National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

Executable Model

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

The economic model enclosed and its contents are confidential and are protected by intellectual property rights, which are owned by **Southampton Health Technology Assessment Centre**. It has been sent to you for information only. It cannot be used for any other purpose than to inform your understanding of the appraisal. Accordingly, neither the model nor its contents should be divulged to anyone other than those individuals within your organisation who need to see to them to enable you to prepare your response. Those to whom you do show the documents must be advised they are bound by the terms of the Confidentiality Acknowledgement and Undertaking Form that has already been signed and returned to the Institute by your organisation.

You may not make copies of the file and you must delete the file from your records when the appraisal process, and any possible appeal, are complete. You must confirm to us in writing that you have done so. You may not publish it in whole or part, or use it to inform the development of other economic models.

The model must not be re-run for purposes other that the testing of its reliability.

Please set out your comments on reliability in writing providing separate justification, with supporting information, for each specific comment made. Where you have made an alteration to the model details of how this alteration was implemented in the model (e.g. in terms of programme code) must be given in sufficient detail to enable your changes to be replicated from the information provided. Please use the attached pro-forma to present your response.

Please prepare your response carefully. Responses which contain errors or are internally inconsistent (for example where we are unable to replicate the results claimed by implementing the changes said to have been made to the model) will be rejected without further consideration.

Results from amended versions of the model will only be accepted if their purpose is to test robustness and reliability of the economic model. Results calculated purely for the purpose of using alternative inputs will not be accepted.

No electronic versions of the economic model will be accepted with your response.

Responses should be provided in tabular format as suggested below (please add further tables if necessary).

March 2011

Issue 1 Cost of managing adverse events

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th><th>SHTAC response</th></tr>
<tr>
<td>The cost of managing adverse events (AEs) was retrieved from TA171. The following inconsistencies have been found:
Distribution of management settings of grade 3/4 neutropenia (Y30:AD30, Costs sheet) was not the same as in the quoted source (p. 69 of the ERG report of TA171)
In TA171, AEs could be managed in primary care or community care settings, which was not accounted for in the SHTAC model., Although the cost of treating AEs was under-estimated in the model, this was not acknowledged in the report.</td>
<td>To be consistent with TA171, the following values were used to populate the cells Y30:AD30 on the Costs sheet:
<table>
<tr><th></th><th colspan="3">Grade 3</th><th colspan="2">Grade 4</th></tr>
<tr><th></th><th>IP</th><th>DC</th><th>OP</th><th>IP</th><th>DC</th></tr>
<tr><td>Neutropenia</td><td>5.00%</td><td>55.56%</td><td>39.44%</td><td>12.80%</td><td>42.00%</td></tr>
</table>
IP: inpatient; DC: day case; OP: outpatient

As the data were not available for dizziness/fatigue and infection from TA171, no change was made to these values.

Due to a lack of data, the cost of primary care and community care was not included in the model.</td>
<td>The model was corrected for all the inconsistencies identified – the corresponding results after adjustments are reported below in issue 4.</td>
<td>The adverse event costs for neutropenia contain an error as noted by Janssen-Cilag (J-C). When corrected, changes to the ICER are very small with the ICER changing by -£17/QALY for VMP vs MP.

Although it is accurate that some patient's adverse events could be managed in primary and community care settings, it is thought to account for ≤ 5% patients (see supporting documents for NICE TA171) and, as such, it would be unlikely to have a significant effect on the ICERs.</td>
</tr>
</table>

Issue 2 Treatment duration

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	SHTAC response
The long term efficacy data for MPT were taken from the trials reported by Facon and Hulin. For consistency, the treatment duration used in the model should be set to the mean duration observed in these two trials. Similarly, as the VMP efficacy data are based on the VISTA trial, the treatment duration observed in VISTA should be used in the model.	In the trials reported by Facon and Hulin, patients on MPT had a median treatment duration of 11 and 13.5 months respectively. The number of MPT cycles was therefore set to 10 cycles to reflect a mean treatment duration of 53 weeks. Based on the number of vials actually used in the VISTA trial, the average number of vials was set to 31.5. In the model, the treatment duration was set to 4 cycles for VMP to reflect the average of 31.5 vials, as this was done in the SHTACs updated analyses incorporating this change.	The model was corrected for all the inconsistencies identified – the corresponding results after adjustments are reported below in issue 4.	The rationale for the duration of treatment for each of the interventions has been explained in the SHTAC assessment report in section 5.5.3.5 and was discussed previously at the NICE Appraisal Committee meeting. The treatment duration for MPT was chosen after consultation with clinical experts who advised that a shorter duration of 8 cycles was more representative of clinical practice in the UK. The treatment duration for VMP was chosen as recommended in the SPC for bortezomib, and by clinical experts. Variations around the estimates of treatment duration were investigated through sensitivity analyses in the model and reported in the assessment report.

Issue 3 Estimation of QALYs

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	SHTAC response
In the SHTAC model, QALYs were estimated by multiplying the duration of staying in a state by the corresponding health-state utility value (HSUV) instead of using the Markov trace..	The Markov trace was generated for pre-progression on treatment (PFS), pre-progression off-treatment (PFS – pre-progression on treatment), progressed (OS – PFS) and died (1 – OS). The probability of being in each state was then multiplied by the HSUV, and then multiplied to cycle length in order to estimate the number of QALYs.	The model was corrected for all the inconsistencies identified – the corresponding results after adjustments are reported below in issue 4.	We acknowledge that there are other methods to estimate the duration of pre-progression on treatment period. The method suggested by J-C may provide a more accurate estimate. However, the change to the model using this method results in a very small change to the model results with the ICERs changing by +£110/QALY for VMP vs MP.

Issue 4 Cost of the second-line treatment

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)	SHTAC response
The following inconsistencies have been found: • The SHTAC model assumed a basket cost for the second-line treatment and all patients who progressed were assumed to incur such cost. This approach does not account for the duration of the second-line treatment and results in an overestimation of the cost when a discount rate is applied. • A half-cycle adjustment was applied to the cost of the second-line treatment – the model applied an increment of 0.5 to the discount rate (cell K40 on VMP sheet and to cell K39 on other results sheets), while the increment should be of half a cycle (0.5*42/365=0.058 year).	The cost of the second-line treatment was re-estimated based on the protocol treatment duration, proportion of patients who received the second-line treatment and the split between treatments. For the half-cycle adjustment, 0.5*42/365 was used instead of 0.5	After adjustment for these inconsistencies, the ICER of MPT vs. MP increased from £9,174 to £11,511 per QALY gained.	We acknowledge that there are other methods to estimate the duration of second-line treatment and that the method suggested by J-C may provide a more accurate estimate. However, the method used in the SHTAC model provides a very close approximation to the method suggested above. Furthermore we note that the approach used by SHTAC is the same method that was used in the J-C model submitted as part of their original submission. Also that the estimates of second line costs are consistent between the two models, for example the 2nd line cost of MP is £16,348 (SHTAC) and £16,160 (J-C). Half cycle adjustment A half cycle adjustment is

			not necessary for a model with short treatment cycles. A half cycle adjustment has not been included for second-line treatment. The value of 0.5 adjusts the calculation of the discounted second-line cost, so that the discounting is for the mid-point of the period during which second-line treatment is taken.

Issue 5 Selection of evidence

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th><th>SHTAC response</th></tr>
<tr>
<td>Despite the claim in the SHTAC report of the economic analysis that where possible values from the pre-maintenance phase of maintenance studies was used, this is clearly not the case in the model. The cells of the model F6 and potentially F7 on the ‘trial data’ sheet should have included a value</td>
<td>The hazard ratios were re-estimated through a fixed effect meta-analysis for the first year as follows:
The studies by Hulin and Facon were considered over the full follow-up period
The “maintenance studies” (Palumbo, Wijermans, Gulbrandsen) were considered only over the duration of the induction</td>
<td>After applying these data to the updated model, the results were as follows:
<table>
<tr><th>Scenario</th><th>MPT vs. MP</th><th>VMP vs. MP</th><th>CTDa vs. MP</th></tr>
<tr><td>Corrected*</td><td>£11,511</td><td>£19,505</td><td>£34,014</td></tr>
<tr><td>Corrected & adjusted for 1 cycle**</td><td>£12,893</td><td>£19,505</td><td>£11,890</td></tr>
</table>
</td>
<td>As SHTAC have stated previously, 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</td>
</tr>
</table>

based on the full trial data, as these relate to periods unaffected by maintenance. Had this been done it would not have been necessary for the committee to take these maintenance studies into account 'but not give them undue weight' as they would have been weighted only for the period of induction MPT treatment in the economic analysis. Given the stated equivalence of MPT and CTDa the same approach should have been followed for this comparison with the MMIX data used for the first induction period and MPT data thereafter.

phase (24, 32 and 24 weeks respectively. As this corresponds to one to two cycles in the model, the model was re-run according to two scenarios: a first scenario using the estimates from the maintenance studies only for the first 6-month period and a second scenario using the estimates for the first year.

- For CTDa, the hazard ratios from the MMIX trial were applied for one or two cycles depending on the selected scenario, and the hazard ratios observed in the MPT arm were applied thereafter. The previously described adjustment to length of treatment for MPT was also made.

The following hazard ratios were used in the model:

	OS vs. MP		PFS vs. MP	
Months	**MPT**	**CTDa**	**MPT**	**CT**
0 - 6	1.26	[redacted]	0.75	[redacted]
6 – 12	0.73	[redacted]	0.68	[redacted]

OS: overall survival; PFS: progression-free survival

Corrected & adjusted for 2 cycles**	£13,722	£19,505	£14'677	£26,734

Dom'ed: dominated
* Issues 1 to 4 accounted for
** Issues 1 to 5 accounted for

participants who have received maintenance therapy were not included in the SHTAC systematic review. At the time the assessment was undertaken only abstracts and a conference presentation were available for the two studies mentioned (Wijermans, & Gulbrandsen). Since these contained insufficient details to allow an appraisal of the methodology and an assessment of the results to be undertaken they were not included. For consistency and quality purposes the model drew on clinical effectiveness data that had been included in the systematic review. To obtain MPT overall survival hazard ratios, data for 36 months of follow up were included. Due to the use of maintenance thalidomide in the MPT arm of the Palumbo study OS to 36 months could not be included and SHTAC do not believe that it would be appropriate to include only the initial 6 months of data from the MPT arm of this

			study.

SHTAC model results

Updating the SHTAC model to take account of the changes identified from issues 1 and 3 above results in very small changes to the model results, which are presented in table 1 and 2 below.

Table 1: Deterministic analysis

	MP	MPT	VMP	CTDa
Total cost, £	£21,439	£32,598	£57,168	£29,983
Total QALY	2.43	3.65	3.63	2.69
Inc Cost vs MP	-	£11,159	£35,729	£8,544
Inc QALY vs MP	-	1.21	1.19	0.25
ICER vs MP	-	£9,189	£29,930	£33,703
Original Basecase ICER*		£9,174	£29,837	£33,216
Change from Original Basecase**		**£16**	**£93**	**£487**

* Original base case results from the AR. ** Difference in results between updated results and original base case results

Table 2: Incremental analysis

	QALY	Cost	ICER vs next best option (£/QALY)	ICER comment
MP	2.43	£21,439	-	
CTDa	2.69	£29,983	£33,703	vs MP. Extendedly dominated
VMP	3.63	£57,168	£28,913	vs CTDa. Dominated by MPT
MPT	3.65	£32,598	-£1,193,429	vs VMP. Dominates VMP