All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

AWMSG ADVICE SUPERSEDED BY NICE GUIDANCE (TA586)

NICE GUIDANCE ISSUED MAY 2019

(Refer to NICE website for full guidance on NICE recommendations, including any specific restrictions on the use of the technology)

Final Appraisal Report

Lenalidomide (Revlimid®) for multiple myeloma

Celgene UK

Advice No: 0908

Recommendation of AWMSG

Lenalidomide (Revlimid®) is not recommended for use within NHS Wales for the treatment of multiple myeloma.

Key factor influencing the recommendation:
The case for cost-effectiveness of lenalidomide (Revlimid®) has not been proven.

This report should be cited as:

All Wales Medicines Strategy Group Final Appraisal Report
Lenalidomide (Revlimid®) – June 2008

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, medical expert opinion, lay perspective and discussions at the AWMSG meeting.

Date: Friday, 13th June 2008.

The recommendation of AWMSG is:

Lenalidomide (Revlimid®) is not recommended for use within NHS Wales for the treatment of multiple myeloma.

Key factor influencing the recommendation:

The case for cost-effectiveness of lenalidomide (Revlimid®) has not been proven.

2.0 PRODUCT DETAILS:

2.1 Licensed indication:
Lenalidomide (Revlimid®) in combination with dexamethasone is indicated for the treatment of multiple myeloma (MM) patients who have received at least one prior therapy[1].

2.2 Dosing:
The recommended starting dose of lenalidomide is 25 mg orally once daily on days 1–21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on days 1–4, 9–12, and 17–20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg once daily on days 1–4 every 28 days. Dosing is continued or modified based upon clinical and laboratory findings[1].

2.3 Market authorisation date: UK marketing authorisation was granted on 14th June 2007[2].

2.4 UK Launch date: Lenalidomide was launched in the UK 25th June 2007[2].

3.0 DECISION CONTEXT
MM is a plasma cell neoplasm that mainly affects older people (approximately 85% of patients are aged 60 years and over). The clinical presentation is varied but may include symptoms of bone disease (typically unexplained persistent back pain), impaired renal function, anaemia, and hypercalcaemia. Despite advances in treatment, it remains incurable. From the time of diagnosis, survival without treatment is between 6 and 12 months and extends to a median of 3 years with chemotherapy[3-5].

The 2005 British Committee for Standards in Haematology (BCSH) guidelines indicate that initial treatment for newly diagnosed, symptomatic MM patients depends on their potential to benefit from stem cell transplant (SCT). In those who relapse following initial treatment, management should be determined on an individual basis depending on timing of relapse, age, prior therapy, bone marrow function and other clinical circumstances[3].

There have been significant developments since the BCSH guidelines were issued. Regimens that were previously considered standard initial treatments (e.g. vincristine + doxorubicin + dexamethasone [VAD]-type regimens in those suitable for SCT and melphalan or cyclophosphamide for those unsuitable for SCT[3]) are being superseded. Thalidomide has been increasingly used at earlier stages of the disease[3,5] and a positive opinion was granted recently following a marketing authorisation application to the EMEA for its use in combination with melphalan and prednisone as first line treatment of patients with MM aged ≥ 65 years or ineligible for high dose chemotherapy[6]. A large MRC-funded trial, Myeloma IX, is also currently assessing thalidomide in combination with cyclophosphamide and dexamethasone against standard induction chemotherapy regimens in younger/fitter patients and older/less fit patients[7]. In addition, bortezomib is now licensed as monotherapy following relapse and has recently been recommended by NICE as a treatment option in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, SCT[8].

Lenalidomide is designated orphan drug status, but does not fall within the AWMSG criteria for ultra orphan drug status. Although the licensed indication is (in combination with dexamethasone) for the treatment of MM patients who have received at least one prior therapy[1], the company state they have limited the submission to AWMSG to two specific subgroups: (i) patients who have received only one prior therapy and are unsuitable for treatment with bortezomib, and (ii) patients who have received at least two prior therapies[2].

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Studies MM009 (n=353) and MM010 (n=351) compared a regimen of lenalidomide plus dexamethasone (Len/Dex) against dexamethasone monotherapy (Dex) in patients who had received at least one prior therapy for MM. These studies were unblinded early when interim analyses showed a significant improvement in the primary endpoint measure of time to progression (TTP) with Len/Dex (pooled data: 48.3 weeks versus 20.1 weeks, hazard ratio [HR] 0.35, 95%CI 0.29 to 0.43, $p<0.001$). Secondary endpoints were consistent with these findings. Pre-specified subgroup analyses indicated that response to treatment with Len/Dex was reduced in those who had previously received two or more therapies, and in those who had not previously had SCT, although it was still significantly improved compared with Dex. Median overall survival (OS) had not been reached at the time of unblinding, and 47% of the Dex group crossed over to Len/Dex treatment. Combined data, representing a median follow up of 32.1 months for MM009 and 28.7 months for MM010 participants, indicates that median OS was improved with Len/Dex (35 months versus 31 months, $p<0.05$). The adverse events that were reported to be significantly more frequent with Len/Dex than Dex were mainly haematological (neutropenia, thrombocytopenia) and thromboembolic (deep vein thrombosis, pulmonary embolism).

4.2 Review of the evidence on cost-effectiveness

The company submitted an economic model that compared Len/Dex against Dex in the two subgroups described in 3.0.

There are several uncertainties in the assumptions used in the model. The OS of patients who received Dex in studies MM009 and MM010 has been adjusted using data from other studies and trials conducted several years ago. It is unclear how representative these other populations are of the patients and treatments being modelled currently. Data relating to patients who had received two or more previous therapies has, in effect, been adjusted twice, which has the potential to further compound inaccuracies. There are no quality of life data available specific to lenalidomide treatment, and the utility values assumed in the model are derived from a study conducted in a different MM patient group. The extent to which these and other combined assumptions influence the model outputs is unknown.

In patients who have received only one prior therapy and are unsuitable for treatment with bortezomib, the model predicts a lifetime incremental cost of £34,770 per QALY

gained. In patients who have received at least two prior therapies, the model predicts a lifetime incremental cost per QALY of £30,871.

5.0 LIMITATIONS OF DECISION CONTEXT:

For patients who have failed only one prior therapy, the company states that the submission to AWMSG is limited to those who are unsuitable for treatment with bortezomib, which it implies are those who have pre-existing neuropathy. Studies MM009 and MM010 were not conducted in patients specifically with pre-existing neuropathy, and there are no data provided from this specific subgroup. The safety and efficacy of lenalidomide in this specific subgroup of patients is therefore uncertain.

The recent NICE guidance on bortezomib and the positive regulatory authority opinion on thalidomide may lead to greater uptake of these therapies in practice. Two-thirds of patients in studies MM009 and MM010 had received two or more prior therapies, but relatively few had received prior treatment with bortezomib (approximately 8%) or thalidomide (approximately 39%). The extent to which the outcomes of these trials will be seen in clinical practice, where the prior use of these other agents may be higher, is uncertain.

In those who relapse following treatment, management should be determined on an individual basis depending on timing of relapse, age, prior therapy, bone marrow function and other clinical circumstances. There are no direct comparative data for lenalidomide against therapies other than dexamethasone.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

The company submission[2] describes two pivotal phase III studies (MM009 and MM010) of lenalidomide plus dexamethasone (Len/Dex) versus placebo plus dexamethasone (Dex) in patients who had previously received at least one therapy for MM. These had identical designs but were conducted in different regions[9,10]. Updates to these studies are also briefly discussed.

6.1.1 Study MM009: USA and Canada (n=353)[9]
Study MM010: Europe, Israel and Australia (n=351)[10]

These were multinational, randomised, double-blind, placebo-controlled, phase III studies conducted in adult patients (aged $\geq$18 years) with progressive MM after at least one previous treatment, who had an Eastern Cooperative Oncology Group Performance Status (PS) of $\leq$2, and had measurable disease that was not resistant to Dex (defined as not experiencing progression on previous therapy that contained dexamethasone at a total monthly dose >200mg). In addition, patients were required to have liver enzymes < three times the upper limit of normal (ULN), serum bilirubin levels < two times ULN, serum creatinine levels <221micromol/L, an absolute neutrophil count ≥1000/mm^3, and a platelet count of >75,000/mm^3 in those with <50% bone marrow plasma cells and >30,000/mm^3 for those with $\geq$50% bone marrow plasma cells. Women of childbearing potential were eligible if they agreed to use contraception, had a negative pregnancy test

before enrolment, and agreed to undergo monthly pregnancy testing until 4 weeks after the discontinuation of the study drug.

Patients were randomised (1:1) to 25mg of daily oral lenalidomide or placebo on days 1–21 of each 28-day cycle. All patients also received 40mg of daily oral dexamethasone on days 1–4, 9–2, and 17–20. After the fourth cycle, 40mg of dexamethasone was administered only on days 1–4. Patients were stratified according to the baseline serum β_2-microglobulin level (<2.5 mg/L or ≥2.5 mg/L), previous SCT (none or ≥1), and the number of previous antimyeloma regimens (1 or ≥2). In MM009 at baseline, 70.8% of patients had serum β_2-microglobulin level ≥2.5 mg/L, 61.8% had previously received two or more antimyeloma therapies, and 61.5% had previously had SCT. In MM010, the figures were 71.8%, 67.8% and 54.7%, respectively.

Treatment was to be continued until the occurrence of disease progression or unacceptable toxic effects. The primary endpoint was time to progression (TTP) in the intention-to-treat population (defined in Panel 1A, Appendix 1). Patients who died before there was evidence of disease progression were censored at the time of their last assessment for TTP. Prospectively-defined secondary endpoints included overall survival (OS), partial response (PR), complete response (CR), near complete remission (nCR) and overall response rate (ORR) (defined in Panel 1A, Appendix 1).

An interim safety and efficacy analysis was planned when disease had progressed in 111 patients. If the predetermined criteria for the superiority of lenalidomide over placebo were met, the study would be unblinded and patients would be allowed to receive lenalidomide at the time of disease progression or at the investigator's discretion.

Primary and secondary endpoint results:
At the interim analysis, the boundary for the superiority of Len/Dex over Dex was crossed and the study was unblinded. The results in Table 1 and Table 2 relate to the time point at which the study was unblinded (MM009: median follow up 17.6 months; MM010: median follow up 16.4 months).

TTP, the primary endpoint, was statistically significantly improved with Len/Dex compared with Dex at the time of unblinding of the study. The secondary endpoints CR, nCR and PR also significantly favoured Len/Dex. There was no survival advantage with Len/Dex at this time point in study MM010, but there was in study MM009, and in pooled one-year data from both studies[4]. In addition, the published study reports indicate statistically significant improvements in median OS for Len/Dex compared with Dex, at median follow up periods of 17.1 months in MM009 and 16.5 months in MM010[2,9,10].

Table 1. Primary and secondary endpoint data at point of unblinding (excl. OS) of MM009 and MM010[2,4,9,10]

	MM009		**MM010**		**Pooled data**	
	Len/Dex n=177	Dex n=176	Len/Dex n=176	Dex n=175	Len/Dex n=353	Dex n=351
Primary endpoint						
TTP (median weeks)[4]	48.1 wks	20.1 wks	48.7 wks	20.1 wks	48.3 wks	20.1 wks
	p<0.001		p<0.001		HR 0.35 (95%CI 0.29 to 0.43) p<0.001	
Secondary endpoints[9,10]						
ORR (%)	61.0%	19.9%	60.2%	24.0%	60.6%	21.9%
					HR 0.18 (95%CI 0.13 to 0.25) p<0.001	
CR (%)	14.1%	0.6%	15.9%	3.4%	15.0%	2.0%
					HR 0.12 (95%CI 0.05 to 0.26) p<0.001	
nCR (%)	10.2%	1.1%	8.5%	1.7%	-	-
PR (%)	36.7%	18.2%	35.8%	18.9%	-	-
Overall survival						
% surviving at point of unblinding[4]	79.1%	64.8%	73.3%	66.3%	76.2%	65.5%
	"significant"		"not significant"		-	
Median OS (months)[2]	29.6 mths	20.2 mths	Not reached	20.6 mths	-	-
	HR 0.44 (95%CI 0.30 to 0.65) p<0.001 Median follow up 17.1 mths		HR 0.66 (95%CI 0.45 to 0.96) p=0.03 Median follow up 16.5 mths			
% surviving at one year[4]	-	-	-	-	82%	75%
	-		-		HR 0.75 (95%CI 0.59 to 0.95) p=0.015 Median follow up 22.6 mths	

Subgroup analyses:

Pre-specified subgroup analyses included baseline serum β_2-microglobulin level (<2.5 mg/L or ≥2.5 mg/L), the number of prior antimyeloma treatments received and whether or not patients had previously undergone SCT. Results of these subgroup analyses, conducted at the point of unblinding of the studies, are presented in Table 2.

Table 2. Prespecified subgroup analyses in MM009 and MM010[9,10]

	MM009		MM010	
	Len/Dex n=177	Dex n=176	Len/Dex n=176	Dex n=175
ORR (%)				
β_2-microglobulin level <2.5 mg/L	39/52 (75.0%)	14/51 (27.5%)	36/51 (70.6%)	18/48 (37.5%)
β_2-microglobulin level ≥2.5 mg/L	69/125 (55.2%)	21/125 (16.8%)	70/125 (56.0%)	24/127 (18.9%)
1 previous therapy	44/68 (64.7%)	15/67 (22.4%)	37/56 (66.1%)	17/57 (29.8)
≥2 previous therapies	64/109 (58.7%)	20/109 (18.3%)	69/120 (57.5%)	25/118 (21.2%)
Previous SCT	72/109 (66.1%)	21/108 (19.4%)	60/97 (61.9%)	27/95 (28.4%)
No previous SCT	36/68 (52.9%)	14/68 (20.6%)	46/79 (58.2%)	15/80 (18.8%)
Median TTP (months)				
1 previous therapy	Not reached	5.1 mths	Not reached	4.7 mths
≥2 previous therapies	10.2 mths	4.6 mths	11.1 mths	4.7 mths
P<0.001 for all comparisons of Len/Dex versus Dex				

In all subgroup analyses, Len/Dex was statistically significantly superior to Dex ($p<0.001$). However, in patients with baseline serum β_2-microglobulin level ≥2.5 mg/L, those who had previously received two or more antimyeloma therapies, and those who had not previously had SCT, the magnitude of the ORR was generally reduced compared with the those who had a baseline serum β_2-microglobulin level <2.5 mg/L, those who had previously received only one antimyeloma therapy, and those who had previously received SCT.

In study MM009, 43.7% of patients had previously received thalidomide treatment, and 11.1% had previously received bortezomib. In study MM010, the figures were 34.7% and 4.3%, respectively. Subgroup analyses (see Table 1A in Appendix 1) suggest that the ORR was significantly higher and the median TTP was significantly longer for patients who received Len/Dex compared with Dex, whether or not their prior therapies included thalidomide, but the magnitude of the ORR and the TTP was greater in those who had not previously received thalidomide. In study MM009, previous bortezomib therapy had little influence on ORR. However, such *post hoc* analyses should be interpreted with caution.

Points to note:

- There were some slight differences in the previous treatments received by patients recruited in MM009 (US patients) and those recruited in MM010 (included European patients). More patients had received SCT in MM009 than in MM010 (60.6% versus 55.0%) and fewer had received two or more antimyeloma therapies (61.8% versus 67.8%), including melphalan (32.0% versus 54.1%). However, more patients in MM009 had previously received thalidomide (43.6% versus 34.2%) and bortezomib (11.0% versus 4.3%). In addition, more patients in MM009 had a baseline performance status of 0 or 1 than in MM010 (92.1% versus 83.8%)[4].
- These studies were initiated when the clinical use of bortezomib was less well established. The use of bortezomib was low in these studies, and they therefore provide little information on the use of lenalidomide in patients who have previous exposure to bortezomib. Patients were not selected for these studies on the basis of their suitability for bortezomib treatment.
- When the studies were unblinded, 23.8% of the combined Len/Dex groups and 34.5% of the Dex groups had died. Median OS had therefore not been reached.
- Of the 351 patients who were randomised to Dex in these studies, 170 elected to receive additional lenalidomide at the point of unblinding whilst remaining assigned to the Dex group for analyses[4]. Despite this, significant survival advantages have been found for Len/Dex over Dex in subsequent analyses. However, the timing of those subsequent analyses would influence the extent to which a switch to Len/Dex could influence the outcome.

6.1.2 Extended follow up and pooled analyses of MM009 and MM010

Further analyses of pooled data have been presented at conferences, which re-iterate that response, median TTP and OS is significantly improved in patients receiving Len/Dex versus Dex, and that prior therapy influences the magnitude of these outcomes[11,12]. These are only available in abstract form.

Over a median follow up of 16.8 months[2] median TTP in patients who had received one prior antimyeloma treatment was 15.5 months in the Len/Dex group and 4.65 months in the Dex group ($p<0.001$). In patients who had received two or more prior treatments, median TTP was 10.2 months versus 4.7 months ($p<0.001$). The authors therefore conclude that outcomes are more favourable when Len/Dex treatment is initiated at first relapse rather than as a later salvage treatment[11].

Updated combined data, representing a median follow up of 32.1 months for MM009 and 28.7 months for MM010, has been used to estimate that median OS was 35 months with Len/Dex and 31 months with Dex ($p<0.05$). In patients who had received two or more prior treatments, the median OS was 32.4 months versus 27.3 months ($p<0.05$), but in those who had received only one prior treatment, median OS had not yet been reached in those receiving Len/Dex[12].

6.2 Safety:

The available pooled safety data from studies MM009 and MM010 relate to 353 patients treated with Len/Dex over a median of 44.0 weeks and 351 patients treated with Dex over a median of 23.1 weeks.

The adverse events that were reported to be significantly more frequent with Len/Dex than Dex were mainly haematological and thromboembolic in nature. These included anaemia, neutropenia and thrombocytopenia, deep vein thrombosis (DVT) and pulmonary embolism (PE). Thromboembolic events were found to be associated with the following risk factors: concomitant erythropoietin treatment (EPO), past medical history of thrombosis, older age and lower baseline plasma cell count. Cardiac adverse events were also more frequently reported with Len/Dex, particularly atrial fibrillation; however, of the 69 Len/Dex-treated patients experiencing cardiac adverse events, 56 were found to have had either an underlying conditions or were taking concomitant medications (i.e., beta blocker, calcium channel blocker, anti-arrhythmic, etc.). Other adverse events occurring at a significantly greater frequency in the Len/Dex group included constipation, pneumonia, hypokalaemia, tremor, and rash[4].

In general, the majority of adverse events were Grade 1 or 2, but Grade 3 or 4 adverse events that occurred more frequently in the Len/Dex groups included neutropenia (35.4% versus 3.4%), anaemia (10.8% versus 6.0%), thrombocytopenia (13.0% versus 6.3%), pneumonia (9.1% versus 5.4%) and hypokalaemia (5.7% versus 1.4%). At least one serious adverse event occurred in 57.2% and 46.6% of the Len/Dex and the Dex groups, respectively. DVT (7.1% versus 3.1%), PE (3.7% versus 0.9%), and atrial fibrillation (3.1% versus 0.6%) were among these. Of the 107 deaths in patients receiving Len/Dex, 24 (22.4%) were suspected to be drug related, compared with 24/142 (16.9%) in the Dex group[4].

Discontinuations due to adverse effects occurred more frequently in the Len/Dex group (24.9%) than the Dex group (18.0%). The main contributor was haematological adverse events (6.5% versus 2.9%)[4]. At the point of unblinding of studies MM009 and MM0010, dose reductions had been necessary in around 76% of patients treated with Len/Dex and 57% of patients treated with Dex, primarily due to neutropenia and thrombocytopenia[9,10]. Granulocyte colony-stimulating factor was to be administered only if grade 3 or 4 myelosuppression occurred in isolation of other adverse events. Around 28% of Len/Dex patients had received this (no data reported for the Dex group)[9,10].

In terms of peripheral neuropathies, which are noted adverse effects of bortezomib[13] and thalidomide[1], there were few cases with Len/Dex and Dex in studies MM009 and MM010, and their incidence was comparable[4]. The company submission acknowledges that this finding requires further confirmation[2].

As lenalidomide is a structural analogue of thalidomide, which is a well known teratogenic agent, a pregnancy prevention programme is in place (see 9.1).

As lenalidomide is primarily excreted by the kidneys, dose reduction is required in patients with renal impairment[1].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

Dex was considered a suitable comparator for use in the trials by the regulatory authorities and its use in patients who have relapsed is within its licensed indications[2]. The company submission acknowledges that other agents and combinations of agents are used in the treatment of MM, but considers that these are not superior to high-dose Dex in terms of disease control or tolerability[2].

Bortezomib was licensed in 2004 on the basis of trials that demonstrated its superiority over high-dose Dex in terms of TTP and OS[14]. It has recently been recommended by NICE as an option for the treatment of progressive MM in people who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, SCT[8]. However, bortezomib was not considered cost effective when used to treat patients who had received two or more prior therapies[8]. Thalidomide is acknowledged as an option (unlicensed at the time of writing) in relapsed patients in the 2005 BCSH guidelines[3] and in the recent NICE guidance on bortezomib[8]. However, WMP has sought Welsh expert opinion which confirms that, in the patients who have relapsed on prior therapy and are unsuitable for bortezomib, or have relapsed on bortezomib, high-dose Dex would be an appropriate treatment[15].

7.2 Comparative effectiveness issues:

The company states it has limited the submission to AWMSG to two specific subgroups: (i) patients who have received only one prior therapy and are unsuitable for treatment with bortezomib, and (ii) patients who have received at least two prior therapies[2].

Data specific to the first sub group is limited. Studies MM009 and MM010 were initiated when the clinical use of bortezomib was less well established. Prior bortezomib exposure was low in these studies, patients were not selected for participation on the basis of their suitability for bortezomib treatment, and no efficacy or safety data is presented specifically in patients who are classed by the company as being unsuitable for bortezomib. The only reference to which patients are classed as unsuitable for bortezomib is in the budget impact section, i.e. those with pre-existing neuropathy. There were reportedly few cases of peripheral neuropathy in studies MM009 and MM010, and no excess noted compared with Dex. However, these data are not derived in a population specifically with pre-existing neuropathy. The Summary of Product Characteristics for lenalidomide states that, at this time, the neurotoxic potential of lenalidomide associated with long-term use cannot be ruled out[1].

In terms of the second subgroup, around two-thirds of patients in studies MM009 and MM010 had previously received two or more prior therapies. Pre-specified analyses indicate that the magnitude of response and median TTP was reduced in patients who had previously received two or more prior therapies compared with patients who had received one prior therapy. These studies provide little data on the use of lenalidomide in patients who have previous exposure to bortezomib, which the company submission notes is an important consideration given the potential uptake of bortezomib following the recent NICE guidance[2]. In addition, thalidomide has been increasingly used at earlier stages of the disease in clinical practice[3] and has recently been granted a positive opinion following a license application to the EMEA for its use as a first line treatment (in

combination with other agents)[6]. *Post hoc* analyses of data from MM009 and MM010 suggest that the magnitude of the response to lenalidomide was lower in those who had previously received thalidomide. Although this finding requires confirmation, the extent to which the lenalidomide response observed in these trials (in which thalidomide was used by 43.6% of patients in MM009 and 34.2% in MM010) will be realised in clinical environments, where thalidomide may be used increasingly more frequently, is uncertain.

Bortezomib is administered as an intravenous bolus injection and an oral alternative such as lenalidomide would potentially offer several advantages. The company submission states that lenalidomide was developed from thalidomide with the aim of achieving an improved tolerability profile. However, there are no direct comparative efficacy or safety data for lenalidomide with bortezomib or thalidomide at any stage of the disease. Haematological adverse effects, such as neutropenia and thrombocytopenia, are common with lenalidomide treatment, as they are with bortezomib, thalidomide and other antimyeloma agents. Regular haematological monitoring is therefore required. There was also an increased incidence of serious thromboembolic adverse events (DVT and PE) in patients taking Len/Dex compared with Dex in studies MM009 and MM010, as has been seen in studies of thalidomide[6]. The Summary of Product Characteristics for lenalidomide states that prophylactic antithrombotic medicines, such as low molecular weight heparins or warfarin, should be recommended, especially in patients with additional thrombotic risk factors[1]. As lenalidomide is a structural analogue of thalidomide, a potential for teratogenic effects cannot be ruled out. A risk minimisation programme is in place (see 9.1). Only a small proportion of MM patients who would be eligible for lenalidomide treatment are likely to be of child bearing potential (the company submission estimates this to be 1.7%[2]).

There are no quality of life data specific to lenalidomide presented in the company submission.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for AWMSG to consider

The key economic issues for AWMSG to consider are whether any additional benefits offered by the use of lenalidomide justify any associated increase in costs over relevant comparators and whether the total budgetary impact of supporting the use of lenalidomide is acceptable. The company state they have limited the submission to AWMSG to two specific subgroups[2]:

(i) patients who have received only one prior therapy and are unsuitable for treatment with bortezomib, and
(ii) patients who have received at least two prior therapies.

8.2 Review of published evidence on cost-effectiveness

Standard searches conducted by WMP have not identified any other published economic studies of the use of lenalidomide in patients with MM.

8.3 Review of the company's submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company submission describes a cost-utility analysis of Len/Dex compared with Dex[2]. Discrete event simulation modelling using combined patient-level data from the key phase III studies of lenalidomide (MM009 and MM010) has been used to simulate a cohort of 1000 patients. Two subgroups of patients are considered, as in 8.1.

There are some uncertainties in the assumptions used in the model. Patient data was pooled together irrespective of the treatment received in the trial to create a single starting population, which was broken down into categories based on the best response achieved (CR, PR, stable disease [SD] and progressive disease [PD]). This implies that, within each best response category, the course of future events is unrelated to the treatment they received. Instead, the different distributions of the four response categories in the Len/Dex and the Dex arms of the studies are assumed to influence the overall survival achieved with each treatment. The OS of patients who received Dex has been adjusted using data from other studies and trials conducted several years ago. It is unclear how representative these other populations are of the patients and treatment being modelled currently. There are no quality of life data available specific to lenalidomide treatment, and the utility values assumed in the model are derived from a study conducted in a different MM patient group.

8.3.2 Population

Pooled patient level data from studies MM009 and MM010 have been used in the simulation. Patients represented in the model are likely to adequately represent those in Wales, but there were some slight differences in the previous treatments received by patients in the two studies (see section 6.1.1).

The studies were conducted in patients who had received one or more prior treatments. No data is provided in relation to patients who are considered unsuitable for bortezomib and the model implicitly assumes that those who had received only one prior therapy in the studies are representative of patients in practice who are unsuitable for bortezomib (e.g. those at increased risk of neuropathies).

The majority of patients (around two-thirds) had received two or more prior treatments, although the prior use of bortezomib (and possibly thalidomide) was lower in the trials than may be likely in current clinical practice. This is an important consideration, as *post hoc* analyses indicate that the magnitude of response to lenalidomide may be influenced by prior thalidomide use (see section 7.2) and there is little data on which to judge the influence of prior bortezomib use.

8.3.3 Perspective and time horizon

The model considers costs from the perspective of NHS Wales. No consideration is given to any personal and social service costs/resources, which could be substantial for these patients. Although a two-year time horizon is used in the base case analysis, a lifetime time horizon is more appropriate, as lenalidomide improves patients' survival.

8.3.4 Comparator

Dex is used as the comparator in the model. This was considered an appropriate comparator by the regulatory authorities for use in the clinical trials, and Welsh expert

opinion sought by WMP confirms that it would be an appropriate treatment in the two subgroups of patients considered in the economic model (see section 7.1).

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

Pooled patient data from studies MM009 and MM010 have been re-analysed to provide the proportion of patients attaining best response categories of CR, PR, SD and PD in the subgroup that had received only one prior therapy and the subgroup that had received two or more prior therapies. Patient data were pooled together irrespective of the treatment received in the trial to create a single starting population. This implies that, within each best response category, the treatment the patients received has no effect beyond that best response (i.e. the course of future events is unrelated to the treatment they received). Instead, the different distributions of the four response categories in the Len/Dex and the Dex arms of the studies are assumed to influence the overall survival achieved with each treatment[2].

Non-evaluable patients were excluded in the re-analysed data, which in each best response category leads to a small change in the proportion of patients achieving a given response that appears to favour Len/Dex more than Dex (e.g. in the data from patients who had previously received two or more therapies, when non-evaluable patient data are included a partial response is achieved in 45.0% of the Len/Dex group and 18.1% of the Dex group. When non-evaluable patient data are excluded, the partial responses change to 49.0% and 19.5%, respectively)[2]. Non-evaluable patient data are included in a sensitivity analysis.

Prediction of median OS in the model is composed of separate risk equations for TTP from initiation of treatment and time to death from the point of progression. It is broken down in this way as, at the time of unblinding of the studies, median OS had not been reached (see 6.1.1) and almost half of the Dex recipients crossed over to Len/Dex treatment. OS for the model has therefore been constructed using additional data from other sources, as data derived from the Dex arm of the MM009 and MM010 studies may be influenced by the patients who were actually receiving Len/Dex.

For the Len/Dex arm, a post progression survival equation has been derived using data from studies MM009 and MM010 from December 2005 (after the point of unblinding). The predicted survival curve for the Len/Dex group based on this survival equation has then been compared against actual MM-009/010 survival data which became available January 2007. This is reported to demonstrate a good fit[2].

For the Dex arm, the predication equation for post progression survival in patients who had received only one prior therapy in MM009 and MM010 has been adapted using data from Medical Research Council (MRC) myeloma trials that were initiated between 1980 and 1997[2,16]. These MRC trial data have been analysed to determine the factors that influence survival in patients who received various treatment regimens after failing one prior therapy. Patients in the MRC trials received a range of chemotherapy regimens and only 9% received dexamethasone-containing regimens[2]. On the basis that the survival curves obtained in this 9% of patients were not significantly different from the survival curves of patients receiving non-dexamethasone regimens, the data from all patients in the MRC trials who had received any treatment regimen having previously failed on one

prior therapy have then been used to modify the survival equation for Dex derived from studies MM009 and MM010.

The extent to which these MRC trial-derived data sufficiently eliminate the influence of Len/Dex from the Dex survival curves from studies MM009 and MM010 is uncertain. It is not stated if or what proportion received dexamethasone alone in the MRC trials and, although prior therapy was not found to influence survival upon relapse and response to second line therapy in these trials, they were initiated one-three decades ago when treatments such as thalidomide and bortezomib were not available for use as they are in current clinical practice.

For patients who had received two or more prior therapies, the Dex prediction equation derived above using MRC data has been further adapted using patient data collected between 1985 and 1998 in a prospective database study conducted at the Mayo Clinic, Rochester[17]. The company submission states that these Mayo Clinic data suggest the median OS for patients who received two prior therapies is 23.3% lower than that for patients who received one prior therapy. This relative reduction in OS has then been applied to the median OS data for the one prior therapy group obtained via the MRC myeloma trial data, to produce a post progression survival equation for patients who had received two prior therapies. There are further uncertainties in this approach, which build upon the uncertainties of the application of MRC data. The median age of patients at diagnosis appears older in the Mayo clinic cohort than in the MM009 and MM010 study patients, which could influence their prognosis, and it is not clear how many patients received Dex as a third line treatment. In addition, the pattern of use of first and second line treatments one-two decades ago is likely to be different to that in current practice.

8.3.5.2 Adverse events

Adverse event data is taken from studies MM009 and MM010. Only grade 3 and 4 adverse events are included on the basis that these are the most relevant in terms of resource use and health outcomes. The adverse events included are: anaemia, thrombocytopenia, neutropenia, hypercalcaemia, diarrhoea, constipation, pneumonia, peripheral neuropathy and DVT. Grade 3-4 hypokalaemia and PE as a serious adverse event both occurred more frequently in the Len/Dex group than the Dex group but have not been included in the model. Rates of adverse events were calculated in each successive three-month period, rather than over the entire study period. These were then converted into three-month probabilities of events. These calculations and conversions are referenced to data on file and so cannot be verified. These data are used only for costing purposes, as disutility associated with adverse events is not explicitly incorporated[2].

8.3.5.3 Utility weights

No specific utility data for lenalidomide treatment has been presented in the company submission. Utility weights have been assumed from a published study that evaluated the efficacy of intensive chemotherapy with or without subsequent myeloablative therapy with autologous stem cell rescue in newly diagnosed MM patients[18]. From this study, it has been assumed that an EQ-5D derived utility value for patients who respond to treatment would be 0.81, which is based on the age-matched general public utility value that was assumed in the published study for the intensive chemotherapy group. For patients who do not respond, a utility value of 0.64 is assumed. In the published study

from which these values are derived, a utility value of 0.77 at 24 months is also presented for those who respond to treatment with intensive chemotherapy[18], but this has not been used in the base case model.

In the base case analysis, the utility value of 0.64 has been applied to the patients with PD, and 0.81 for CR, PR and SD. No utility decrements for adverse events or complications are incorporated into the model[2]. It is uncertain how representative these utility values are of patients in the MM009 and MM010 studies. The assumption that SD has the same utility as PR and CR would appear to be favourable to Dex, as fewer patients on Dex achieved PR and CR. However, the adverse events that are considered in the model generally occurred at a greater frequency in patients receiving Len/Dex than Dex, so the lack of consideration of the disutility associated with these in the model favours Len/Dex.

8.3.6 Healthcare resource utilisation and cost

NHS resource use estimates associated with the treatment of relapsed MM have been obtained by the company by using a structured questionnaire administered to two Welsh specialists. Resource use for three states was collected: patients during relapse and/or on treatment, patients in remission/plateau on maintenance treatment, and patients in remission/plateau off treatment. The number and type of disease monitoring tests, and resource use involved in the treatment of disease-specific complications and treatment-related adverse events (including inpatient / day case / outpatient setting, etc.) were included, and the profiles that were generated were applied to patients depending on their status over time.

The mean values of the number of each type of resource use reported by the specialists were calculated. These were then costed using published unit cost data (NHS reference costs) and the BNF. Unit costs for inpatient and day case treatment for MM disease-related complications and treatment-related adverse events were calculated as the average Health Related Group costs for those complications or events that occurred in patients who had an index admission of MM recorded between January 2000 and June 2006 in UK Trusts. Outpatient costs were taken from NHS reference costs. It was assumed that the costs of treatments/interventions administered during inpatient or day case hospitalisation would be included in the hospitalisation cost. Those that were assumed to be administered in the community or following hospital discharge were considered separately.

Lenalidomide drug costs assumed in the model reflect the actual usage in the trial, rather than the planned usage. Doses, dose interruptions and dose reductions in each cycle of treatment were calculated from the trial data for each patient. The weighted mean average of the breakdown across all cycles was calculated using the total number of days on treatment in each cycle. The resulting average times spent on different lenalidomide doses or no treatment was then used to cost the lenalidomide treatment using BNF listed costs. The average cost per cycle without treatment interruptions or dose reductions was then compared with the average cost per cycle with treatment interruption and dose reductions. The relative reduction in cost per cycle was then applied to the overall lenalidomide drug use cost in the model. Dose reductions and interruptions for Dex were not considered in the model due to the low cost of Dex and shorter treatment duration[2].

8.3.7 Discounting

All costs and outcomes were discounted at 3.5% in the base case analysis, which is the preferred discount rate[2].

8.3.8 Results

8.3.8.1 Base case analysis: patients who had received only one prior treatment

The model predicts an incremental cost per QALY gained for Len/Dex over Dex of £28,943. This is based on a 2-year horizon of analysis, selected by the company for the base-case. The more appropriate lifetime horizon of analysis results in an incremental cost of £34,770 per QALY gained (or £32,898 excluding disease monitoring and complication costs after 2 years).

8.3.8.2 Base case analysis: patients who had received at least two prior treatments

The model predicts an incremental cost per QALY for Len/Dex over Dex of £28,184. This is based on a 2-year time horizon of analysis; a lifetime horizon of analysis results in an incremental cost effectiveness ratio of £30,871 per QALY gained (or £29,310 excluding disease monitoring and complication costs after 2 years).

8.3.9 Sensitivity analysis

8.3.9.1 One-way sensitivity analyses

Several one-way sensitivity analyses were performed to assess the impact of the model parameter estimates. Of the parameters explored (excluding discount values), the model was most sensitive to the time horizon (5 years, 10 years), adjustment of the median OS for Dex recipients using the MRC myeloma trial data ($\pm$1 month change to the MRC trial derived OS used to calibrate the Dex survival curve), and the utility values assumed ($\pm$10%). Within the values explored for these parameters, the incremental cost per QALY remained within the range £26,311 to £34,770 for those patients who had received only one prior therapy, and within the range £25,622 to £31,316 for those patients who had received at least two prior therapies.

8.3.9.2 Probabilistic sensitivity analysis (PSA)

Cost-effectiveness acceptability curves have been generated by sampling the TTP and post progression survival equations, utility scores and management cost parameters of the model. The model was run 10 times for each new set of input values and the average values of the outcomes were collected from 10 replications. This represents one scenario, and 1,000 scenarios were run. Appropriate distributions appear to have been assumed for sampling purposes.

In patients who had received only one prior therapy, the PSA estimated the mean incremental cost per QALY to be £31,926 (95%CI £21,675 to £45,987). The probability of Len/Dex being cost-effective at a willingness to pay (WTP) threshold of £20,000 is <2.5%, and at a WTP of £30,000, it is around 40%.

In the patients who had received two or more prior therapies, the PSA estimated the mean incremental cost per QALY to be £30,699 (95%CI £21,901 to £42,900). The probability of Len/Dex being cost-effective at a WTP of £20,000 is <2.5%, and at a WTP of £30,000, it is around 50%.

8.4 Review of evidence on budget impact:

8.4.1 Description and critique of the company's submission

The company's submission considers the budget impact of the use of lenalidomide in two subgroups of the licensed indication[2]:

(i) patients who have received only one prior therapy and are unsuitable for treatment with bortezomib, and
(ii) patients who have received at least two prior therapies.

As patients remain on lenalidomide only as long as disease progression (or death), the impact analysis is based on an estimate of the current number of patients eligible for treatment and the annual number of patients expected to become eligible for treatment. There are several assumptions and data sources used in the estimation of patients numbers, which introduce a degree of uncertainty. The company submission states that the current number of patients being treated for MM is unknown[2].

8.4.2 Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon.

8.4.3 Data sources

8.4.3.1 Incident cases

The company submission estimates that there will be 54 patients who become eligible for treatment with lenalidomide each year (7 in the first subgroup and 47 in the second subgroup).

This is based on data obtained from a global database of cancer incidences, which indicates that in 2002 there 4033 cases of MM (ICD-10 definition C 90) in the UK[19]. These incident cases have been scaled down to the Welsh population by assuming the same incidence rates in Wales as in the UK as a whole. NHS Hospital Episodes Statistics data from 2005-6 has then been used to determine the approximate proportion of cases that are due to MM (ICD 90.0) (94.5%). It has then been assumed that 39% of cases of MM are relapsed cases (on the basis of Synovate Healthcare, Tandem Oncology Monitor data from 2005 – not verifiable). The proportions of patients recruited to studies MM009 and MM010 having received one prior therapy (35.23%) or at least two prior therapies (64.77%) are then assumed to be the same in the Welsh MM population. It is estimated that 28% of patients are unsuitable for bortezomib therapy due to having pre-existing peripheral neuropathy, which is based on adverse event rates observed with thalidomide/dexamethasone treatment in a placebo controlled study[20]. This is equivalent to 7 patients who have relapsed having had one prior therapy and are unsuitable for bortezomib treatment, and 47 patients who have had at least two prior therapies (but are suitable for bortezomib).

There are several areas of uncertainty in these assumptions, including that peripheral neuropathies are a more common side effect with thalidomide than with some other regimens. It is likely that thalidomide will increasingly be used as a first line treatment for MM (see section 7.2) and, it is uncertain what proportion of patients will be deemed ineligible for bortezomib in clinical practice.

8.4.3.2 Prevalent cases

The company submission estimates that there are 106 patients with MM who are eligible for treatment with lenalidomide (14 in the first subgroup and 92 in the second).

This is based on prevalence data obtained from the same database above, which indicates that in 2002 the 5-year prevalence was 7893 patients in the UK. The same assumptions as used in the estimation of the incident cases have been used, and the same uncertainties exist.

8.4.3.3 Rates of adoption

The company submission estimates that the uptake in the two subgroups will be equal, and that this will be 60% in the first year, rising by an absolute 10% each year to 100% in year 5.

8.4.3.4 Costs and resource use

The acquisition costs of lenalidomide have been assumed from the cost-effectiveness model. This estimated the mean average cost per cycle of lenalidomide to be £4,036, based on the proportions of patients who experienced dose reductions or interruptions in the two phase III trials MM009 and MM010. Lenalidomide is administered in combination with dexamethasone, but dexamethasone is not included in the cost estimate, as it is assumed that this would also be the alternative treatment (these costs would cancel out). No monitoring costs are included in the analysis, which is a limitation as the cost-effectiveness model predicts that mean monitoring costs per patient were £1,000 greater with Len/Dex than with Dex alone in both subgroups (although this is small relative to the impact of the drug acquisition costs).

The mean number of cycles of treatment received by patients in the first subgroup, as predicted by the cost-effectiveness model, is reported to have been 13.26. For the second subgroup, the predicted number of cycles of treatment is reported to have been 10.58.

8.4.4 Results

In estimating the cost impact, it is assumed that patients initiating treatment each year are divided evenly across the year, rather than all being treated for a whole year. The annual resource implication is calculated by multiplying the net number of patients initiating treatment by the average cost per cycle, and then by the respective average number of treatment cycles within the year. This depends on when during the year the patients initiate treatment. For those patients in whom the average number of treatment cycles extends beyond the end of the year, the remaining number of cycles is carried through to the next year. Additionally, a proportion of those patients who are not treated with lenalidomide in the current year are assumed to be treated with lenalidomide in the next year. The process is repeated until year 5. The net resource impact is calculated by summing all resources within each year. These estimates would seem to be based on several assumptions that are all subject to uncertainty.

Table 3. Net resource impact of lenalidomide over 5 years

	One prior therapy and are unsuitable for treatment with bortezomib			At least two prior therapies		
Year	**Net Number initiating treatment**	**Net resource implication (ex VAT)**	**Net resource implication (incl VAT)**	**Net Number initiating treatment**	**Net resource implication (ex VAT)**	**Net resource implication (incl VAT)**
1	13	£362,866	£426,368	84	£2,267,345	£2,664,130
2	7	£521,462	£612,718	47	£2,575,512	£3,026,227
3	9	£422,904	£496,912	56	£2,259,296	£2,654,673
4	10	£499,633	£587,069	66	£2,661,765	£3,127,574
5	11	£576,363	£677,226	75	£3,064,234	£3,600,475

8.4.5 Sensitivity analysis

No sensitivity analyses have been conducted.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- Celgene Ltd has agreed with the MHRA to implement a series of measures to minimise the risk of adverse events for patients taking lenalidomide, and in particular the risk of foetal exposure. Lenalidomide is contraindicated for use in pregnancy and in women of childbearing potential unless all of the conditions of the lenalidomide Pregnancy Prevention Programme are met. These stipulate that all women of childbearing potential must:
  -Receive counselling regarding the potential teratogenic effects of lenalidomide and the need to avoid pregnancy.
  -Use an effective method of contraception for four weeks before therapy, during therapy, during dose interruptions and four weeks after therapy has finished, unless the woman commits to absolute and continued abstinence confirmed on a monthly basis.
  -Have a medically supervised negative pregnancy test once she has been established on contraception for 4 weeks, at 4-weekly intervals during therapy and 4 weeks after the end of therapy.
  In addition, male patients with partners of childbearing potential must use barrier methods of contraception. Each prescription must be accompanied by a prescription authorisation form, which is signed by both the prescriber and the dispensing pharmacist. Pharmacies must be registered with Celgene before they can dispense the drug. All details are provided in a Health Care Professional Information pack[21].
- Lenalidomide would currently not be deemed suitable for a shared-care agreement. Treatment, monitoring, and supervision should be retained under specialist care.

9.2 Previous AWMSG/NICE advice:
Bortezomib (Velcade®) was appraised by AWMSG in June 2005 and was accepted for use in NHS Wales for the treatment of MM in patients who had received two prior treatments and had demonstrated disease progression[22]. NICE guidance on the use of bortezomib in MM was issued in August 2007[8] and supersedes the AWMSG guidance.

Lenalidomide, for use within its licensed indication, has been referred for single technology appraisal by NICE as part of the 15th work programme.

9.3 Related AWMSG/NICE advice and guidance:
National Institute for Health and Clinical Excellence. Bortezomib monotherapy for relapsed multiple myeloma. Technology Appraisal No. 129, October 2007. Accessed 24/01/08 from: http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf.

National Institute for Health and Clinical Excellence. Referral guidelines for suspected cancer. Clinical Guideline No. 27, June 2005. Accessed 24/01/08 from: http://www.nice.org.uk/nicemedia/pdf/word/cg027niceguideline.doc.

National Institute for Clinical Excellence. Improving outcomes in haematological cancers: the manual. Cancer Service Guidance, October 2003. Accessed 24/01/08 from: http://www.nice.org.uk/nicemedia/pdf/NICE_HAEMATOLOGICAL_CSG.pdf.

9.4 Ongoing studies
Follow-up of studies MM009 and MM010 is ongoing and further subgroup analyses are expected. A number of studies are exploring the use of lenalidomide in patients with newly diagnosed MM, but none are expected to report within the next 6–12 months[2].

9.5 Patient Interest Group Information
Two patient interest group submissions one by the Rarer Cancers Forum and one by Myeloma UK were provided to AWMSG members.

References

1. Summary of Product Characteristics. Revlimid®. Celgene UK & Ireland Ltd, December 2007. Accessed 22/01/08 from: http://emc.medicines.org.uk.
2. Form B: Detailed appraisal information: lenalidomide (Revlimid®). Celgene UK & Ireland Ltd, January 2008.
3. Smith A, Wisloff F, Samson D, et al. Guidelines on the diagnosis and management of multiple myeloma 2005. B J Haematol 2005;132:410–51. Accessed 24/01/08 from: http://www.bcshguidelines.com/pdf/multiplemyeloma0206.pdf.
4. Revlimid®. European Public Assessment Report, 2006. Accessed 22/01/08 from: http://www.emea.europa.eu/humandocs/Humans/EPAR/revlimid/revlimid.htm.
5. London Cancer New Drugs Group. Lenalidomide (Revlimid) for multiple myeloma. APC/DTC Briefing, February 2007.
6. EMEA news release. Committee for Medicinal Products for Human Use summary of positive opinion for Thalidomide Pharmion; 24th January 2008. Accessed 27/02/08 from: http://www.emea.europa.eu/pdfs/human/opinion/Thalidomide_2877308en.pdf.
7. Current Controlled Trials. MRC Myeloma IX; ISRCTN68454111. Accessed 27/02/08 from: http://www.controlled-trials.com/mrct/trial/234143/myeloma+IX.
8. National Institute for Health and Clinical Excellence. Bortezomib monotherapy for relapsed multiple myeloma. Technology Appraisal No. 129, October 2007. Accessed 24/01/08 from: http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf.
9. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007;357(21):2133–42.
10. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357(21):2123–32.
11. Stadtmauer E, Weber D, Dimopolous M, et al. Lenalidomide in combination with dexamethasone is more effective than dexamethasone at first relapse in relapsed multiple myeloma. Blood: ASH Annual Meeting Proceedings 2006;108 (11 Part 1 of 2):1014a, Abstract # 3552 and poster.
12. Weber D, Knight RD, Chen C, et al. Prolonged Overall Survival with Lenalidomide Plus Dexamethasone Compared with Dexamethasone Alone in Patients with Relapsed or Refractory Multiple Myeloma. Blood 2007;110:Abstract 412.
13. Summary of Product Characteristics. Velcade®. Janssen-Cilag Ltd, September 2007. Accessed 24/01/08 from: http://emc.medicines.org.uk.
14. Velcade®. European Public Assessment Report, 2004. Accessed 25/01/08 from: http://www.emea.europa.eu/humandocs/Humans/EPAR/velcade/velcade.htm.
15. Personal Communication. Welsh Haematology Pharmacist; February 2008.
16. Drayson MT, Augustson BM, Begum G, et al. Survival from relapse and the influence of therapy. Haematologica/The Hematology Journal: XIth International Myeloma Workshop Proceedings 2007;92(6, s2):173-, Abstract # PO-665.
17. Kumar SK, Therneau TM, Gertz MA, et al. Clinical course of patients with relapsed multiple myeloma. Mayo Clin Proc 2004 Jul;79(7):867–74.
18. van Agthoven M, Segeren CM, Buijt I, et al. A cost-utility analysis comparing intensive chemotherapy alone to intensive chemotherapy followed by myeloablative chemotherapy with autologous stem-cell rescue in newly

diagnosed patients with stage II/III multiple myeloma; a prospective randomised phase III study. Eur J Cancer 2004 May;40(8):1159–69.

19. International Agency for Research on Cancer. Globocan 2002. International Agency for Research on Cancer 2002. Available from: http://www-dep.iarc.fr/

20. Fermand JP, Jaccard A, Macro M, et al. A randomized comparison of dexamethasone + thalidomide (dex/thal) vs dex + placebo (dex/P) in patients (pts) with relapsing multiple myeloma (MM). Blood 2006;108(11 (Part 1 of 2)):1017a-8a, Abstract # 3563.
21. Celgene Ltd. Revlimid®▼ (lenalidomide) Healthcare Professional Information Pack for UK. Accessed 27/02/08 from: http://www.nelm.nhs.uk/Record%20Viewing/viewRecord.aspx?id=582161.
22. AWMSG. Bortezomib (Velcade®). Appraisal programme 2005. Accessed 27/02/08 from: http://www.wales.nhs.uk/sites3/Documents/371/AWMSG%20Appraisal%20work%20programme%20updated%2012th%20February%202008.pdf.

Appendix 1. Additional Clinical Information

Panel 1A. Definitions of endpoints and response in studies MM009 and MM010[9,10]

The primary endpoint was time to progression (TTP) in the intention-to-treat population, with progression defined as any of:

- an increase of at least 25% in serum monoclonal protein (M protein) from nadir;
- an absolute increase of more than 500 mg of M protein per deciliter, as compared with the nadir value;
- an absolute increase of more than 200 mg of urinary M protein in 24 hours;
- a new bone lesion or plasmacytoma, or an increase in the size of such lesions;
- development of hypercalcaemia (serum calcium level >11.5 mg per deciliter [2.9 mmol/L]).

Prospectively-defined secondary endpoints included overall survival (OS), and response to therapy defined as:

- Partial response (PR) - reduction of M protein by $\geq$ 50% in serum, 90% in urine, or both, as confirmed by at least two electrophoretic measurements.
- Complete response (CR) - complete disappearance of M protein in serum and urine by immunofixation, as confirmed by two measurements, and the presence of < 5% marrow plasma cells
- Near complete remission (nCR) - identical to CR but without confirmation of marrow plasmacytosis of < 5% or the disappearance of M protein.
- Overall response rate (ORR) - PR + CR + nCR rates

Table 1A. Post hoc analyses by previous thalidomide and bortezomib treatment in studies MM009 and MM010[9,10]

	MM009		**MM010**	
	Len/Dex n=177	Dex n=176	Len/Dex n=176	Dex n=175
ORR (%)				
Prior thalidomide	42/74 (56.8%)	10/80 (12.5%)	26/53 (49.1%)	11/67 (16.4%)
No prior thalidomide	66/103 (64.1%)	25/96 (26.0%)	80/123 (65.0%)	31/108 (28.7%)
Prior bortezomib	13/19 (68.4%)	2/20 (10.0%)	-	-
No prior bortezomib	95/158 (60.1%)	33/156 (21.2%)	-	-
Median TTP (months)				
Prior thalidomide	8.5 mths	4.1 mths	8.4 mths	4.6 mths
No prior thalidomide	14.2 mths	4.7 mths	13.5 mths	4.7 mths
Prior bortezomib	10.3 mths	3.3 mths	-	-
No prior bortezomib	-	-	-	-
$P \leq 0.002$ for all comparisons of Len/Dex versus Dex				