Janssen-Cilag Ltd.

Bortezomib for Multiple Myeloma: Cost-Effectiveness Evidence Submission

1. Introduction

In this submission, we provide further information on the first three scenarios requested by the Appeal Panel. The Panel suggests reassessing the evidence for the cost-effectiveness of VELCADE (bortezomib):

1) When used only for patients after first relapse;
2) When used only for patients after first relapse, and when treatment ceases after three cycles if patients fail to respond;
3) When used only for patients after first relapse, and when treatment ceases after three cycles if patients fail to respond, and when the company pays for treatment in patients who fail to respond.

The fourth scenario, which considers combination use of VELCADE with dexamethasone, is not included in this report as the proposal to refer this scenario as a separate appraisal is still under consideration and is the subject of a separate NICE consultation.

The structure of this report is as follows:

PART 1 describes the health economic methodology and provides an overview of the proposed VELCADE response scheme.

PART 2 reports results for each of the scenarios using the original NICE model.

PART 3 provides additional analyses exploring the impact of stopping rule criteria on the cost-effectiveness of VELCADE.

Data deemed to be commercial in confidence appears as shaded text.

PART 1. Health Economic Methods

1.1. Economic modelling approach

In Appendix 1 we have provided an overview of the model, which is an abridged version of the information submitted to the Institute in our original submission. Following the ERG review of the model, we implemented a number of changes to address their comments. Please note that all changes described below were implemented and reported in our ACD response.

- The model uses QALYs rather than life-years gained.
- The cycle length is now 3-monthly across the entire model time horizon.
- Adverse event costs are now based on the frequency of events that were observed in the APEX study.
- VELCADE administration costs now include costs of pharmacy time.
- The cost of "other care" associated with myeloma has been increased to account for a small inflationary error.
- We have widened sensitivity analysis ranges to more fully explore uncertainty.

1.1.2. Incorporation of utilities into the model

A literature review was undertaken in order to identify published utility data for multiple myeloma (MM). This review revealed three potential studies, all of which were conducted alongside clinical trials. In two of the studies, utilities were derived by an indirect mapping exercise from disease-specific quality of life instruments (Nord et al 1997, Gulbrandson et al 2003) while the other (van Agthoven, et al 2004) used the EQ-5D. A summary of the three studies is provided in Table 1. The van Agthoven study also confirmed that utility values show little decline over time from 6 to 24 months.

The van Agthoven study was considered to be the most appropriate source of utility values for two reasons. Firstly, it is the only study that reports utility values according to responder rates, which fits more closely the data needs of the model and secondly, utility values were derived using the EQ-5D rather than the less methodologically robust indirect mapping approaches used in the other studies. To calculate cost per QALYs in the model, we have incorporated utility values as follows. In the *pre-progression* phase of the model, we use a utility value of 0.81, which is the average utility score from the responder group at 18 months in the van Agthoven study. In the *post-progression* phase we use a utility value of 0.644. This is the utility score for non-responders reported in the van Agthoven study. The impact of the selected utility estimates on the cost per QALY has been tested in sensitivity analyses.

Table 1. Summary of the identified utility studies in multiple myeloma

Study feature	Study		
	Nord et al 1997	Gulbrandsen et al 2001	van Agthoven et al 2004
Country, N	Scandinavia N = 583	Scandinavia N = 344	Netherlands N=261
Patient demographics	Age: median 67/68 years Gender: 56%/60% male	Age: median 51/54 years Gender: 65%/56% male	Age: median 55/56 years Gender: 57%/61% male
Study design	Multicentre RCT	Multicentre non-randomised trial with matched control group	Multicentre RCT
Treatments, n	MP, n = NR MP + αINF, n = NR	HDT/SCT, n = 274 Oral MP, n = 70 [a]	Intensive chemo, n =129 HDT/SCT, n = 132
Health value methodology(s)	EORTC QLQ-C30 mapped to EuroQol Index, IHQL and 15-D	EORTC QLQ-C30 mapped to 15-D	EuroQol Index
Reporting of utilities	6 months	6 months	6, 12, 18 and 24 months
Utilities available for multiple myeloma disease stages	No	No	Yes, for responders. Assumptions made to obtain utility of 0.644 for non-responders
Utility values	EuroQol MP 0.65 MP+ αINF 0.65 IHQL MP 0.70-0.80 MP+ αINF 0.60-0.70 15-D MP 0.60-0.70 MP+ αINF 0.60-0.65	15-D HDM/SCT 0.7334 MP 0.7896	EuroQol for responders 6m Chemo 0.81 HDT/SCT 0.65 12m Chemo 0.80 HDT/SCT 0.62 18m Chemo 0.81 HDT/SCT 0.69 24m Chemo 0.77 HDT/SCT 0.75

RCT = randomised controlled trial, MP = oral melphalan and prednisone, HDM/SCT = high dose melphalan and stem cell transplant, αINF = subcutaneous interferon α2b, EuroQol Index = time trade off values, IHQL = Index of Health-Related Quality of Life (uses standard gamble values), 15-D = 15 dimensional scale using rating scale values, m = months, NR = not reported.
[a] Subgroup of patients from Nord et al 1997.

1.1.3. Time Horizon

In our original model we used quarterly cycles from 0-3, 4-6 months, then six monthly from months 7-12, and then annual cycles for the remaining time horizon of the model. In line with the ERG's recommendation, quarterly cycles are now used throughout the model.

1.1.4. Revised Healthcare Resource Use Costing

Administration costs

VELCADE administration costs are increased from £79.00 to £112.50. This now includes the cost of pharmacy preparation time (£22.50).

Adverse event costs

Following ERG recommendations, adverse events from the APEX trial are now included in the model. The model calculates costs associated with the management of grade 3 or 4 adverse events that were reported within the APEX RCT in four key categories: thrombocytopenia, anaemia, neutropenia and all other listed grade 3 or 4 events such as nausea and vomiting. Costs of managing these events were derived from the NICE health technology assessment report for rituximab as third-line treatment for refractory or recurrent stage III or IV follicular non-Hodgkin's lymphoma by Wake et al in 2002 (Table 2), inflated to current prices.

Table 2. Incidence and costs of adverse events

		Incidence		Cost (GBP 2006)	
Severe Adverse Event	Cost per event (GBP 2006)	Velcade	HDD	Velcade	HDD
Anaemia	3,228	10.0%	11.0%	323	355
Thrombocytopenia	1,653	30.0%	6.0%	496	99
Neutropenia	3,854	14.0%	1.0%	540	39
Others	501	21.0%	42.0%	105	210
	Totals	75.0%	60.0%	1,463	703

Sources: Richardson, NEJM, 2005(Table 3 on page 2495). Wake et al. Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation. Health Tech Assessment 2002; 6:3. Available for downloading free of charge for personal use from the HTA website (http://www.ncchta.org).

Inflation from 2002 to 2006 is 13.5%.

Other care costs

In the original model, we slightly under-inflated the cost of "other care" of managing myeloma. The error occurred because these costs were inflated from 1999 instead of from 1997. We have now corrected this error and the revised cost has been increased from £448 per month to £478 (SD £63) per month.

1.1.5. Sensitivity Analysis Ranges

We have revised the ranges used in both the one-way and probabilistic sensitivity analyses to include greater levels of uncertainty. Table 3 summarises the key inputs and ranges that are used in the sensitivity analyses. Probabilistic sensitivity analyses were similarly updated using 95% confidence intervals for the hazard ratios and a range of +/- 25% for the costs.

Table 3. Summary of key sensitivity analysis input ranges and data sources

Parameters	VELCADE	HDD	Range*	Data source
Discount rate †	3.5%	3.5%	--	NICE Guidelines
Utilities pre-progression	0.81	0.81	+/-10%	van Agthoven et al 2004
Utilities post-progression	0.644	0.644	+/-25%	van Agthoven et al 2004
Time horizon, years †	15	15	--	Covers lifetime
Duration of treatment effect, years††	3	3	2 – 4	Richardson et al 2005[b]
Hazard ratios – TTP	0.56		0.44-0.71	ERG recommendation
Hazard ratio - OS	0.42	--	0.30-0.59	ERG recommendation
Cost per course of treatment (assuming 8 full cycles of treatment)	£21,860	£82	+/-25%	ERG recommendation
Cost of other care per month	£478	£478	+/-25%	Bruce et al 1999, APEX (Richardson et al 2005[a])
Cost of adverse events	£1,463	£702	+/-25%	Wake et al 2002

* Variables were simulated as normal distributions with 5th and 95th percentiles as presented.
† No range used for these parameters as they are policy variables set by NICE guidance.
†† based on median survival of the APEX trial having been updated to 29.8 months (Richardson et al)

1.2. Economic Evaluation of the VELCADE Response Scheme (VRS).

1.2.1. Overview of the VELCADE response scheme (VRS)

VELCADE has been proven to increase survival in a patient group who have few alternative treatment options. The company is therefore committed to finding a solution to ensure that patients have access to this clinically effective treatment in a cost-effective manner. Janssen-Cilag would therefore be willing to implement the VRS as part of NICE guidance to use this treatment in multiple myeloma patients who are experiencing their 1st relapse. We would be willing to implement this scheme across the whole of the UK to ensure patient access in the event that the Appraisal Committee concludes that other scenarios presented are not acceptably cost-effective.

Overview of the VRS

An overview of the scheme is presented in Figure 1. To ensure that the scheme is practical and workable in the NHS, we have developed it in close consultation with a broad group of Senior Haematologists (including members of the UK Myeloma Forum), hospital pharmacists and PCT representatives. In these discussions, we have been assured that the scheme would be workable in practice. We would be happy to provide names of physicians and pharmacists who have been consulted during the development of the scheme, which has also been reviewed in detail by the Department of Health. The Welsh Assembly

Government is currently reviewing the scheme and it is our understanding that they will provide comments directly to NICE.

The major elements of this scheme are as follows:

- The NHS would fund the entire course of treatment for patients at first relapse who achieve a response to VELCADE during the first four cycles of treatment. (For example, a patient who responds in the second cycle but subsequently dies or discontinues treatment will be paid for by NHS)
- Patients who fail to respond within the first four cycles of treatment would discontinue VELCADE. (For example, VELCADE costs for a patient who stops treatment before the 4^{th} cycle but who did not reach any response would be covered by the company)
- The company would provide replacement stock or credit for these non-responders (depending of their preference) direct to hospital units equivalent to the number of vials used by the patient and up to a maximum of four cycles (16 vials).
- The company would not rebate in situations where vials had been shared across more than one patient, as it would greatly complicate decisions around response and rebate.

The scheme will be run on trust, in that claims will be accepted as valid on completion of the form in Appendix 2. Each participating hospital would be asked to sign up to the scheme in the form of a written agreement. The company would request the right to audit anonymised patient-level data only where unusual rebate patterns are observed. This is both to protect patient safety and to protect the company from false claims.

Figure 1. VELCADE response scheme process flow

Confidential information removed

Definition of response

In scenarios presented to NICE, response has been defined using the rigorous EBMT (European Group for Blood and Marrow Transplantation) criteria. These criteria take into account a number of disease parameters including serum M-protein levels, the percentage of plasma cells in the bone marrow, and also the size of lytic bone lesions. In developing this scheme, we have had extensive discussions with leading myeloma clinicians. During these discussions it became clear to us that whilst EBMT is the gold standard response definition in randomised controlled trials, it is rarely practical to measure response according to full EBMT criteria in routine clinical practice in the UK. Thus, the consensus from clinicians is that a more pragmatic definition of response, such as that used in daily clinical practice is needed so that the scheme will be workable.

To ensure the scheme is as simple and pragmatic as possible, the VRS would need to use reduction in serum M-protein to assess response. This measure was chosen because it is well established, being an important component of the EBMT response definition, and also because it is the most consistently used definition of response used in the management of myeloma in UK clinical practice.

Clinicians routinely monitor serum M-protein at each treatment cycle. In this scheme, response to VELCADE is defined as a patient achieving at least a

minimal response (MR), which is 25% or greater reduction in serum M-protein (the degree of reduction specified in the EBMT criteria) within the first four cycles of treatment. Non-response is defined as no change or progressive disease (i.e. less than a 25% improvement in serum M-protein) within the first four cycles of treatment.

We have used "up to four cycles" as the stopping point because clinicians indicate that they would wish to have the option of continuing for a fourth cycle in some non-responders. However, we would require patients to receive four cycles in order to make a claim under the VRS. Most UK clinicians we spoke to about the scheme felt that they would not wish to continue treatment beyond four cycles, as they would be increasingly concerned about the balance of risks and benefits.

Around 10-15% of myeloma patients do not have measurable serum M-protein levels. For these patients, response would be assessed in terms of percentage reduction in urine free-light chain (Bence Jones) excretion. In line with EBMT criteria, response in these individuals would also be defined as at least an MR, which equates to a 50% reduction in free-light chains during the first four cycles of treatment.

Practical considerations

This scheme can be operated simply and with minimal incremental administrative burden for the following reasons:

- There is a clear, objective measure of response - serum M-protein (or urine free-light chain where serum M-protein is not present).
- The company directly distributes VELCADE to hospital units, which means that rebates can be dealt with efficiently by the company's customer services team. The supply chain is not complicated by involvement of wholesalers.
- Myeloma is a rare cancer. Low patient numbers in each unit mean that there is a low level of administrative burden.
- Rebates will be claimed through completion of a simple one page fax-back form (Appendix 2).

The company will review this scheme on an annual basis, but we would undertake not to withdraw it without prior discussion with NICE and DH. We envisage that the scheme would be offered to the NHS until the next NICE review, [redacted]

An issue that warrants exploration is the divergence between response definitions in clinical trials (EBMT) and routine practice (serum M-protein). We are aware that it is possible that this could impact the transferability of the economic results into UK practice.

To address this issue we have adapted the model to enable calculation of cost-effectiveness using serum M-protein rather than EBMT as the definition of response. Results using the original model with an EBMT response criterion are presented in Part 2. An analyses using serum M-protein as the response definition is presented in Part 3.

1.2.2. Modifications to the model to assess VRS

From a modelling perspective, the only difference between the stopping rule scenario previously presented to NICE and the VRS scenario is that the company covers the cost of non-response under the VRS scheme, but not under the stopping rule scenario. Therefore, in the VRS analysis, VELCADE costs of non-responders up to the point that they cease treatment are removed from the economic analysis as the company, not the NHS meets these costs.

PART 2. Health Economic Model Results – Original NICE Model

In this section, we summarise the results for the scenarios requested by the Appeal Panel using the original NICE model.

2.1. VELCADE monotherapy in patients at first relapse

As previously presented, in this scenario the cost-effectiveness of VELCADE is £38,000.

Table 4. Cost-effectiveness of VELCADE versus HDD at 1st relapse

Outcomes	VELCADE	HDD	Difference VELCADE v HDD
Mean overall survival, months	37.3	25.8	11.5
Mean discounted overall survival	34.0	23.9	10.1
% Alive			
1 year	87%	72%	15%
2 years	65%	45%	20%
5 years	23%	12%	11%
QALYs, months	26.08	17.47	8.6
Costs			
VELCADE and/or HDD	£21,860	£82	£21,778
Other care	£15,592	£10,808	£4,784
Adverse events	£1,463	£703	£760
Total	£38,914	£11,593	£27,322
Cost per discounted LYG			£32,452
Per QALY gained			£38,064

2.2. VELCADE monotherapy in patients after first relapse, and when treatment ceases after three cycles if patients fail to respond

This scenario was also presented in our original submission to NICE, using an analysis of patient-level data from the APEX study.

It is common in the UK for clinicians to cease VELCADE treatment in patients who fail to respond after several cycles of treatment. This means that patients who do not respond would rarely if ever receive eight cycles of treatment. In this scenario, the economic impact of developing a stopping rule for non-responding patients is evaluated.

The patient level data analysis (previously presented to NICE) showed that 85.2% (115/135) of patients who achieved a complete or partial response in APEX did so within three cycles. Varying the number of cycles at which the stopping rule was implemented demonstrated that the cost-effectiveness ratio was optimal when treatment was stopped after three cycles. Stopping earlier

means that the loss of survival makes the results less favourable, whilst prolonging treatment for more than three cycles means that VELCADE costs associated with treating non-responders raises the ICER. As requested, we also provide the analysis that evaluates the cost-effectiveness ratio when treatment is stopped after four cycles.

In these analyses, the 85.2% of patients who respond to VELCADE treatment would receive up to an additional five cycles (maximum of eight cycles as per SmPC). The benefits accrued by the remaining 14.8% of patients who had a response in APEX after three cycles would not be realised in this scenario. The model predicts that the incremental overall survival benefit would fall from (discounted) 10.1 months to 8.5 months (Tables 4 and 5). This analysis assumes that there would be no "carry-over" effect of VELCADE in those patients who discontinue. In other words, patients who cease treatment at three cycles cannot subsequently go on to have any later VELCADE benefits in the model.

In this scenario, the incremental cost-effectiveness of VELCADE is £33,515.

Table 5. Cost-effectiveness – three-cycle stopping rule

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	35.5	25.8	9.7
Mean discounted overall survival	32.4	23.9	8.5
% Alive			
1 year	79%	72%	7%
2 years	61%	45%	16%
5 years	22%	12%	10%
QALYs, months	24.95	17.47	7.5
Costs			
Velcade and/or HDD	£16,220	£82	£16,138
Other care	£14,806	£10,808	£3,998
Adverse events	£1,463	£703	£760
Total	£32,489	£11,593	£20,896
Cost per discounted LYG			£29,649
Per QALY gained			£33,515

Sensitivity analyses

One-way sensitivity analyses

Results of the one-way sensitivity analyses are presented in Table 6.

Table 6. One-way sensitivity analyses - three-cycle stopping rule

Variable	Basecase	Inputs		CE ratios		Range
		Left	Right	Left	Right	
Duration of treatment effect, years	3.00	4.00	2.00	£30,361	£40,490	£10,128
Utilities - relative change	1.00	1.10	0.90	£29,587	£38,645	£9,057
Vial wastage adjustment	1	2	1	£25,009	£33,515	£8,506
Cost of other care - Velcade pre-progression	478	381	599	£30,451	£37,354	£6,903
Hazard ratio - TTP	0.56	0.51	0.61	£30,623	£37,309	£6,686
Cost of other care - pre- and post-progression	477.53	381.00	598.53	£31,300	£35,282	£3,982
Cost of Velcade per course	21859.50	20819.00	22952.00	£32,276	£34,815	£2,538
Hazard ratio - OS	0.77	0.70	0.85	£32,764	£34,386	£1,622
Cost of adverse events - relative change	1.00	1.25	0.75	£33,210	£33,820	£610
Cost of HDD per course	£82	£86	£78	£33,508	£33,521	£13

Additional Sensitivity Analyses

As discussed in section 1.2.1, clinicians indicate that it would be preferable to have a stopping rule that would allow patients to continue for up to four cycles of treatment. We therefore provide a sensitivity analysis to investigate the impact of a four-cycle stopping rule on the cost-effectiveness results.

Another issue which requires consideration is the definition of response used in determining whether or not to stop treatment, and in particular whether patients who achieve a minimal response (MR) should have the option to continue treatment. For reasons discussed previously, the proposed VRS includes MR in the response definition. We have therefore provided an additional analysis here to evaluate the impact of inclusion of MR on the cost-effectiveness results.

These results confirm that the cost-effectiveness ratio is lowest when treatment is stopped after three cycles in non-responders however the absolute difference between these two options is small (Table 7). Similarly, inclusion of MR in the definition of response only results in small changes to the ICER. Further detail on these analyses is presented in Appendix 3

Table 7. Sensitivity Analyses: Stopping Rules and Response Definitions

Scenario	CR+PR ICER (PSA CI)	CR+PR+MR ICER (PSA CI)
EBMT		
3-cycle stopping Rule	£33, 515 (£28,385-£44,284)	£34,599 (£29,734-£44,530)
4-cycle stopping Rule	£34,359 (£29,834-£44,349))	£35,568 (£30,653-£45,131)

2.3. VELCADE monotherapy versus HDD when used for patients at first relapse, and when treatment ceases after three cycles if patients fail to respond, and when the company pays for treatment in patients who fail to respond

An overview of the proposed VELCADE response scheme (VRS) is provided in Section 1.2. The only difference between the stopping rule scenario above and this VRS scenario is that the company rebates non-responders under the VRS scheme, but not under the stopping rule scenario.

The previous results demonstrate that it is optimally cost-effective to cease treatment after three cycles when a (no-rebate) stopping rule is used. However, as discussed previously, physicians we have consulted indicated a preference to have the flexibility to continue treatment for up to four cycles. Beyond four cycles clinicians tell us that they would not usually continue treatment in non-responders. Indeed, the APEX data demonstrates that few patients would respond beyond this time point. We have therefore evaluated the cost-effectiveness of VELCADE within the VRS using both a three and four-cycle stopping rule.

Although in practice the scheme would need to define response in terms of serum M-protein, these analyses evaluate the cost-effectiveness of VELCADE in the VRS using EBMT criteria so that it is possible to compare the results directly with those previously submitted to NICE for the (no rebate) stopping rule. Analyses based on a serum M-protein response definition are provided in Part 3 of this report. Sensitivity analyses are also provided here which evaluate the impact of including MRs within the response definition.

The cost-effectiveness results for VELCADE within the VRS scheme are presented in Table 8 assuming a three-cycle stopping rule to allow comparison with the (no rebate) stopping rule analysis.

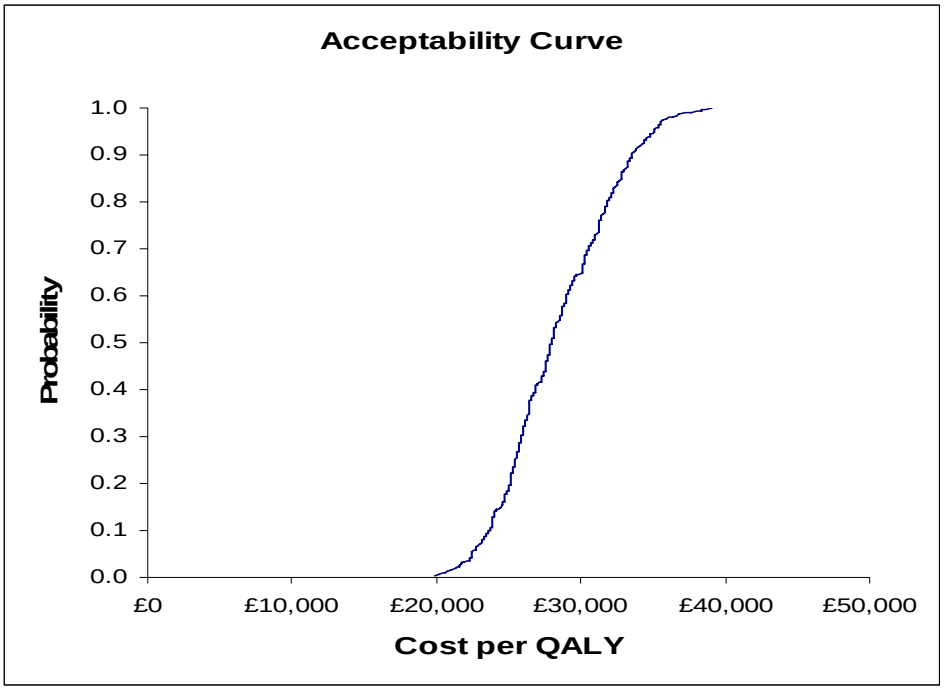
The results of this scenario show that the ICER for VELCADE within the VRS with a three-cycle stopping rule and a CR+PR definition of response is £26,605 (£22,392 - £35,135). When compared to the (no-rebate) scenario with identical response and stopping criteria, it is clear that the VRS significantly improves the cost-effectiveness of VELCADE. Compared to the no-rebate ICER (£33,515), the VRS reduces the cost-effectiveness ratio by almost £7,000. This difference is due to the rebate that would be provided back to the NHS by the company for those patients who fail to respond.

Table 8. Cost-effectiveness - VRS plus three-cycle stopping rule

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	35.5	25.8	9.7
Mean discounted overall survival	32.4	23.9	8.5
% Alive			
1 year	79%	72%	7%
2 years	61%	45%	16%
5 years	22%	12%	10%
QALYs, months	24.95	17.47	7.5
Costs			
Velcade and/or HDD	£11,912	£82	£11,830
Other care	£14,806	£10,808	£3,998
Adverse events	£1,463	£703	£760
Total	£28,181	£11,593	£16,588
Cost per discounted LYG			£23,537
Per QALY gained			£26,605

The cost-effectiveness acceptability curve for this scenario is presented in Figure 2.

Figure 2. Acceptability Curve – VRS plus three-cycle stopping rule



One-Way Sensitivity Analyses

Table 9 shows that within the VRS, the uncertainty around the cost-effectiveness results is reduced compared to sensitivity analyses shown in Table 6 for the no rebate stopping rule scenario. Within all ranges tested, the cost-effectiveness results remained below or around £30,000.

Table 9. One-way sensitivity analyses - VRS plus three-cycle stopping rule

		Inputs		CE ratios		Range
Variable	**Basecase**	**Left**	**Right**	**Left**	**Right**	
Vial wastage adjustment	1.00	1.60	1.00	£18,100	£26,605	£8,506
Duration of treatment effect, years	3.00	4.00	2.00	£24,272	£31,767	£7,495
Utilities - relative change	1	1	1	£23,488	£30,678	£7,190
Cost of other care - Velcade pre-progression	478	381	599	£23,542	£30,445	£6,903
Hazard ratio - TTP	0.56	0.51	0.61	£24,460	£29,421	£4,961
Cost of other care - pre- and post-progression	477.53	381.00	598.53	£24,391	£28,373	£3,982
Cost of Velcade per course	16053.79	15289.63	16856.13	£25,696	£27,560	£1,864
Hazard ratio - OS	0.77	0.70	0.85	£26,061	£27,237	£1,177
Cost of adverse events - relative change	1.00	1.25	0.75	£26,301	£26,910	£610
Cost of HDD per course	£82	£86	£78	£26,599	£26,612	£13

Additional Sensitivity Analyses

In common with the no rebate stopping rule (section 2.2), additional analyses have been undertaken to evaluate the impact of response definition and stopping rules.

Under the VRS (and in contrast to the no rebate stopping rule analysis), cost-effectiveness actually improves when treatment is stopped after four, rather than three cycles (Table 10). This is explained by the fact that the VELCADE costs of non-responders remain zero (as the company meets this cost), but there are additional effectiveness (survival) gains. It is slightly more cost-effective to exclude MRs, but differences are small and in all results, the cost-effectiveness remains under £30,000. The most relevant result in Table 10 is for the four-cycle stopping rule with a CR+PR+MR definition of response as this analysis most closely replicates the design of the VRS. In this scenario, the ICER is £26,991 (£23,608 - £34,850). Further detail is provided in Appendix 3.

Table 10. Additional sensitivity analyses - VRS plus stopping rule

Scenario	**CR+PR ICER (PSA)**	**CR+PR+MR ICER (PSA)**
EBMT		
3-cycle stopping Rule + VRS	£26,605 (£22,392-£35135)	£28,091 (£24,117-£36,230)
4-cycle stopping Rule + VRS	£25,252 (£22,121-£32,295)	**£26,991 (£23,608-£34,850)**

Although the VRS scheme would use serum M-protein as a response definition, these results provide a useful comparison to understand the impact of a stopping rule plus response scheme relative to the no-rebate stopping scenario. Comparing the results presented in Tables 5 and 8 shows that the VRS reduces the ICER by around £7000 and also reduces the level of uncertainty around the ratios.

PART 3. Health Economic Model Results – Updated Model with Serum M-Protein Response Definition

In this section, we provide an analysis that replicates the VRS in usual clinical practice. These results are designed to investigate whether the definition of response used in the stopping decision will impact on the cost-effectiveness of VELCADE compared to results presented in Part 2. In developing this analysis we have used the original NICE model, updated to use serum M-protein rather than EBMT as the response criteria. All other elements of the model are unchanged.

In the VRS, response to VELCADE is defined as a patient achieving at least a minimal response (MR) within the first four cycles of treatment. To be classed as an MR, patients must achieve a 25% or greater reduction in serum M-protein (the degree of reduction specified in the EBMT criteria) within the first four cycles of treatment. Non-response is defined as no change or progressive disease (i.e. less than a 25% improvement in serum M-protein) within the first 4 cycles of treatment.

In this analysis, the patient-level data from the APEX study has been reanalysed using serum M-protein as a measure of response rather than the full EBMT criteria. This analysis provides initial patient response rates (according to serum M-protein) by treatment cycle. Type of response is defined exactly according to the serum M-protein component of the EBMT criteria (Table 11).

Table 11. Definitions of response according to serum M-protein

Level of Response*	M Protein
CR	None (IF neg)
PR	≥50% decrease
MR	≥25% decrease
PD	>25% increase or min 5 g/L

*CR = complete response; PR = partial response; MR = Minor response; PD = progressive disease. Responses falling between MR and PD are classed as stable disease

From the reanalysis of the patient level data reported in Table 12, it is clear that some patients who initially have a minor response later go on to achieve partial or complete “best” responses. Based on this finding, it is appropriate to consider MRs as being responders.

Table 12. Reanalysis of APEX patient level data*.

Cycle (a)	Initial M-Protein Response				Best M-Protein Response			
	Total	CR	PR	MR	Total	CR	PR	MR
1 Prior Line (N=[redacted])								
1	**Confidential information removed**							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
Total								

*note that the SmPC does not recommend treatment beyond cycle 8

The conclusions of this analysis are as follows:

[redacted]

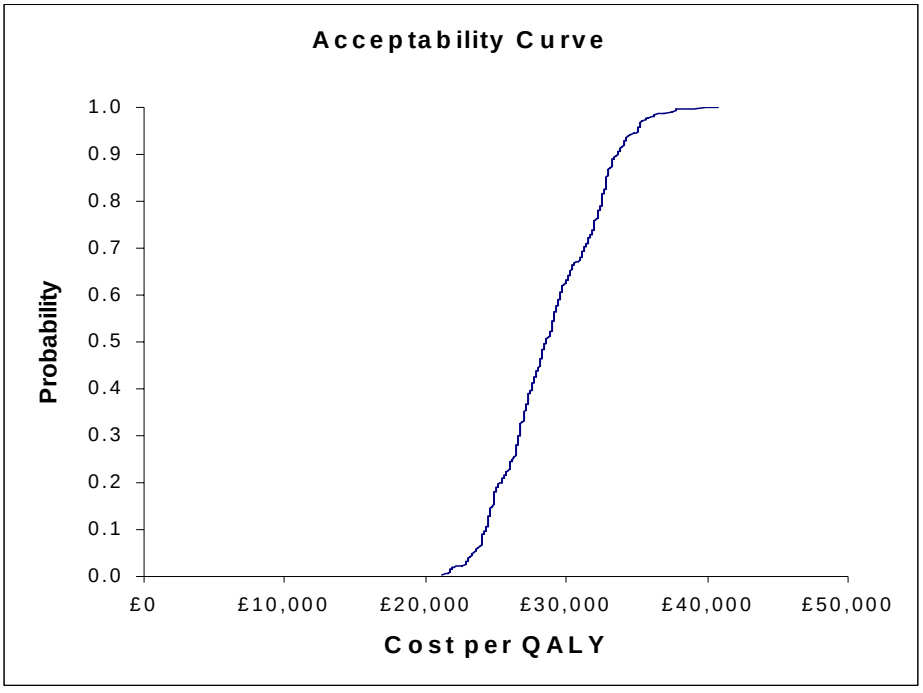
3.1. VELCADE monotherapy versus HDD when used for patients at first relapse, and when treatment ceases after three cycles if patients fail to respond, and when the company pays for treatment in patients who fail to respond

The cost-effectiveness results for this scenario are presented in Table 13. When serum M-protein, rather that EBMT criteria are used to define response (using a four-cycle stopping rule within the VRS and a CR+PR+MR definition of response) the incremental cost per QALY is £27,413 (£23,269-£35,039). The acceptability curve (Figure 3) shows that there is a high probability that VELCADE is cost-effective relative to stated thresholds. Further information is provided in Appendix 3.

Table 13. Cost-effectiveness - VRS plus four-cycle stopping rule

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	36.9	25.8	11.1
Mean discounted overall survival	33.7	23.9	9.8
% Alive			
1 year	85%	72%	13%
2 years	64%	45%	19%
5 years	23%	12%	10%
QALYs, months	25.85	17.47	8.4
Costs			
Velcade and/or HDD	£13,844	£82	£13,762
Other care	£15,430	£10,808	£4,622
Adverse events	£1,463	£703	£760
Total	£30,738	£11,593	£19,145
Cost per discounted LYG			£23,528
Per QALY gained			£27,413

Figure 3. Acceptability Curve – VRS plus four-cycle stopping rule



One-Way Sensitivity Analyses

Table 14 shows that the results remain below £30,000 for most scenarios tested within the selected ranges of the one-way sensitivity analyses.

Table 14. One-way Sensitivity Analyses for VRS

Variable	Basecase	Inputs		CE ratios		Range
		Left	Right	Left	Right	
Vial wastage adjustment	1.00	1.60	1.00	£20,245	£28,231	£7,986
Duration of treatment effect, years	3.00	4.00	2.00	£25,890	£33,252	£7,363
Utilities - relative change	1	1	1	£25,109	£32,241	£7,133
Cost of other care - Velcade pre-progression	478	381	599	£25,420	£31,756	£6,336
Hazard ratio - TTP	0.56	0.51	0.61	£26,084	£30,991	£4,907
Cost of other care - pre- and post-progression	477.53	381.00	598.53	£26,372	£29,715	£3,343
Cost of Velcade per course	18492.19	17611.97	19416.40	£27,248	£29,264	£2,016
Hazard ratio - OS	0.56	0.51	0.62	£27,815	£28,707	£892
Cost of adverse events - relative change	1.00	1.25	0.75	£27,952	£28,511	£560
Cost of HDD per course	£82	£86	£78	£28,225	£28,237	£12

Other Sensitivity Analyses

In this analysis, we evaluate the impact of the stopping rule on the cost-effectiveness results (Table 15).

Consistent with the VRS results presented in Part 2, these results demonstrate that it is most cost-effective to stop treatment after four rather that three cycles.

Table 15. Sensitivity Analysis Results

Scenario	ICER (PSA)
Serum M-Protein	
3-cycle stopping Rule + VRS	£28,231 (£24,275-£35,903)
4-cycle stopping Rule + VRS	£27,417 (£23,269-£35,039)

Summary

These analyses demonstrate that VELCADE can be considered to be a cost-effective treatment relative to NICE's stated thresholds. VELCADE is optimally cost-effective when used within the proposed VRS scheme and when treatment is stopped after four cycles in non-responders. The fact that the company rebates the NHS for patients who fail to respond means that drug costs are reduced and the cost-effectiveness improves when compared to other scenarios previously presented. Table 16 summarises cost-effectiveness results presented in this submission using the EMBT criteria and includes a column to show the difference in the ratios that would be delivered through the proposed VRS. All tested scenarios show that the VRS reduces costs compared to an equivalent (no-rebate) stopping rule and produces ratios that are cost-effective at a £30,000 threshold.

Table 16: Cost-effectiveness comparison: VRS vs. no rebate stopping rule

Scenario	**CR+PR ICER**	**CR+PR+MR ICER**
EBMT		
3-cycle stopping Rule (A)	£33,515	£34,599
3-cycle stopping Rule + VRS (B)	£26,605	£28,091
Difference (A-B)	**£6,910**	**£6,508**
4-cycle stopping Rule (C)	£34,359	£35,568
4-cycle stopping Rule + VRS (D)	£25,252	£26,991
Difference (C-D)	**£9,107**	**£8,577**

From the results presented in Part 3, it can also be concluded that the cost-effectiveness of VELCADE within the VRS is maintained when a serum M-protein definition of response is used. A comparison of the ratios obtained using EMBT or serum M-protein definitions of response are presented in Table 17 and shows that there are only marginal differences between them. These results indicate that the economic benefits of the VRS are maintained whether EBMT or serum M-protein is used as a definition of response. This indicates that the use of VELCADE in usual clinical practice within the VRS would be cost-effective.

Table 17. Cost-effectiveness comparison: Serum M-protein vs. EBMT*

Scenario	EBMT	Serum M-Protein
3-cycle stopping Rule + VRS	£28,091	£28,231
4-cycle stopping Rule + VRS	£26,991	£27,417

*Response defined as MR+PR+CR

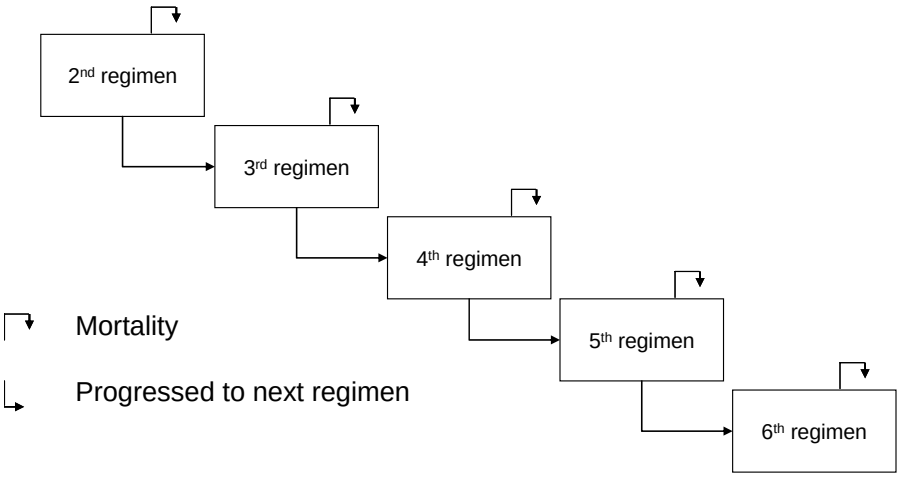
Appendix 1. Overview of model structure

For further information, please refer to our original submission.

Model Framework

A semi-Markov model was developed, the structure of which is presented in Figure 14. It is assumed that all patients entering the model do so at first relapse (2nd regimen). Through subsequent cycles of the model, patients can remain on their current regimen, die or transition to subsequent treatments. The time horizon of the model is 15 years.

Figure 1: Semi-Markov Structure



Modelling treatment effectiveness

Time to progression (TTP) and 1-year survival rates were taken from the APEX trial for patients who were receiving the treatment at 1st relapse at the start of the trial. These estimates are taken from the Richardson et al paper which reports 8.3 months of follow-up within the assigned treatment arms.

The early termination, however does affect the ability to model long-term outcomes and mortality data with HDD. In an attempt to model lifetime survival following the termination of APEX, a review of published epidemiological data was undertaken with the objective of identifying suitable data to use as the basis for modelling lifetime survival for both VELCADE and HDD.

From this search one relevant peer-reviewed publication was identified. This observational study was conducted in 578 relapsed MM patients at the Mayo Clinic in the US.

Summary of Mayo Observational Study Patient Population and Data

The objective of the Mayo Observational Study was to observe the clinical course and outcomes of patients with MM who experience relapse following treatment. The study population consisted

of patients diagnosed with MM who presented at the Mayo Clinic in Rochester, Minnesota, between January 1, 1985, and December 31, 1998. To ensure complete clinical and laboratory follow-up information the Mayo Clinic patient database was searched to identify patients who were seen at least six times per year, on average, over the course of their treatment and disease course. Five hundred seventy-eight patients, of a potential pool of 1027 patients, had complete treatment records and were included in the study. The median age of patients was 65 years (range, 26-92 years), and 228 patients (39%) were women. The median follow-up for those still alive (n=71) was 55 months (range, 0-202 months with only 4 patients having <1 year of follow-up).

As this was an observational study, patients were treated with a variety of regimens according to the standard of care for their particular disease stage and needs. No patients were treated with VELCADE as it was not available during this time period. However, 188 patients (32.5%) were treated at some point during the course of their follow-up with a combination of vincristine, adriamycin and dexamethasone (VAD), a regimen in which dexamethasone is believed to be the dominant agent (54). Of the 188 patients who ever received dexamethasone, 114 patients (60.6%) received it as their first regimen (i.e., prior to first relapse) and 74 patients (39.4%) received it after their first relapse.

The baseline patient characteristics of the APEX trial population and Mayo Observational Study were compared. In terms of patient demographics and disease characteristics the patient groups from both datasets were comparable. Available prognostic factors, including performance status and β_2-microglobulin levels, are well matched.

The results of this analysis supported the use of the data from the Mayo Observational Study for estimating longer-term survival within the economic model. The Mayo Observational Study reported an overall survival at 1 year of 72%, at 2 years 55%, and at 5 years 22%. The median overall survival for 578 patients in the study group was 28.4 months. At ten years from diagnosis, nearly all patients had died of either their disease or other causes.

HDD Survival Modelling Approach.

TTP and 1-year survival estimates for HDD were taken from the APEX trial. The following steps were taken to model the survival estimate for patients receiving HDD:

Step 1: Enter reported information on percent of patients who stayed on a regimen, switched to another regimen, or died. (Table 3 of Kumar et al)

Step 2: Construct a probability transition matrix from these data.

Step 3: Use the probability transition matrix to compute the percent of patients over time in each regimen.

Step 4: Check goodness of fit of this model with observed survival from time of diagnosis reported in the Mayo Observational Study.

Step 5: The1st relapse patients in the Mayo Observational study reflects treatment with a variety of therapies not just HDD. Therefore, the transition probabilities were adjusted through a single common hazard reduction so that the model predictions replicate the survival at 1 year in the APEX trial's HDD arm of patients who have relapsed after only one prior therapy. We use the hazard ratios directly from APEX trial to estimate the survival. This step is undertaken to ensure

that the model is able to replicate the reported survival at 1 year in APEX by using the reported hazard ratios from the study.

A comprehensive description of each of these steps can be found in Appendix 12 of our original submission.

VELCADE Survival Modelling Approach

Hazard ratios for time to progression and overall survival with VELCADE were estimated from the APEX trial data for patients with 1st relapse. We used these ratios in the model as outlined in the steps below.

Step 1: Apply a probability of staying in regimen 2 based on the APEX trial's TTP hazard ratio of 0.56 (page 2492 of Richardson et al.).

Step 2: Apply a probability of dying in regimen 2 based on the APEX trial's OS hazard ratio of 0.42 (page 2493 of Richardson et al.).

Step 3: Compare the predicted 1-year survival from this model with the survival reported in the VELCADE arm of APEX for patients after 1st relapse (who had only one prior line of therapy).

A more detailed summary of the approach is presented in Appendix 13 of our original submission.

Appendix 2. VRS Claim Fax-Back Form (Commercial in confidence)

Confidential information removed

Appendix 3: Detailed Sensitivity Analyses

Section 2.2. Sensitivity Analysis Results: Stopping Rule Scenario

Three cycle stopping rule, including MR in definition of response

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	35.8	25.8	10.0
Mean discounted overall survival	32.7	23.9	8.8
% Alive			
1 year	81%	72%	9%
2 years	62%	45%	17%
5 years	22%	12%	10%
QALYs, months	25.17	17.47	7.7
Costs			
Velcade and/or HDD	£17,377	£82	£17,295
Other care	£14,959	£10,808	£4,151
Adverse events	£1,463	£703	£760
Total	£33,800	£11,593	£22,207
Cost per discounted LYG			£30,360
Per QALY gained			£34,599

Four Cycle Stopping Rule using PR+CR definition of response

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	36.5	25.8	10.7
Mean discounted overall survival	33.4	23.9	9.4
% Alive			
1 year	84%	72%	12%
2 years	63%	45%	18%
5 years	23%	12%	10%
QALYs, months	25.62	17.47	8.2
Costs			
Velcade and/or HDD	£18,198	£82	£18,116
Other care	£15,271	£10,808	£4,463
Adverse events	£1,463	£703	£760
Total	£34,933	£11,593	£23,340
Cost per discounted LYG			£29,697
Per QALY gained			£34,359

Four Cycle Stopping Rule, including MR in definition of response

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	36.5	25.8	10.7
Mean discounted overall survival	33.4	23.9	9.4
% Alive			
1 year	84%	72%	12%
2 years	63%	45%	18%
5 years	23%	12%	10%
QALYs, months	25.62	17.47	8.2
Costs			
Velcade and/or HDD	£19,019	£82	£18,937
Other care	£15,271	£10,808	£4,463
Adverse events	£1,463	£703	£760
Total	£35,753	£11,593	£24,161
Cost per discounted LYG			£30,741
Per QALY gained			£35,568

Section 2.3. Sensitivity Analysis Results: VRS plus Stopping Rule Scenario

VRS plus three cycle stopping rule, including MR in definition of response

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	35.8	25.8	10.0
Mean discounted overall survival	32.7	23.9	8.8
% Alive			
1 year	81%	72%	9%
2 years	62%	45%	17%
5 years	22%	12%	10%
QALYs, months	25.17	17.47	7.7
Costs			
Velcade and/or HDD	£13,201	£82	£13,119
Other care	£14,959	£10,808	£4,151
Adverse events	£1,463	£703	£760
Total	£29,623	£11,593	£18,030
Cost per discounted LYG			£24,649
Per QALY gained			£28,091

Four Cycle Stopping Rule using PR+CR definition of response

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	36.5	25.8	10.7
Mean discounted overall survival	33.4	23.9	9.4
% Alive			
1 year	84%	72%	12%
2 years	63%	45%	18%
5 years	23%	12%	10%
QALYs, months	25.62	17.47	8.2
Costs			
Velcade and/or HDD	£12,012	£82	£11,930
Other care	£15,271	£10,808	£4,463
Adverse events	£1,463	£703	£760
Total	£28,746	£11,593	£17,153
Cost per discounted LYG			£21,825
Per QALY gained			£25,252

Four Cycle Stopping Rule, including MR in definition of response

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	36.5	25.8	10.7
Mean discounted overall survival	33.4	23.9	9.4
% Alive			
1 year	84%	72%	12%
2 years	63%	45%	18%
5 years	23%	12%	10%
QALYs, months	25.62	17.47	8.2
Costs			
Velcade and/or HDD	£13,193	£82	£13,111
Other care	£15,271	£10,808	£4,463
Adverse events	£1,463	£703	£760
Total	£29,927	£11,593	£18,335
Cost per discounted LYG			£23,328
Per QALY gained			£26,991

Part 3. Sensitivity Analysis Results for Serum M-Protein Analysis - VRS plus Stopping Rule Scenario

VRS plus three cycle stopping rule

Outcomes	Velcade	HDD	Difference Velcade v HDD
Mean overall survival, months	36.5	25.8	10.7
Mean discounted overall survival	33.4	23.9	9.4
% Alive			
1 year	84%	72%	12%
2 years	63%	45%	18%
5 years	23%	12%	10%
QALYs, months	25.62	17.47	8.2
Costs			
Velcade and/or HDD	£14,036	£82	£13,954
Other care	£15,271	£10,808	£4,463
Adverse events	£1,463	£703	£760
Total	£30,770	£11,593	£19,177
Cost per discounted LYG			£24,400
Per QALY gained			£28,231