP. SHTAC would like to point out that the paragraph on p140 is reporting on all five included studies (i.e. 1 VMP vs MP, 3 MPT vs MP, 1 CTDA vs MP) and clearly states that more participants in the intervention arms of the included RCTs achieved a complete response to treatment than in the MP comparator arms.

One consultee states that the basic conclusion appears to be a recommendation for use of MPT as first line therapy in multiple myeloma for patients not eligible for stem cell transplantation, rather than VMP or CTDA. SHTAC would like to emphasise that they have not made a clinical recommendation about any of the interventions included in the systematic review and economic evaluation. That task will be undertaken by the NICE appraisal committee.