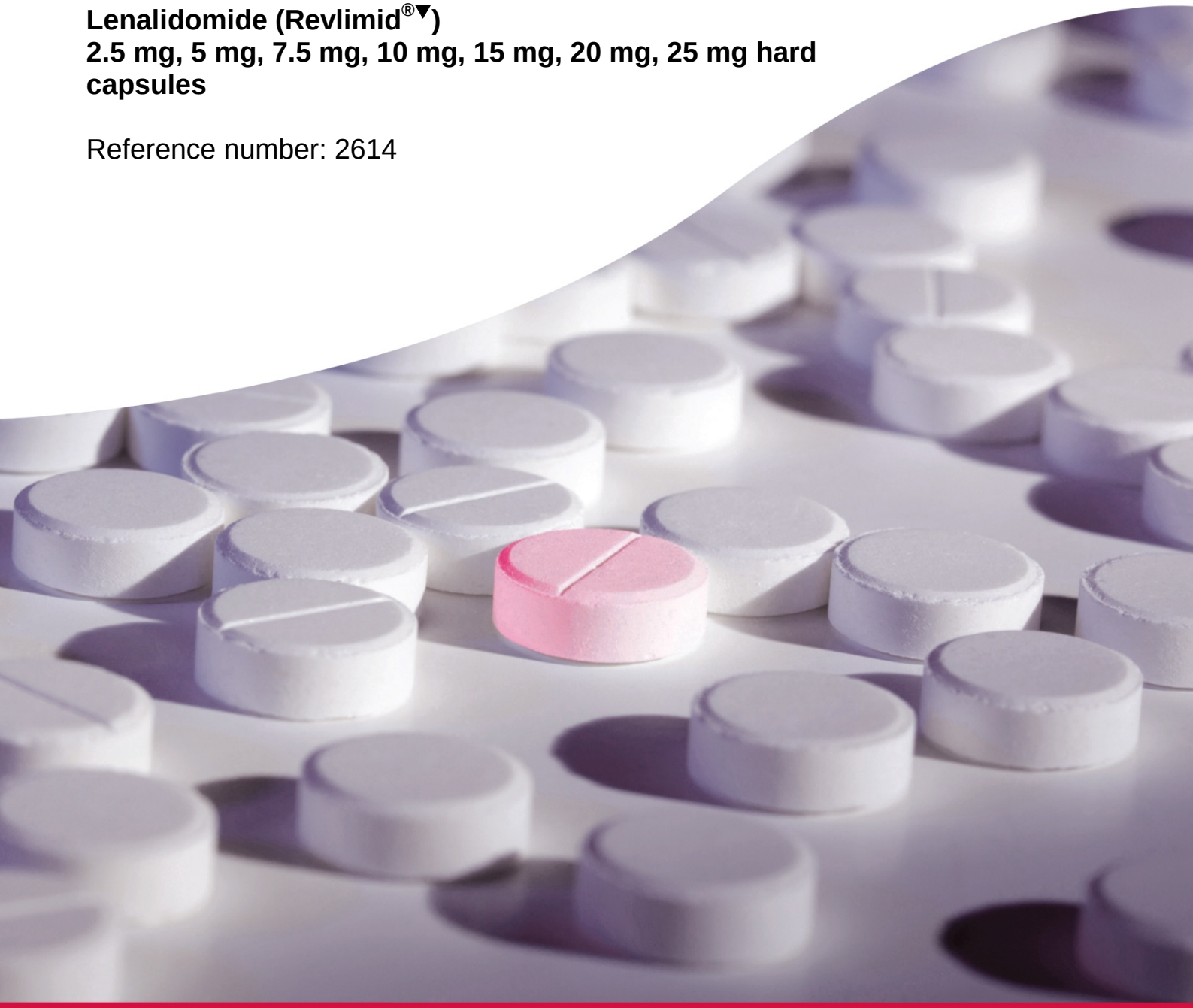
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Lenalidomide (Revlimid®▼)
2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg hard capsules

Reference number: 2614



This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics and Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Lenalidomide (Revlimid®▼) 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg. Reference number: 2614. June 2016.

AWMSG Secretariat Assessment Report
Lenalidomide (Revlimid®▼) 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 25 mg hard capsules

This assessment report is based on evidence submitted by Celgene Ltd[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Lenalidomide (Revlimid®▼) for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. Refer to the summary of product characteristics (SPC) for the full licensed indication[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, 8, 15 and 22 of repeated 28–day cycles. Dosing is continued or modified based on clinical and laboratory findings. Treatment may continue until disease progression or intolerance. Refer to the SPC for further information about dose adjustments[2].
Marketing authorisation date	19 February 2015[1] (first licensed on 14 June 2007 for the treatment of multiple myeloma, in combination with dexamethasone, in patients who have received at least one prior therapy)[3].

2.0 DECISION CONTEXT

2.1 Background

It has been acknowledged that the complications of myeloma and its treatment cause an increasing long-term strain on supportive and palliative care services, and on carers[4]. The median age at manifestation of multiple myeloma is around 70 years[5]. There is no cure and relapse occurs in almost all cases[6]. In 2013 there were 285 new cases diagnosed in Wales[7]. Figures for England and Wales show a one-year survival rate of approximately 77% for adults. The survival rate decreases over time, with five-year and ten-year survival reported to be approximately 47% and 33%, respectively[8].

Treatment options after diagnosis will depend on a person's age, health and their ability to undergo high-dose chemotherapy with autologous stem cell transplantation[5]. For people in whom high-dose chemotherapy and stem cell transplantation(SCT) would not be appropriate, the National Institute for Health and Care Excellence (NICE) guideline on the diagnosis and management of myeloma recommends treatment with thalidomide in combination with an alkylating agent and a corticosteroid given for 12 cycles[9,4]. If thalidomide is not tolerated or is contraindicated, NICE recommends treatment with bortezomib in combination with an alkylating agent and a corticosteroid (for nine treatment cycles)[4,9].

The applicant company has requested that lenalidomide (Revlimid®▼) is considered for use in treating newly diagnosed multiple myeloma in adults who are not eligible for transplant and for whom thalidomide is contraindicated or not tolerated[1]. A Wales Patient Access Scheme (WPAS) has been submitted which provides a further discount

to NHS Wales. The company suggests lenalidomide is cost effective in this sub-group of the licensed population where there exists an unmet need for an additional treatment option.

Lenalidomide is a structural derivative of thalidomide[10]. Its mechanism of action includes anti-neoplastic, anti-angiogenic, pro-erythrocytic and immunomodulatory properties, including inhibiting the proliferation of multiple myeloma plasma tumour cells[2]. It was granted orphan designation by the European Commission in 2003 for the treatment of multiple myeloma[11].

2.2 Comparators

The comparators included in the company's submission were*:*

- thalidomide (Thalidomide Celgene®) plus an alkylating agent plus a corticosteroid
- bortezomib (Velcade®) plus an alkylating agent plus a corticosteroid[1].

2.3 Guidance and related advice

- NICE guideline NG35 (2016) Myeloma: diagnosis and management[4]
- NICE pathway (2016) Myeloma[12]
- British Society for Haematology (2014) Guidelines for the diagnosis and management of multiple myeloma 2014[13]
- European Society for Medical Oncology (2013) Multiple myeloma. ESMO clinical practice guidelines for diagnosis, treatment and follow-up[14]
- NICE technology appraisal guidance TA228 (2011) Bortezomib and thalidomide for the first-line treatment of multiple myeloma[15]
- NICE technology appraisal guidance TA171 (2009) Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy[10]

The All Wales Medicines Strategy Group has previously issued a recommendation for use of subcutaneous bortezomib in combination with melphalan and prednisone for treating adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant[16].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

Key efficacy data are reported from the pivotal MM-020 study and from the MM-015 study included in the company's submission, which investigate the use of lenalidomide combinations as continuous therapy and as fixed-cycle therapy as first-line treatment in transplant-ineligible patients with newly diagnosed multiple myeloma. Because no studies have been conducted to directly compare lenalidomide with bortezomib in the treatment of multiple myeloma, the results of a network meta-analysis (NMA) conducted by the company are included in Section 3.3[1].

3.1 Study MM-020

Study MM-020 is an ongoing, open-label, three-group, randomised study conducted at 246 centres worldwide including in the UK, investigating the safety and efficacy of standard doses of lenalidomide plus dexamethasone given until disease progression or for a fixed number of cycles (72 weeks; 18 cycles), in comparison with a regimen of melphalan plus prednisone plus thalidomide (MPT; 72 weeks; 12 cycles), to treat newly diagnosed multiple myeloma in people who were not eligible for stem cell transplantation[17]. A total of 1,623 adults with newly diagnosed multiple myeloma and an Eastern Cooperative Oncology Group (ECOG) status of 0–2, were randomly assigned in a 1:1:1 ratio[17].

For a patient to be included in the study they had to be at least 65 years of age or older or, if younger than 65 years of age, they were not a candidate for SCT because they refused SCT therapy or the subject did not have access to SCT.

At baseline, 35% of patients were aged over 75 years, 40.6% had International Staging System disease stage III, 9.1% had severe renal insufficiency (creatinine clearance < 30 mL/min), 71.2% had a history of bone disease and 13.5% had received radiation for multiple myeloma[1].

The primary endpoint was progression-free survival with continuous lenalidomide plus dexamethasone compared with MPT and was based on median follow up of 37 months[17]. Results demonstrate that continuous lenalidomide and low-dose dexamethasone delivered superior progression-free survival (25.5 versus 21.2 months; hazard ratio [HR] = 0.72; $p < 0.001$) compared with MPT given for 72 weeks. Secondary endpoints included overall survival and health-related quality of life[17]. Interim overall survival data were also reported.

A second analysis at a median of 45.5 months follow-up was conducted which included further overall survival data and post hoc progression-free survival; this second cut-off analysis is based on investigator assessment[5]. Final data for overall survival from the study are not yet available[1].

Results of the second interim analysis which were used in the economic evaluation (see section 4.0) are presented in Table 1. Data showed a statistically significant improvement in progression-free survival for lenalidomide plus dexamethasone continuously-treated patients compared with patients receiving MPT for 72 weeks[5]. There was a 31% reduction in the risk of progressive disease or death in patients receiving continuous lenalidomide plus dexamethasone compared with those receiving MPT[5].

Table 1 Study MM-020 efficacy results at the second data cut-off point (March 2014)[5].

	Rd (n=535)	Rd18 (n=541)	MPT (n=547)
Post hoc analysis of progression-free survival			
Median PFS time (months)	26.0	21.0	21.9
(95% CI)	(20.7-29.7)	(19.7-22.4)	(19.8-23.9)
Comparison	**Rd versus MPT**	**Rd versus Rd18**	**Rd18 versus MPT**
Hazard ratio (95% CI)	0.69 (0.59–0.80)	0.71 (0.61–0.83)	0.99 (0.86–1.14)
p value	< 0.001	< 0.001	0.866
Overall survival			
Median overall survival	58.9	56.7	48.5
(95% CI)	(56.0-NE)	(50.1-NE)	(44.2-52.0)
Comparison	**Rd versus MPT**	**Rd versus Rd18**	**Rd18 versus MPT**
Hazard ratio (95% CI)	0.75 (0.62-0.90)	0.91 (0.75-1.09)	0.83 (0.69-0.99)
p value	0.002	0.305	0.034

CI: confidence interval; MPT: melphalan plus prednisone plus thalidomide; NE: not estimable; PFS: progression-free survival; Rd: lenalidomide plus dexamethasone until disease progression; Rd18: lenalidomide plus dexamethasone for 18 cycles

Patient-reported outcome measures for health-related quality of life were collected for a maximum of 18 months or until progressive disease using three questionnaires: European Organisation for Research and Treatment of Cancer (EORTC) quality of life – Multiple Myeloma 20; EORTC quality of life – Core 30; and European Quality of Life (EQ-5D)[18]. Both lenalidomide regimens showed statistical superiority to MPT in the side effects of treatment domain, with no evidence of inferiority to MPT in any of the pre-selected health-related quality-of-life domains[18].

3.2 Study MM-015

Study MM-015 was a multicentre, randomised, double-blind, placebo-controlled study of lenalidomide induction and maintenance treatment of newly diagnosed multiple myeloma in people who were not eligible for transplantation[19]. A total of 459 adults (≥ 65 years) were randomised 1:1:1 to receive nine cycles of standard doses of either: lenalidomide plus melphalan plus prednisone followed by lenalidomide maintenance; or lenalidomide plus melphalan plus prednisone, or melphalan plus prednisone plus placebo, followed by placebo maintenance[19].

The primary endpoint was progression-free survival. After a median duration of follow-up of 30 months, lenalidomide induction treatment followed by lenalidomide maintenance significantly prolonged progression-free survival (median 31 months), compared with lenalidomide induction treatment and placebo maintenance (median 14 months; hazard ratio 0.49; $p < 0.001$) or melphalan plus prednisone induction treatment and placebo maintenance (median 13 months; hazard ratio 0.40; $p < 0.001$)[19].

The landmark analysis compared lenalidomide maintenance with placebo maintenance from cycle 10 onwards. Analysis showed that the median progression-free survival was significantly longer for patients receiving maintenance therapy with lenalidomide (median 26 months) compared with patients receiving placebo (median 7 months; hazard ratio 0.34; $p < 0.001$)[19].

3.3 Network meta-analysis

Evidence indirectly comparing lenalidomide with bortezomib is provided using a network meta-analysis (NMA), and included all identified studies for overall survival and progression-free survival using fixed-effects models within a Bayesian modelling framework[1].

For overall survival, lenalidomide was associated with a statistically significant lower risk of death compared with melphalan plus prednisone, MPT, and bortezomib plus melphalan plus prednisone (BMP)[1]. For progression-free survival, lenalidomide showed a statistically significant lower risk of death compared with melphalan plus prednisone, and MPT. The comparison with BMP demonstrated a lower risk of death, although this was not statistically significant[1].

3.4 Comparative safety

In the MM-020 study, as of May 2013, the proportions of patients with more than one adverse event leading to discontinuation of the entire regimen were: 13.1% in the thalidomide treatment arm, 15.6% in the arm receiving lenalidomide for 18 cycles, and 18.0% in the arm receiving lenalidomide until disease progression[5]. Cataract was reported more frequently in patients treated with lenalidomide, increasing with treatment beyond 18 months[17], and occurred in more than twice as many patients who continued lenalidomide until disease progression than in those who received fixed cycles[5]. Grade 3 and 4 events in the lenalidomide treatment groups occurred less frequently than in the MPT group (85% and 80% compared with 89%, respectively)[1]. Both lenalidomide treatment groups had lower rates of haematological adverse events, haematological secondary primary cancers and peripheral neuropathy than the MPT group[1,18]. Grade 3–4 infection was reported more frequently in patients who received lenalidomide until disease progression (28.9%) than patients treated with lenalidomide for 18 cycles (21.9%) or those in the thalidomide group (17.2%). An exploratory analysis of trends in adverse events during up to 2 years of treatment showed no increase in incidence of adverse events during months 18–24[1].

In study MM-015 the most frequent adverse events were haematological and occurred during induction, most often in the lenalidomide group. During the maintenance phase the incidence of new or worsened Grade 3–4 adverse events was low[19]. There was an increased risk of invasive secondary primary malignancies reported with the lenalidomide regimens (see section 3.5)[1]. The addition of lenalidomide to the melphalan plus prednisone induction regimen resulted in reduced tolerability of the triple regimen in patients aged over 75 years, which led to a higher frequency of dose reductions and a higher frequency of treatment discontinuations because of adverse events. Only one-third of patients aged over 75 completed induction and started lenalidomide maintenance treatment, compared with two-thirds of patients under 75[1].

The summary of product characteristics (SPC) for lenalidomide states that in people with multiple myeloma, the combination of lenalidomide with dexamethasone may be associated with an increased risk of thromboembolic events, predominantly deep vein thrombosis, pulmonary embolism, myocardial infarction and cerebrovascular event[2]. A higher rate of infections is observed with lenalidomide in combination with dexamethasone than with the melphalan plus prednisone plus thalidomide combination[2]. Lenalidomide is structurally related to thalidomide, and is also expected to have teratogenic effects. The SPC provides details of the pregnancy protection programme which must be fulfilled for all patients of childbearing potential[2].

The SPC for bortezomib states that treatment is commonly associated with sensory peripheral neuropathy and with haematological toxicities, including thrombocytopenia, neutropenia and anaemia[20].

3.5 AWTTC critique

- The company has provided direct evidence comparing continuous lenalidomide with a regimen of MPT. Results of study MM-020 support the use of continuous lenalidomide therapy given until disease progression and there are statistically significant and clinically meaningful changes in health-related quality of life[18].
- As MPT was given for a fixed duration of 72 weeks, quality of life data were only collected for this period to enable a direct comparison between continuous lenalidomide therapy and MPT.
- Patients in this pivotal study were not limited to the sub-population of interest[17] as all patients were eligible for thalidomide treatment.
- The MM-020 study population included 92 subjects (5.7%) who were <65 years and not necessarily ineligible for SCT i.e. patients may have refused to undergo such therapy or did not have access to it. The number of patients in this category was balanced between treatment arms and had no clinically meaningful differences in demographic and disease-related characteristics.
- Company-sought expert opinion considered the patient cohort in study MM-020 reflected typical clinical practice, and included a large proportion of elderly patients and a reasonable percentage of patients with severe renal insufficiency[1]. Differences that they highlighted were that MPT may often be used for shorter periods than 72 weeks.
- Study MM-015 also supports the use of continuous lenalidomide compared to a fixed-cycle therapy as first-line treatment in transplant-ineligible patients with newly diagnosed multiple myeloma. Participants in this trial received a dose of lenalidomide of 10 mg/day; it should be noted this is lower than the recommended starting dose of 25 mg[2,19].
- In the context of the patient group specified in the submission, a more appropriate comparator would be bortezomib. No head-to-head studies were however available; the provision of indirect evidence using a NMA by the company is therefore welcome. Results showed longer progression-free survival with lenalidomide plus dexamethasone compared with BMP; however, this was not statistically significant[1]. Heterogeneity between the studies included for example, age of patients and duration of follow-up, and may have reduced the reliability of comparison between treatments.
- Lenalidomide has a different mechanism of action and toxicity profile to thalidomide and bortezomib which allows for its continuous use. Lenalidomide may be administered until disease progression, unlike bortezomib and thalidomide, and therefore it could be a treatment option that may extend the period until first relapse [1].
- Lenalidomide is administered orally and can be self-administered by patients at home, whereas bortezomib is administered intravenously, or subcutaneously, by a healthcare professional in a hospital setting[1].
- Both studies (MM-020 and MM-015) plus a separate meta-analysis of pooled data from 3,254 patients showed that the increased risk of developing haematological secondary primary malignancies was mainly driven by co-exposure to lenalidomide and melphalan; the incidence of death due to myeloma or treatment-associated adverse events was however substantially higher than that due to secondary primary malignancies[1].

4.0 SUMMARY OF THE EVIDENCE ON COST EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost-utility analysis comparing the combination of lenalidomide plus low dose dexamethasone, with a combination regimen of melphalan plus prednisone plus thalidomide (MPT), in transplant-ineligible patients with newly diagnosed multiple myeloma[1]. The analysis further compares lenalidomide plus dexamethasone with a combination regimen of bortezomib plus melphalan plus prednisone (BMP) in a subgroup of transplant-ineligible patients for whom thalidomide is not tolerated or is contraindicated. These comparators are consistent with NICE's technology appraisal 228 for first-line treatments[15].

The cost-utility analysis is a cohort Markov model, which adopts an NHS Wales and Personal Social Services perspective, comprising 28–day cycles and a lifetime time horizon (38.33 years). Costs and outcomes are discounted at 3.5%. The submission incorporates a complex Wales Patient Access Scheme discount: when lenalidomide is administered as first-line therapy, treatment after the first 26 cycles of use is provided free of charge. The model is characterised by three health states: progression-free survival, post-progression, and death. Patients may transition to death from any health state. The efficacy data used to inform the transition probabilities are derived from extrapolating data from the MM-020 study (which compared lenalidomide plus dexamethasone with MPT), the VISTA study (the pivotal study for BMP) and from the NMA[21,22]. Progression-free patients on treatment may transition to progression-free off-treatment or post-progression. The post-progression state is also sub-divided in order to calculate the costs of second- and third-line treatment.

Treatment pathways for post-progression were based on the expert opinion of three haematologists in Wales, given that these data were not complete in the MM-020 and VISTA studies[21,22]. These sub-divisions further allow time between subsequent treatments to be included within the model. Time between first and second treatments was taken from the MM-020 study for lenalidomide plus dexamethasone, and MPT, and from NICE's technology appraisal TA228 for bortezomib given with melphalan and prednisone[15,21]. Unlike the lenalidomide plus dexamethasone and the MPT regimens, times to second-line progression and third-line therapy for the BMP regimen are based on assumptions rather than study data. Accordingly, the base case assumes equivalence to lenalidomide plus dexamethasone; equivalence to MPT is tested in the sensitivity analyses. Fatal progression rates were obtained from the MM-020 study for first-line fatal progression, and the MM-009 and MM-010 studies for second-line fatal progression[23,24]. Rates for the BMP regimen were assumed to be the same as those for MPT.

Observed data were fitted to a variety of common parametric distributions, and goodness-of-fit statistical tests were conducted. Even though the Weibull distribution did not have the best fit for progression-free survival or overall survival according to statistical tests, the company selected it for the extrapolation of lenalidomide plus dexamethasone, and MPT. This selection was based on the rationale that it offers a more conservative approach for lenalidomide plus dexamethasone in terms of progression-free survival, and is more reflective of long-term outcomes in clinical practice. The progression-free survival curve for BMP was not fitted with individual patient data. Instead, it was estimated by applying a hazard ratio of BMP against MPT from the NMA to the fitted progression-free survival curve of the MPT arm (hazard ratio 0.98). The company has taken this approach because BMP has not been directly compared with lenalidomide plus dexamethasone or MPT. The company claims this is reasonable because BMP and MPT are fixed-duration treatments with similarly shaped progression-free survival curves.

The model also estimates the number of patients with treatment-related adverse events in each interval before progression. Only Grade 3 or 4 adverse events that occurred in more than 5% of patients in the phase III studies of the first-line treatments are considered in the model[21,22]. For lenalidomide plus dexamethasone, annual incidence rates (cases per patient-year) are derived over the four time periods considered (cycles 0–6, 7–12, 13–18 and > 18), to capture the likely decrease in the rate of adverse events over time. For BMP, the rates are derived by calculating the proportion of patients who experienced each adverse event as reported in the study publication; they are therefore constant over time[22].

The model included the costs of first-, second- and third-line cancer treatments, together with the prophylactics: aspirin, enoxaparin sodium and aciclovir. The base case uses dosing from the MM-020 study for lenalidomide plus dexamethasone and MPT. These data gave the number of patients on each dosage at every cycle within each treatment, which was combined with the medicine acquisition costs to give a cost per cycle for each patient. For BMP, dosing is guided by the VISTA study; maximum dosing is assumed[22]. The company suggests this should not bias treatment costs because the model assumes no vial sharing and accounts for premature treatment discontinuation. Acquisition costs are sourced from Monthly Index of Medical Specialities (MIMS)[25]. Delivery costs of intravenous cancer treatments and the costs associated with each adverse event experienced during treatment are derived from NHS reference costs[26]. To simplify the model, adverse event costs associated with each treatment were not included in post-progression cost estimations.

Mean costs associated with routine laboratory tests and monitoring, and the number of assessments per year for each first-line treatment were obtained from a questionnaire completed by physicians in the UK (including Wales) in 2015. Unit costs for each routine laboratory test were obtained from NHS reference costs[26]. Resource use for first-line and subsequent therapies were calculated after physician interviews conducted by the company[1]. Platelet and red blood cell transfusions are accounted for separately within the model using data from the MM-020 study for lenalidomide plus dexamethasone and MPT[21]. For BMP, rates for red blood cell transfusions were taken from the NICE technology appraisal TA228 assessment report[15] and for platelet transfusion, the base case assumes equivalence to lenalidomide plus dexamethasone.

Health outcomes are accrued in both the progression-free and post-progression states, using treatment and state-specific utility weights. The EQ-5D utilities for the progression-free state are taken from the MM-020 study for lenalidomide plus dexamethasone and MPT. For BMP, these are mapped from the EORTC QLQ-C30 scores reported in the VISTA study[8] using a validated algorithm[27]. The utility value for the post-progression state is estimated to be 0.59, which is the average EQ-5D value measured at the treatment discontinuation visit for all patients who had experienced disease progression during the follow-up period of the MM-020 study. It is assumed to stay constant over the rest of model time horizon. Age-related utility decrements are included in the model[28]; the impact of removing these is tested in the sensitivity analyses. Utility decrements for adverse events are not explicitly modelled, to avoid double counting.

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results for both the wider population base case and the sub-population base case. The parameters tested, among others, included: overall survival – Gompertz extrapolation; time horizon; hazard ratios for progression-free survival and overall survival; and time to treatment failure using Kaplan–Meier data.

4.1.2 Results

The results of the base cases are detailed in Tables 2 and 3 for the wider population and sub-population, respectively. The submission comprises the whole licensed population; however, a cost-effectiveness case cannot be made against MPT because of its low acquisition cost; the incremental cost-effectiveness ratio (ICER) generated is in excess of £80,000. Instead, the evaluation of interest is the comparison with BMP in the identified subgroup of transplant-ineligible patients for whom thalidomide is not tolerated or is contraindicated, which yields an ICER of £17,961. When compared with BMP, lenalidomide plus dexamethasone delays progression, increases overall survival, and generates more quality-adjusted life years (QALYs). Given these findings, all further considerations will specifically focus on this smaller patient population.

Table 2. Results of the wider population analysis (with Wales Patient Access Scheme [WPAS])

	Rd	MPT	Difference
Total costs	£111,326	£43,185	**£68,141**
Total life-years	6.31	5.01	**1.31**
Total QALYs	3.61	2.79	**0.81**
ICER (£/QALY gained)	**£83,635**		

ICER: incremental cost-effectiveness ratio; MPT: melphalan plus prednisone plus thalidomide; QALY: quality-adjusted life year; Rd: lenalidomide plus low-dose dexamethasone; WPAS: Wales patient access scheme

Table 3. Results of the sub-group analysis (with WPAS)

	Rd	BMP	Difference
Total costs	£111,390	£92,706	**£18,685**
Total life-years	6.31	4.50	**1.82**
Total QALYs	3.61	2.57	**1.04**
ICER (£/QALY gained)	**£17,961**		

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; Rd: lenalidomide plus low-dose dexamethasone; BMP: bortezomib plus melphalan plus prednisone; WPAS: Wales patient access scheme

The results of the univariate sensitivity analysis show that the ICER for the sub-group is most sensitive to the Weibull intercepts associated with progression-free survival and overall survival for lenalidomide plus dexamethasone, the hazard ratio for overall survival of BMP, and the time horizon used. For each of these, except the progression-free survival Weibull intercept for lenalidomide plus dexamethasone, variations in parameter estimates produce ICERs exceeding the usual accepted thresholds. These are explored further in terms of plausibility in the scenarios in Table 4 which details the scenarios that generated the most pronounced ICERs.

Probabilistic sensitivity analyses reveal that at a willingness-to-pay threshold of £20,000 and £30,000 per QALY gained, lenalidomide plus dexamethasone has a 39.5% and 57.9% chance, respectively, of being the most cost-effective treatment.

Table 4. Results of the scenario analyses for the sub-group

Scenarios	ICER	Plausibility
OS curve extrapolation – substituting the Weibull with the Gompertz distribution	**£22,301**	The AIC and BIC tests suggest this distribution is a better fit to the study data than the Weibull. However, the company suggests that Weibull is a better fit for longer-term outcomes.
Time horizon of 5 years	**£36,135**	This alternative time horizon is unlikely to capture all the costs and effects associated with this patient group. Time horizons of 10, 15, and 20 years generate ICERs of £22,101, £19,822 and £18,771, respectively.
HR for OS of BMP reduced from 1.51 to 1.07	**£49,826**	This lower bound is guided by the NMA conducted by the company. It is uncertain whether this is more plausible than the base case HR.
OS Weibull intercept for Rd varied in line with upper and lower bounds	**£41,037–£104,939**	This scenario is unlikely to be a plausible alternative to the base case, given that it effectively assumes all patients will be alive for the entire time horizon.
AIC: Akaike information criteria; BIC: Bayesian information criteria; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; NMA: network meta-analysis; OS: overall survival; Rd: lenalidomide plus low-dose dexamethasone; BMP: bortezomib plus melphalan plus prednisone		

4.1.3 AWTTC critique

The submission is characterised by both strengths and limitations:

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model.
- The inclusion of second- and third-line treatments aims to more closely replicate the experience of people with multiple myeloma treated in Wales.
- Extensive sensitivity and scenario analyses have been conducted.
- Numerous methods have been used to try to validate the model, including: extreme value analysis conducted by an internal programmer, and clinical expert validation in relation to the clinical plausibility (including choice of parametric curves, survival estimates, adverse events included and utility values, among other model characteristics).
- Extrapolation is inherently associated with uncertainty. However, the company have sought to address this uncertainty via a number of measures. Choice of distribution was guided by statistical tests, clinical expert opinion and the literature. To address the uncertainty associated with use of the Weibull distribution, sensitivity analysis explores the use of the distribution that provided the best statistical fit (the Gompertz distribution).
- The mapping of utilities for BMP represents good practice.

Limitations:

- The time horizon used by the company reflects the NICE reference case, but may possibly be considered excessive for this patient group given that the mean life years modelled are between five and seven years. However, the company has conducted a sensitivity analysis to explore how the ICER changes in response to a considerably shorter horizon.

- The probabilities for patients remaining in the progression-free survival state are based on investigator assessment of progression-free survival from the MM-020 study, instead of the Independent Response Adjudication Committee (IRAC) assessment, because the IRAC assessment lacked completeness in comparison due to differences in cut-off dates for assessment. This introduces some uncertainty surrounding these estimates. The use of data from NMA to populate the model introduces uncertainty surrounding efficacy estimates.
- The estimates for progression-free survival and overall survival for BMP calculated by the model appear to over-predict efficacy. This could possibly bias the relative effects of treatments in favour of BMP.
- Post-progression treatment distributions are based on expert opinion only and have not been validated against any real-world data.
- The assumptions applied for time to second-line progression and third-line therapy for BMP inevitably introduce uncertainty around these estimates.
- The use of a constant post-progression utility value may possibly oversimplify the model and introduce uncertainty surrounding relative utility decrements associated with progression.
- Resource use has been estimated by experts, and examination of individual estimates reveals some notable differences for some cases. As a result, there is some uncertainty surrounding these estimates. However, these are not the main cost drivers of the model.

4.2 Review of published evidence on cost effectiveness

A literature review conducted by All Wales Therapeutics and Toxicology Centre (AWTTC) identified a number of economic evaluations which include lenalidomide plus dexamethasone as one of the medicines of analysis; however, only one conference paper and one published paper focused on the sub-population of interest and the medicines compared in this submission[29,30]. Both of these have authors affiliated with the company and relate to the same clinical studies and network meta-analyses as this submission. The cost-utility analyses reported in these papers focus on the USA, and report incremental QALY gains associated with the use of lenalidomide plus dexamethasone of 1.47[30] and 0.91[29] These differ from the 1.4 QALY gain reported in the company's submission[1], as a result of: adopting different hazard ratios for OS of BMP and for PFS of lenalidomide plus dexamethasone vs BMP; and using slightly different post-progression utilities

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company has estimated that there will be 290 people newly diagnosed with multiple myeloma in 2016, based on the Office for National Statistics population and population growth data for Wales and Cancer Research UK incidence data[7,31]. The company assumes that 65% of these people will be ineligible for autologous stem cell transplantation (ASCT)[1]. Based on market research, the company further estimates that thalidomide will be contraindicated or not tolerated by approximately 30% of these people ineligible for transplantation. A market share of 20% in year 1, increasing to 32% in year 5 for lenalidomide plus dexamethasone is further applied to estimate the number of people in Wales likely to be prescribed lenalidomide for this indication. The costs used in the budget impact model have been taken from the cost-utility analysis model, and take into account changes to: the treatment pathway for first-, second- and third-line treatments; prophylaxis and adverse event costs; other resource use (which reflects associated laboratory tests and monitoring); and resource use post-progression[1].

Sensitivity analyses have been performed to assess the impact of changes to: the percentage of patients ineligible for ASCT; the percentage of patients who are intolerant of/contraindicated for thalidomide; and a combination of these two parameter changes.

5.1.2 Results

The budget impact analyses show an initial medicine cost saving in year 1, followed by increased medicine acquisition costs over the following four years, up to £190,883 in year 5 (see Table 5). Lenalidomide plus dexamethasone costs are spread over 26 cycles (approximately two years); BMP costs are spread over approximately 13 months. This results in a negative impact in year 1, and positive impacts in subsequent years (since only half of the lenalidomide plus dexamethasone costs per patient are accounted for in year 1, compared with nearly all per patient costs for BMP). For lenalidomide plus dexamethasone patients, approximately 50% of their remaining costs are applied in year 2, but then new patients are also added in year 2. When wider resource use is taken into account, the company estimates that introducing lenalidomide plus dexamethasone will result in an increased spend associated with this sub-population of £198,630 in year 5.

The sensitivity analyses conducted resulted in year 1 net savings of between £92,012 and £125,750, and year 5 net costs of between £207,797 and £283,990.

Table 5. Net budget impact for the thalidomide intolerant/contraindicated sub-group (including WPAS)

	Year 1 (2016)	Year 2 (2017)	Year 3 (2018)	Year 4 (2019)	Year 5 (2020)
Number of eligible patients (indication covered in this submission)	57	57	57	58	58
Uptake (%)	20%	22%	23%	29%	32%
Treated patients	11	13	13	17	19
Net costs					
Medication costs (including first-line, prophylaxis, second-line and third-line treatments)	**-£87,305**	**£178,420**	**£169,044**	**£134,099**	**£190,883**
Costs of treating adverse events	£2,144	£1,567	£976	£1,363	£1,479
Secondary and tertiary care	-£2,793	-£3,003	-£981	£1,895	£6,268
Overall net cost (including wider resource use)	**-£87,953**	**£176,984**	**£169,038**	**£137,357**	**£198,630**

5.1.3 AWTTC critique

- The model incorporates a number of assumptions to derive the patient population eligible for treatment. This introduces uncertainty surrounding the true budget impact.
- Given that all costs are derived from the economic model, any potential limitations of the economic model therefore apply to the budget impact estimates, including costs associated with the assumed distribution of second- and third-line treatments.
- The net financial costs of introducing lenalidomide in practice may not be equivalent to the opportunity costs calculated for the economic analysis. Therefore, it may be more appropriate to consider the net medicine costs when evaluating the budget impact in Wales.

5.2 Comparative unit costs

Table 6 provides examples of combination treatments used in patients who are ineligible for autologous stem cell transplantation. These costs differ slightly to those used in the cost-utility analysis model, because they are based on one dosing regimen only for each medicine, not a variety of dosing. Unit costs are based on list price.

Table 6. Examples of acquisition costs for medicines used in transplant-ineligible patients with newly diagnosed multiple myeloma for whom thalidomide is contraindicated or not tolerated

Regimens	Example doses	Approximate costs per patient (per cycle)
Lenalidomide (Revlimid®) plus dexamethasone	For a 28-day cycle: LEN: 25 mg once daily on days 1–21 DEX: 40 mg once daily on days 1,8,15,22	£4,407
Bortezomib (Velcade®) plus melphalan plus prednisone	For a 6-week cycle: BOR: 1.3 mg/m^2 once daily on 8 days in cycles 1–4 and once daily on 4 days in cycles 5–9. MEL: 9 mg/m^2 daily on days 1–4 PRE: 60 mg/m^2 daily on days 1–4.	£7,497 (cycles 1–4) £3,447 (cycles 5–9)
Thalidomide plus melphalan plus prednisone	For a 6–week cycle: THA: 100 mg or 200 mg once daily for 42 days MEL: 0.1–0.25 mg/kg daily on days 1–4 PRE: 2 mg/kg daily on days 1–4	£1,071–£2,097

Calculations based on average body surface area per patient of 1.79 m^2 or an average weight per patient of 77.9 kg[32,33]
Costs are based on British National Formulary (lenalidomide, bortezomib, melphalan and dexamethasone) and MIMS (thalidomide and prednisone) list prices as of April 2016, assuming vial wastage[25,34].
Costs of administration are not included.
This table does not imply therapeutic equivalence of medicines or the stated doses.
BOR: bortezomib; DEX: dexamethasone; LEN: lenalidomide; MEL: melphalan; PRE: prednisone; THA: thalidomide

5.3 Other key considerations and sources

The applicant company suggests that lenalidomide fulfils the All Wales Medicines Strategy Group (AWMSG) criteria for consideration as an orphan medicine. The AWMSG process for appraising orphan, ultra-orphan and rare-disease medicines defines an orphan medicine as a medicine that has been granted EMA-designated

orphan status and is used to treat conditions affecting not more than 1,500 patients in Wales[35]. This definition applies to the full population of the licensed indication.

Lenalidomide was designated by the EMA's Committee for Orphan Medicinal Products as an orphan medicine for the treatment of multiple myeloma[36]. The incidence of multiple myeloma is reported by the company to be 290 patients in Wales. Of these, the company estimates that 189 patients would be ineligible for stem cell transplantation, which is the relevant licensed population, and the population relevant to the consideration of orphan status.

Lenalidomide is also licensed in combination with dexamethasone, for the treatment of multiple myeloma in adult patients who have received at least one prior therapy (approximately 187 people in Wales[7,10]) and for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate (approximately 4 people in Wales[35-37]). The cumulative number of patients with conditions for which lenalidomide is indicated is therefore estimated as 380[1].

AWTTC considers that lenalidomide may be eligible to be considered under the policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases as the full population of the licensed indication is likely to be less than the 5 in 10,000 persons (or 1,500 patients in Wales) threshold. Should the New Medicines Group (NMG)/AWMSG consider lenalidomide an orphan medicine, additional criteria for appraising the medicines will be considered if the medicine is considered as having a cost per QALY above normal thresholds[38] (see Table 7).

Table 7. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG

NMG/AWMSG Considerations	AWTTC Comments
The degree of severity of the disease as presently managed, in terms of survival and quality of life impacts on patients and their carers.	Myeloma is a chronic disease requiring long-term care. The disease is characterised by regression, remission and ultimately treatment failure. There is no cure and relapse occurs in almost all cases. The complications of myeloma and its treatment cause an increasing long-term strain on supportive and palliative care services and on carers.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	The company have requested that lenalidomide be considered for patients with multiple myeloma for whom transplant is not an option and for whom thalidomide is contraindicated or not tolerated. Bortezomib may also be a suitable medicine for this group of patients[20]. Like thalidomide, lenalidomide is an oral therapy, whilst bortezomib requires subcutaneous or intravenous administration in a hospital setting.
Whether the medicine can reverse or cure, rather than stabilise the condition	The applicant company do not claim that lenalidomide can reverse or cure this condition. Network meta-analysis of overall survival however showed that lenalidomide was associated with a statistically significantly lower risk of death compared to bortezomib and melphalan.
Whether the medicine may bridge a gap to a "definitive" therapy (e.g. gene therapy) and that this "definitive" therapy is currently in development	Not applicable.
The innovative nature of the medicine	The applicant company claims that lenalidomide has a different mechanism of action and toxicity profile than thalidomide and bortezomib, which allows continuous use to suppress residual disease and extension of the period of first relapse.
Added value to the patient which may not adequately be captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity)	Since lenalidomide is an oral therapy it can be self-administered by patients at home whilst intravenous bortezomib must be administered at hospital. Lenalidomide may be given until disease progression, unlike bortezomib and thalidomide, and therefore it could be a treatment option that may extend the period until first relapse.
Added value to the patient's family (e.g. impact on a carer or family life)	
AWMSG: All Wales Medicines Steering Group	

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, lenalidomide (Revlimid®▼) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

The company does not anticipate that lenalidomide (Revlimid®▼) will be supplied by a home healthcare provider.

6.2 Ongoing studies

The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search

Date of evidence search: 7 March 2016
Date range of evidence search: No date limits were applied to database searches.

REFERENCES

1. Celgene Ltd. Form B: Detailed appraisal submission. Lenalidomide (Revlimid®▼). Feb 2016.
2. Celgene Ltd. Revlimid®▼. Summary of Product Characteristics. Aug 2015. Available at: https://www.medicines.org.uk/emc/medicine/29490. Accessed Mar 2016.
3. European Medicines Agency. Revlimid: EPAR - procedural steps taken before authorisation. Jun 2007. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_before_authorisation/human/000717/WC500056023.pdf. Accessed Apr 2016.
4. National Institute for Health and Care Excellence. NICE guideline NG35. Myeloma: diagnosis and management. Feb 2016. Available at: https://www.nice.org.uk/guidance/ng35. Accessed Mar 2016.
5. European Medicines Agency. Assessment Report: Revlimid®▼. Procedure No. EMEA/H/C/000717/X/0073/G. Feb 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000717/WC500184943.pdf. Accessed Mar 2016.
6. Guglielmelli T, and Palumbo A. Multiple myeloma: is a shift toward continous therapy needed to move forward? *Expert Review of Hematology.* 2015;8(3):253-256. Available at: http://www.tandfonline.com/doi/full/10.1586/17474086.2015.1001360. Accessed Mar 2016.
7. Cancer Research UK. Myeloma incidence statistics. 2013. Myeloma incidence by sex and UK region. Apr 2016. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/incidence#heading-Zero. Accessed Apr 2016.
8. Cancer Research UK. Myeloma survival statistics. Myeloma 2010-2011. One-, five- and ten-year net survival (%), adults aged 15-99, England & Wales. Apr 2016. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma/survival#heading-Zero. Accessed Apr 2016.
9. Celgene Ltd. Thalidomide Celgene®. Summary of Product Characteristics. Dec 2015. Available at: https://www.medicines.org.uk/emc/medicine/21005. Accessed Apr 2016.
10. National Institute for Health and Care Excellence. Technology Appraisal TA171. Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. Jun 2009. Available at: https://www.nice.org.uk/guidance/ta171. Accessed Mar 2016.
11. European Medicines Agency. Public summary of opinion on orphan designation of 3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione for the treatment of multiple myeloma. Jun 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500005402.pdf. Accessed Apr 2016.
12. National Institute for Health and Care Excellence. Myeloma. 2016. Available at: http://pathways.nice.org.uk/pathways/myeloma. Accessed Mar 2016.
13. British Society for Haematology. Guidelines for the diagnosis and management of multiple myeloma 2014. 2014. Available at: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. Accessed Apr 2016.
14. European Society for Medical Onology. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2013. Available at: http://www.esmo.org/Guidelines/Haematological-Malignancies/Multiple-Myeloma. Accessed Apr 2016.

15. National Institute for Health and Care Excellence. Technology Appraisal TA228. Bortezomib and thalidomide for the first-line treatment of multiple myeloma. Jul 2011. Available at: https://www.nice.org.uk/guidance/ta228. Accessed Mar 2016.
16. All Wales Medicines Strategy Group. Bortezomib (Velcade®) 3.5 mg powder for solution for subcutaneous injection. Reference number: 1254. Appraisal information. Jan 2013. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1254. Accessed Mar 2016.
17. Benboubker L, Dimopoulos MA, Dispenzieri A et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *The New England Journal of Medicine.* 2014;371:906-917. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1402551. Accessed Mar 2016.
18. Delforge M, Minuk L, Eisenmann JC et al. Health-related quality-of-life in patients with newly-diagnosed multiple myeloma in the FIRST trial: lenalidomide plus low-dose dexamethasone versus melphalan, prednisone, thalidomide. *Haematologica.* 2015;100(6):826-833. Available at: http://www.haematologica.org/content/100/6/826.long. Accessed Mar 2016.
19. Palumbo A, Hajek R, Delforge M et al. Continuous lenalidomide treatment for newly diagnosed mutliple myeloma. *The New England Journal of Medicine.* 2012;366(19):1759-1769. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1112704. Accessed Apr 2016.
20. Janssen-Cilag Ltd. Velcade®. Summary of Product Characteristics. Jan 2016. Available at: https://www.medicines.org.uk/emc/medicine/17109. Accessed Apr 2016.
21. Celgene Ltd. Lenalidomide (REVLIMID®). A phase III, randomized, open-label, 3-arm study to determine the efficacy and safety of lenalidomide (REVLIMID®) plus low-dose dexamethasone when given until disease-progression or for 18 four-week cycles versus the combination of melphalan, prednisone and thalidomide given for 12 six-week cycles in patients with previously untreated multiple myeloma who are either 65 years of age or older or not candidates for stem cell transplantation (IFM 07-01). Clinical study report CC-5013-MM-020/IFM 07-01.
22. Mateos MV, Richardson PG, Schlag R et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *Journal of Clinical Oncology.* 2010;28(13):2259-2266. Available at: http://jco.ascopubs.org/content/28/13/2259.long. Accessed Apr 2016.
23. Weber DM, Chen C, Niesvizky R et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *The New England Journal of Medicine* 2007;357:2133-2142. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa070596#t=abstract. Accessed Apr 2016.
24. Dimopoulos M, Spencer A, Attal M et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *The New England Journal of Medicine* 2007;357:2123-2132. Available at: http://www.nejm.org/doi/full/10.1056/NEJMoa070594. Accessed Apr 2016.
25. Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Apr 2016. Available at: http://www.mims.co.uk/. Accessed Apr 2016.
26. Department of Health. NHS reference costs 2013 to 2014. Nov 2014. Available at: https://www.gov.uk/government/publications/nhs-reference-costs-2013-to-2014. Accessed Apr 2016.

27. Proskorovsky I, Lewis P, Williams CD et al. Mapping EORTC QLQ-C30 and QLQ-MY20 to EQ-5D in patients with multiple myeloma. *Health and Quality of Life Outcomes.* 2014;12(35). Available at: http://hqlo.biomedcentral.com/articles/10.1186/1477-7525-12-35. Accessed Apr 2016.
28. Ara R, and Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value in Health.* 2010;13(5):509-518. Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1524-4733.2010.00700.x/full. Accessed Apr 2016.
29. Cavenagh JD, Belch AR, Hulin C et al. Cost-effectiveness in newly diagnosed multiple myeloma (NDMM): Lenalidomide plus low-dose dexamethasone (rd) versus bortezomib plus melphalan and prednisone (VMP). Presented at 19th Congress of the European Haematology Association, Milan, Italy. 12-15 June 2014.
30. Usmani SZ, Cavenagh JD, Belch AR et al. Cost-effectiveness of lenalidomide plus dexamethasone vs bortezomib plus melphalan and prednisone in transplant-ineligible US patients with newly-diagnosed mutliple myeloma. *Journal of Medical Economics.* 2016;19(3):243-258. Available at: http://www.tandfonline.com/doi/abs/10.3111/13696998.2015.1115407?journalCode=ijme20. Accessed Apr 2016.
31. Office for National Statistics. Annual mid-year population estimates: 2014. Estimates of the usual resident population in the United Kingdom and its constituent countries. . Jun 2015. Available at: http://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/2015-06-25. Accessed Apr 2016.
32. Sacco JJ, Botten J, Macbeth F et al. The average body surface area of adult cancer patients in the UK: a multicentre retrospective study. *PLoS One.* 2010;5(1):e8933. Available at: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0008933. Accessed Apr 2016.
33. Moody A, and Health and Social Care Information Centre. Health Survey for England 2012. Chapter 10, Adult anthropometric measures, overwight and obesity. 2013. Available at: http://www.hscic.gov.uk/catalogue/PUB13218/HSE2012-Ch10-Adult-BMI.pdf. Accessed Apr 2016.
34. British Medical Association, and Royal Pharmaceutical Society of Great Britain. British National Formulary. Apr 2016. Available at: https://www.medicinescomplete.com/mc/bnf/current/. Accessed Apr 2016.
35. British Committee for Standards in Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. 2013. Available at: http://www.bcshguidelines.com/documents/BCSH_MDS_guidelines_final_Dec_2013.pdf. Accessed May 2016.
36. Giagounidis AAN, Germing U, Haase S et al. Lenalidomide: a brief review of its therapeutic potential in myelodysplastic syndromes. *Therapeutics and Clinical Risk Management.* 2007;3(4). Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2374932/.
37. Balducci L. Transfusion independence in patients with myelodysplastic syndromes: impact on outcomes and quality of life. *Cancer.* 2006;106(10). Available at: http://www.ncbi.nlm.nih.gov/pubmed?term=((Balducci%5BAuthor%5D)%20AND%20myelodysplastic%5BTitle%5D)%20AND%20(%222006%22%5BDate%20-%20Publication%5D%20%3A%20%223000%22%5BDate%20-%20Publication%5D).

38. All Wales Medicines Strategy Group. AWMSG orphan and ultra-orphan process. May 2015. Available at: http://www.awmsg.org/awmsgonline/grabber?resId=File%2F1770. Accessed Apr 2016.