Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem-cell transplantation

ERG overview of manufacturer's addendum to the original submission

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Commercial in Confidence (CIC) information blue and underlined

Introduction

SHTAC were requested to critique an addendum submitted to NICE by the manufacturer that had incorporated changes to the licence application and the resultant implications. The key changes from the original licence application are:

- A discontinuation rule now applies to the bortezomib, thalidomide and dexamethasone (VTD) regimen whereby patients will receive four cycles of VTD, and those with at least a partial response will receive an additional two cycles. Some patients will therefore only receive four cycles of VTD before stopping, rather than continuing for six cycles.
- Approvable regimens are bortezomib and dexamethasone (VD) and VTD. The bortezomib, adriamycin and dexamethasone (PAD) regimen was deemed not approvable by the Committee for Medicinal Products for Human Use (CHMP) and is thus no longer relevant.

The changes are laid out clearly on p.4 and Table 1 of the MS addendum.

The manufacturer provided an addendum to their original submission highlighting the major differences, an appendix containing the Summary of Product Characteristics, and a modified economic model. These were received by the ERG on 1st August 2013. A summary of the key changes is given below:

Clinical effectiveness

- The studies included in the clinical evidence were restricted to two RCTs (Pethema and Gimema) compared to the original submission which included five RCTs.
- A data set was reported for each of the VTD and TD arms in the Pethema trial reporting the final response during the trial according to the number of cycles each patient received.
- A modified network diagram was presented for the five trials identified for the attempted mixed treatment comparison (MTC).

Cost-effectiveness

- Implementation of the discontinuation rule in the VTD and TD economic model
- Additional sensitivity analyses
- Undocumented changes to many of the costs in the economic model
- Undocumented changes to several clinical parameters used in the economic model

The ERG has focused this addendum on checking the changes to the clinical effectiveness section; assessing the new economic model submitted; checking the changes to the economic model are as described and that the analyses can be reproduced; and assessing what effects the changes make to the base case.

Clinical effectiveness

In their addendum, the manufacturer has only reported on the Pethema and Gimema trials as relevant RCTs. The Hovon, IFM and MRC MMIX trials were not included. This is in line with the original ERG report which stated that only the Pethema and Gimema trials were relevant to the NICE scope as they compared a bortezomib regimen with a thalidomide regimen.

The data presented in the manufacturer's addendum for the Pethema and Gimema trials (Figure 1 and Table 4, p.13-14; Figures 2 & 3, p.16) have been checked by the ERG and are the same data as reported in the original MS. The addendum focuses only on post-induction response rate (whereas the original submission reported both post-induction and post-transplant). Post-induction near complete response (nCR), very good partial response (VGPR) and partial response (PR) were not reported for the Gimema trial in the manufacturer's addendum (Table 4), but these were reported in the original response to questions for clarification. Results for the proportion of patients who underwent stem cell transplant (SCT) and for overall survival (OS) were only reported for the Pethema trial in the addendum and data were as reported in the original submission. The ERG's comments on all the data remain as per our original report.

The manufacturer presented some new data in their addendum (Tables 5 & 6, p.14-15) on 'Treatment duration' in the form of numbers of patients achieving the different levels of post-induction response, as well as progressive disease (PD) and death, according to the number of cycles of treatment they received. Data sets were presented for the VTD and TD arms of the Pethema trial only. The ERG has not been able to check the accuracy of the data as this is commercial in confidence (CiC) data and the original source of data was not provided. These data were incorporated into the manufacturer's updated economic evaluation (see Cost-effectiveness section below).

The manufacturer presented a modified network diagram of trials identified for the MTC. This is different to the diagram presented in the original submission in that there are no longer links between TD and CTD, and between VAD and CVAD. The manufacturer states that the assumptions previously used to connect the bortezomib-based treatment regimens to CTD (the current standard of care) raise considerable uncertainties, leaving the results unreliable. The ERG would agree with this as per our original report.

Cost-effectiveness

The addendum notes that since the VTD discontinuation rule has implications for both the incremental costs and incremental benefits of VTD compared to TD, the results of the original submission are no longer valid. Addendum Section 7.3 discusses the implementation of the discontinuation rule in the economic model. No other model changes are documented in this section. The addendum refers to the original submission for discussion of the measurement and valuation of health effects, and resource identification, measurement and valuation.

The manufacturer was unable to obtain data which tracked each patient's response through the induction period, but did obtain data from the Pethema trial with the number of patients by final post-induction response and the number of cycles received (addendum Table 8). The revised model makes the assumption that patients in the Pethema trial who achieved less than PR at final response, and received 5 or 6 cycles of VTD would not have received the 5th and 6th cycles of VTD with the discontinuation rule. This assumption affects [redacted] patients in the Pethema trial. The addendum notes that this assumption appears plausible but would be violated if patients who achieve PR or better after 4 cycles are likely to deteriorate below PR after the 5th and 6th cycles (addendum p.21). The lack of response tracking also requires a further assumption that 100% of patients who achieved at least PR and received 5 or 6 cycles of VTD achieved at least PR after the 4th cycle. This assumption concerns [redacted] of patients in the Pethema trial and is tested in sensitivity analysis (addendum p.24). The ERG clinical expert estimates that over 90% of people who achieve PR after 5 or 6 cycles would already have achieved PR after 4 cycles.

The addendum notes that the discontinuation rule reduces the costs associated with the VTD regimen as a reduced number of patients are eligible for 6 cycles of treatment (addendum p.21). The addendum also states that, given the assumptions made, the discontinuation rule would not alter VTD's post-induction response rates as input parameters for the economic model (addendum p.22). The ERG agrees with this assessment but, as noted above, considers that the assumption that 100% of patients who achieved at least PR and received 5 or 6 cycles of VTD achieved at least PR after the 4th cycle may not be fully met. If this assumption is not met then a number of patients with a PR or higher after 6 cycles will be lost from the final response numbers for PR and the model input post-induction response rates will not be the same as seen in the Pethema trial. This then has implications for the proportion who receive SCT (as the likelihood of a patient receiving SCT is positively associated with the depth of response to the induction therapy (addendum p.22)).

The addendum assumes that TD is not subject to the same discontinuation rule as VTD (addendum p.15), and no changes to the modelling of TD are discussed in the addendum. However a comparison of results for TD from the original and revised models (Tables A1 and A2) indicates that both QALYs and costs for TD have changed between the models. Induction treatment and post-induction PFS costs have decreased, while other costs have increased. QALYs for all TD outcomes except SCT and post-progression survival show a decrease.

Tables A1 and A2 also show that many QALYs and costs have changed for VTD, beyond the anticipated change in cost in the induction period associated with the discontinuation rule. The ERG has implemented the model changes described in the addendum in the original model and obtains the results given in Table A3. As expected these only show a change in the cost of induction treatment for the VTD arm when compared with the original model results (Table A1). All other results are the same. The ERG amended model has an ICER of £23,958 per QALY (Table A4) which compares with £24,683 per QALY in the original base case (MS Table 93) and £20,468 per QALY in the addendum base case (Table A5).

Table A1. Original model outputs by clinical outcomes (reproduced from MS Table 89)

	VTD			TD		
Outcome	**LY**	**QALY**	**Cost (£)**	**LY**	**QALY**	**Cost (£)**
Induction treatment	0.49	0.28	£25,784	0.49	0.28	£7,320
Stem cell transplant	0.19	0.12	£15,528	0.14	0.09	£11,725
Post-induction PFS	2.69	1.96	£2,668	1.92	1.41	£1,902
Post-progression survival	2.58	1.65	£28,835	2.02	1.28	£28,467
Overall survival	5.95	4.00	£72,815	4.57	3.06	£49,414

LY, life years; PFS, progression free survival; QALY, quality-adjusted life year; TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and dexamethasone

Table A2. Revised model outputs by clinical outcomes (reproduced from addendum Table 12)

	VTD			TD		
Outcome	**LY**	**QALY**	**Cost (£)**	**LY**	**QALY**	**Cost (£)**
Induction treatment	0.49	0.28	£25,167	0.49	0.27	£7,265
Stem cell transplant	0.19	0.12	£16,691	0.14	0.09	£12,405
Post-induction PFS	2.63	1.89	£2,611	1.80	1.29	£1,782
Post-progression survival	2.72	1.73	£31,706	2.14	1.36	£34,042
Overall survival	6.03	4.02	£76,174	4.57	3.01	£55,493

LY, life years; PFS, progression free survival; QALY, quality-adjusted life year; TD: thalidomide and dexamethasone; VTD: Velcade® (bortezomib), thalidomide and dexamethasone

Table A3. Model outputs by clinical outcomes using model changes described in addendum (ERG analysis)

	VTD			TD		
Outcome	**LY**	**QALY**	**Cost (£)**	**LY**	**QALY**	**Cost (£)**
Induction treatment	0.49	0.28	£25,097	0.49	0.28	£7,320
Stem cell transplant	0.19	0.12	£15,528	0.14	0.09	£11,725
Post-induction PFS	2.69	1.96	£2,668	1.92	1.41	£1,902
Post-progression survival	2.58	1.65	£28,835	2.02	1.28	£28,467
Overall survival	5.95	4.00	£72,128	4.57	3.06	£49,414

LY, life years; PFS, progression free survival; QALY, quality-adjusted life year; TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and dexamethasone

Table A4. ERG amended model results

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incre-mental costs (£)**	**Incre-mental LYG**	**Incre-mental QALYs**	**ICER (£) incremental (QALYs)**
TD	£49,414	4.57	3.06	+£22,714	+1.38	+0.95	**£23,958**
VTD	£72,128	5.95	4.00				

LY, life years gained; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and dexamethasone

Table A5: Addendum base-case results (reproduced from addendum Table 16 with technology labels corrected)

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incre-mental costs (£)**	**Incre-mental LYG**	**Incre-mental QALYs**	**ICER (£) incremental (QALYs)**
TD	£55,493	4.57	3.01	+£20,682	+1.47	+1.01	**£20,468**
VTD	£76,174	6.03	4.02				

LY, life years gained; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TD, thalidomide and dexamethasone; VTD, Velcade® (bortezomib), thalidomide and dexamethasone

<u>Undocumented changes to economic model</u>

The ERG has found a number of changes to the economic model which are not documented in the addendum but which may account for the unexpected differences in results between the original and amended models (Tables A1 and A2).

Although the addendum refers to the original submission for discussion of resource identification, measurement and valuation (addendum Section 7.5), the ERG notes that many of the costs in the revised model are different from those in the original model. These include costs for drugs; induction; SCT; 2nd line treatment; 3rd line treatment; and some monitoring costs. Generally these changes are minor, although some are more substantial. For example the administration costs for high dose dexamethasone increase from £168 to £1,242 in 2nd line therapy, and from £168 to £1,288 in 3rd line therapy.

Furthermore SCT rates are now differentiated by post-induction response. The ERG commented on the lack of such differentiation in its original report (ERG report p.40) and considers the revised model to be an improvement in this respect. The revised model uses Bayes' theorem to calculate the probability that a patient was in a particular post-induction response category given that an SCT was, or was not, received. This is not documented in the addendum. The change means that survival is relatively better for VTD patients in the new model compared to the old model, and that survival for TD patients is relatively worse. (This is because of the undocumented assumption in the original model that patients with NR who do not undergo SCT move straight to second-line therapy, with no period of PFS. A higher proportion of TD patients are NR compared to VTD.)

Sensitivity analysis

The addendum describes 3 new sensitivity analyses. One of these relates to the discontinuation rule whilst the others are threshold analyses concerning parameters which were also in the original model. The ERG examines the discontinuation rule SA below.

The revised model base case assumes that the proportion of patients who achieved PR as the final post-induction response had achieved PR after the 4th cycle. A sensitivity analysis was conducted in which a proportion of patients who achieved PR as the final post-induction response was assumed not have achieved PR after the 4th cycle, and consequently discontinued the VTD regimen. Results for this analysis are given in Table A6. The ERG re-ran the three scenarios in the analysis and obtained the same results.

The ERG notes that increasing the proportion of patients with PR as final response that do not achieve PR after the 4th cycle only leads to a decrease in cost in the revised model. It does not affect the post-induction response proportions and overall SCT proportion. (The proportion with post-induction PR should decrease, and the proportion with post-induction NR should increase.)

This is indicated in Table A6 where incremental costs decrease as the proportion achieving less than PR increases, but incremental QALYs do not change at all. The ERG thus considers that this sensitivity analysis only reflects uncertainty in cost, and does not reflect the associated reduction in treatment efficacy.

Table A6. Assumption related to the patient level data analysis (reproduced from addendum Table 21)

% of PR patients in VTD arm of Pethema who have achieved less than PR after cycle 4	Incremental costs	Incremental QALYs	ICER
Base case: *0% (All PR patients in VTD arm will have achieved PR after cycle 4 already)*	+£20,682	+1.01	**£20,468**
Scenario 1: *5% of PR patients in VTD arm will have achieved less than PR after cycle 4*	+£20,533	+1.01	**£20,320**
Scenario 2: *10% of PR patients in VTD arm will have achieved less than PR after cycle 4*	+£20,384	+1.01	**£20,173**
Scenario 3: *25% of PR patients in VTD arm will have achieved less than PR after cycle 4*	+£19,937	+1.01	**£19,730**

ICER, incremental cost-effectiveness ratio; PR, partial response; QALY, quality-adjusted life year; VTD, Velcade® (bortezomib), thalidomide and dexamethasone

Given that the revised model differentiates SCT rates by post-induction response, the ERG considers that a sensitivity analysis should also reflect the correlation which exists between post-induction response and SCT rate, since the likelihood of a patient receiving SCT is positively associated with the depth of response to the induction therapy (addendum p.22). However the revised model does not do this. Thus, for example, although post-induction response rates from the GIMEMA trial are examined in scenario analysis (addendum Table 18), this analysis still uses the overall SCT rates by treatment arm from the Pethema trial, even though the post-induction response rates are somewhat different. The ERG notes that post-induction responses for TD given in the revised model for the GIMEMA trial are better than those seen in Pethema, and given the positive correlation noted above it is likely that the corresponding SCT rate would also have been higher than the 61% achieved on the TD treatment arm in Pethema. (Although the protocol in GIMEMA was for all patients to receive SCT, and use of the SCT rate from this trial would therefore have been inappropriate, the ERG considers that the use of the Pethema trial SCT rate is also inappropriate.) Given this omission, the ERG believes that the ICERs for the post-induction response rate scenarios shown in addendum Table 18 do not reflect the full uncertainty in the decision problem.

Summary

The ERG has checked the changes to the economic model as described in the addendum and has found that additional changes have been made to many of the costs and several clinical parameters used by the model which are not documented in the addendum. The ERG has found that, when considering only model changes and assumptions which are documented in the addendum, the ICER is £23,958 per QALY (for the VTD vs TD regimen), compared to £20,468 as reported in the addendum.