Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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lenalidomide, 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg and 25mg capsules (Revlimid®) SMC No. (1096/15)

Celgene Europe Limited

06 November 2015

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission considered under the orphan process

lenalidomide (Revlimid®) is accepted for restricted use within NHS Scotland.

Indication under review: treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

SMC restriction: for use in patients unsuitable for thalidomide-containing regimens

Continuous lenalidomide plus low-dose dexamethasone, compared with melphalan, prednisolone plus thalidomide, significantly improved progression-free survival in treatment-naive patients with newly diagnosed multiple myeloma who were not eligible for transplant. Overall survival data are immature, but interim analyses suggest a survival benefit for lenalidomide plus low-dose dexamethasone compared with melphalan, prednisolone plus thalidomide.

This submission focuses on lenalidomide in combination with dexamethasone. Lenalidomide is also licensed for use in combination with melphalan and prednisolone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant. The submitting company did not provide evidence for SMC assessment therefore SMC cannot recommend this combination for use in this treatment setting.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Overleaf is the detailed advice on this product.

Vice-Chairman,
Scottish Medicines Consortium

Published 07 December 2015

Indication

Treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant.

Dosing Information*

Lenalidomide is given in combination with dexamethasone until disease progression in patients who are not eligible for transplant. The starting dose of lenalidomide is 25 mg orally once daily on days 1 to 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. For patients ≥75 years of age, the starting dose of dexamethasone is 20mg/day on days 1, 8, 15 and 22 of each 28-day cycle.

Patients may continue lenalidomide and dexamethasone therapy until disease progression or intolerance. Dosing is continued or modified based upon clinical and laboratory findings as described in the summary of product characteristics (SPC), which also notes dose modifications to manage toxicity.

Lenalidomide treatment should be supervised by a physician experienced in the use of anticancer therapies. Lenalidomide treatment must not be started if the absolute neutrophil count is $<1.0 \times 10^9$/L, and/or platelet counts are $<50 \times 10^9$/L.

*Lenalidomide is also licensed in the above indication in a regimen comprising lenalidomide 10 mg/day orally on days 1-21 of repeated 28-day cycles for up to 9 cycles, melphalan 0.18 mg/kg orally on days 1-4 of repeated 28 day cycles, prednisone 2 mg/kg orally on days 1-4 of repeated 28-day cycles. However, this submission focuses on lenalidomide in combination with dexamethasone.

Product availability date

19 February 2015

Lenalidomide meets SMC criteria for orphan status in this treatment setting

Summary of evidence on comparative efficacy

Lenalidomide is an immunosuppressant that inhibits proliferation of some haematopoietic tumour cells, including multiple myeloma (MM) plasma tumour cells and those with deletions of chromosome 5. It also enhances T cell- and natural killer cell-mediated immunity and increases the number of natural killer T-cells. It inhibits angiogenesis by blocking migration and adhesion of endothelial cells and formation of microvessels. It augments foetal haemoglobin production by CD34+ haematopoietic stem cells and inhibits production of pro-inflammatory cytokines (e.g. TNF-α and IL- 6) by monocytes.[1] It is the third medicine, after thalidomide and bortezomib, to be licensed for treatment of patients with newly diagnosed MM unsuitable for haematopoetic stem cell transplant (HSCT) and has been designated as an orphan medicinal product for MM.

The submitting company has requested that the Scottish Medicines Consortium (SMC) considers lenalidomide when positioned for use in patients who are unable to tolerate or have contraindications to thalidomide.

An open-label phase III study (FIRST; MM020) recruited 1,623 treatment-naive adults with newly diagnosed symptomatic and measurable (by protein electrophoresis) MM who were aged at least 65 years or were aged less than 65 years and unsuitable for HSCT due to patient choice or HSCT not available to patient. The diagnosis of MM required that monoclonal plasma cells comprised at least 10% of bone marrow and/or presence of biopsy proven plasmacytoma, monoclonal protein in serum and/or urine and myeloma-related organ dysfunction. Patients also had an Eastern Co-operative Oncology Group (ECOG) performance status of 0 to 2. Randomisation was stratified by age (≤75 versus >75 years), International Staging System (ISS) disease stage (I or II versus III) and country. Patients were equally assigned to 28-day cycles of lenalidomide 25mg daily on days 1 to 21 plus dexamethasone 40mg on days 1, 8, 15 and 22 (Rd) until disease progression (continuous Rd) (n=535), or for 18 cycles (n=541), or 42-day cycles of melphalan 0.25mg/kg and prednisone 2mg/kg daily on days 1 to 4 plus thalidomide 200mg daily (MPT) for 12 cycles (n=547). All study medications were administered orally and all patients received anti-thrombotic prophylaxis. The primary outcome of progression-free survival (PFS), defined as time from randomisation to disease progression confirmed by blinded independent response adjudication committee (IRAC) based on the International Myeloma Working Group (IMWG) criteria or death due to any cause, was primarily compared between continuous Rd and MPT. The analysis was performed in all randomised patients using an unstratified log-rank test and Kaplan-Meier methodology was used to estimate time to event survival curves.[3-5]

The cut-off for the primary analysis of PFS was 24 May 2013, when median follow-up was 37 months.[3] In the primary analysis of PFS, continuous Rd was significantly superior to MPT ($p<0.001$). Kaplan-Meier estimated median PFS was 25.5 and 21.2 months, respectively, with HR for disease progression or death of 0.72 (95% confidence interval [CI]: 0.61 to 0.85). Continuous Rd was additionally significantly superior to 18-cycle Rd ($p<0.001$). Kaplan-Meier estimated median PFS was 25.5 and 20.7 months, respectively, with HR of 0.70 (95% CI: 0.60 to 0.82). Similar outcomes were observed in updated analysis at cut-off 03 March 2014 using investigator-assessed data, where median PFS was 26.0, 21.0 and 21.9 months in the respective groups. Continuous Rd was significantly superior to MPT, with HR 0.69 (95% CI: 0.59 to 0.80), and to 18-cycle Rd, with HR 0.71 (95% CI: 0.61 to 0.83).[5] Risk of disease progression or death was similar in 18-cycle Rd and MPT groups, with HR of 1.03 (95% CI: 0.89 to 1.20), $p=0.70$.[3,5]

At the data cut-off on 24 May 2013 rate of overall response, which includes complete response (CR), very good partial response (VGPR) and partial response (PR), was 75% (402/535), 73% (397/541) and 62% (341/547) in continuous Rd, 18-cycle Rd and MPT groups respectively. Compared with MPT, overall response rate was significantly greater with continuous Rd, odds ratio (OR) 1.83 (95% CI: 1.41 to 2.37) and with 18-cycle Rd, OR 1.67 (95% CI: 1.29 to 2.15). There was no significant difference between continuous Rd and 18-cycle Rd, OR 1.10 (95% CI: 0.83 to 1.44).[4,5] Median duration of response was significantly longer in the continuous Rd group, 35.0 months, compared with the MPT group, 22.3 months (HR 0.63) and compared with the 18-cycle Rd group, 22.1 months (HR 0.60).[3,4]

To date overall survival (OS) has been assessed in two interim analyses. At data cut-off on 24 May 2013, 32% (173/535), 36% (192/541) and 38% (209/547) of patients had died within the continuous Rd, 18-cycle Rd and MPT groups, respectively. Median OS was 55.1, 53.6 and 48.2 months in the respective groups. This was significantly longer with continuous Rd versus MPT, with a HR of 0.78 (95% CI: 0.64 to 0.96), but not versus 18-cycle Rd, with a HR of 0.90 (95% CI: 0.73 to 1.10). For the comparison of 18-cycle Rd to MPT the HR was 0.88 (95% CI: 0.72 to 1.07), $p=0.184$.[3,5] In an updated analysis at data cut-off 03 March 2014, 39% (208/535), 42% (228/541) and 48% (261/547) of patients had died within the continuous Rd, 18-cycle Rd and MPT groups, respectively. Median OS was 58.9, 56.7 and 48.5 months. This was significantly longer with continuous Rd versus MPT, with a HR of 0.75 (95% CI: 0.62 to 0.90), and for 18-cycle Rd versus MPT, with a HR of 0.83 (95% CI: 0.69 to 0.99). For the comparison of continuous Rd with 18-cycle Rd the HR was 0.91 (95% CI: 0.75 to 1.09), $p=0.305$.[5]

A supportive double-blind study (MM015) recruited 459 treatment-naive patients with newly diagnosed symptomatic and measurable (by protein electrophoresis) MM who were aged at least 65 years. The same criteria as in study MM020 were required for diagnosis of MM. Patients also had a Karnofsky performance status of at least 60%. Randomisation was stratified by age (65 to 75 years versus >75 years) and ISS stage (I or II versus III). Study medications were administered orally. All patients received nine 28-day cycles of melphalan 0.18mg/kg plus prednisone 2mg/kg daily on days 1 to 4. Patients were randomised equally to concurrent treatment with placebo (MP; n=154); lenalidomide 10mg daily on days 1 to 21 of each cycle for nine cycles then placebo (MPR; n=153) or lenalidomide 10mg daily on days 1 to 21 of each cycle, continued until disease progression (MPR-R; n=152). Following disease progression, patients were offered open-label lenalidomide (25mg once daily for 21 days in each 28-day cycle, with or without dexamethasone). The primary outcome of PFS was defined as time from randomisation to progressive disease based on standard criteria or death due to any cause, whichever occurred first. This was assessed by a central adjudication committee in the intent-to-treat population that included all randomised patients and was primarily compared between MPR-R and MP using an unstratified log-rank test.[5,8]

At cut-off on 11 May 2010 (when study was unblinded) median follow-up was 37 months and approximately 76% of planned PFS events had occurred. PFS was significantly longer with MPR-R versus MP, HR of 0.40 and versus MPR, HR of 0.49. Median PFS in the MPR-R, MPR and MP groups was 31, 14 and 13 months, respectively. In a pre-specified landmark analysis lenalidomide maintenance, compared with placebo, significantly increased PFS from the start of maintenance therapy, with median of 26 versus 7 months. The HR for the MPR-R versus MPR was 0.34.[8,9]

At cut-off on 11 May 2010 within MPR-R, MPR and MP groups 28%, 34% and 29% of patients had died. There were no significant differences between the groups for OS, with HR for MPR-R versus MPR of 0.79 and MPR-R versus MP of 0.95.[8] In updated analysis at data cut-off 30 April 2013, median OS was 55.9, 51.9 and 53.9 months in the respective groups and there were no significant differences between groups, with a HR for OS of 0.95 (95% CI: 0.70 to 1.29) for MPR-R versus MPR; and 0.88 (95% CI: 0.65 to 1.20) for MPR-R versus MP.[5]

At cut-off on 11 May 2010 within MPR-R, MPR and MP groups, 77% (117/152), 68% (104/153) and 50% (77/154) of patients had a best response of complete or partial response. These were significantly greater with both MPR groups versus MP. Median duration of response was 29, 13 and 13 months in respective groups and this was significantly longer with MPR-R versus MPR and versus MP.[8] Similar outcomes were observed at the cut-off on 30 April 2013, assessed by local investigators. Within the MPR-R, MPR and MP groups 79% (120/152), 76% (116/153) and 55% (84/154) of patients had a best response of complete or partial response. These were significantly greater with both MPR groups versus MP. Median duration of response was 26.5, 12.4 and 12 months in the MPR-R, MPR and MP groups, respectively. This was significantly longer with MPR-R versus MP.[5]

Quality of life was assessed in studies MM020 via EORTC QLQ-C30 (a 30-item oncology-specific questionnaire) and QLQ-MY20 (a 20-item MM-specific questionnaire), with six domains selected for analysis *a priori* based on perceived clinical relevance: EORTC QLQ-C30 global health status; physical functioning; pain; fatigue and EORTC QLQ-MY20 disease symptoms and side effects of treatment. In MM020 any between group differences were small (less than 5 points on a 100-point scale) and unlikely to be clinically significant.

*Other data were also assessed but remain commercially confidential.**

Summary of evidence on comparative safety

The European Public Assessment Report (EPAR) notes that the major dose-limiting toxicities with lenalidomide include neutropenia and thrombocytopenia. These were reported less frequently in the continuous Rd group compared with the MPT group in study MM020: neutropenia (35% [186/532] versus 61% [328/541]); leucopenia (12% [63/532] versus 17% [94/541]); thrombocytopenia (20% [104/532] versus 25% [135/541]).[2] Grade 3 or 4 neutropenia was reported in 28% (148/532) versus 45% (243/541) of patients, febrile neutropenia occurred in 1% and 3% of patients in the respective groups and rates of grade 3 or 4 thrombocytopenia and anaemia were similar between the groups. Infections of grade 3 or 4 were reported by 29% (154/532) and 17% (93/541) of patients.[3]

In study MM015, haematological adverse events, including neutropenia, thrombocytopenia and anaemia occurred with greater frequency in the MPR-R group compared to the MP group. During the induction phase neutropenia was reported by 79% (239/302) of patients who had the MPR regimen (i.e. MPR-R and MPR groups combined) versus 50% (77/153) of patients in the MP group and the neutropenia was of grade 3/4 severity in 68% (205/302) and 30% (46/153) of patients, respectively. The MPR regimen was also associated with higher rates of thrombocytopenia, 67% (203/302) versus 42% (64/153), which was of grade 3/4 severity for 38% (116/302) versus 12% (19/153); and of anaemia, 64% (194/302) versus 50% (77/153), which was of grade 3/4 severity for 26% (77/302) versus 14% (21/153).

In study MM020, grade 3 or 4 peripheral sensory neuropathy was reported in 1.1% (6/532) of patients in the continuous Rd group compared with 9.4% (51/541) of patients in the MPT group.[3]

It has been noted in clinical studies of previously-treated patients with myeloma that there was an increase of secondary malignancies (SPM) with lenalidomide plus dexamethasone (3.98 per 100 person-years) compared with controls (1.38 per 100 person-years). In patients with untreated MM patients receiving continuous Rd or 18-cycle Rd, haematologic SPM rate (0.16 per 100 person-years) was not increased compared with MPT, (0.79 per 100 person-years). There was a 1.3-fold increase in rate of solid tumour SPM in patients receiving continuous Rd or 18-cycle Rd (1.58 per 100 person-years) compared with MPT (1.19 per 100 person-years). There was a 4.9-fold increase in rate of haematologic SPM (cases of AML, MDS) with MPR-R (1.75 per 100 person-years) compared with MP (0.36 per 100 person-years) and a 2.12-fold increase in incidence rate of solid tumour SPM with 9 cycles of MPR (1.57 per 100 person-years) compared to MP (0.74 per 100 person-years).[5]

Summary of clinical effectiveness issues

Lenalidomide is the third medicine, after thalidomide and bortezomib, licensed for treatment of patients with newly diagnosed MM unsuitable for HSCT and has been designated as an orphan medicinal product for MM. Lenalidomide meets SMC orphan criteria.

MM is a B-cell neoplasm from malignant transformation of plasma cells in the bone marrow that is characterised by accumulation of clonal plasma cells in the bone marrow. It is a disease of the elderly with median age at diagnosis of approximately 70 years.[5] There is heterogeneity in the natural history of MM and prognosis can be influenced by disease-related factors (e.g. time of diagnosis, disease stage, cytogenetics and tumour biology) plus patient-related factors (e.g. age, performance status and renal function).[5,11] Some patients present with highly refractory disease, whereas others may be disease free for up to 15 years after initial therapy.[5] In young and fit patients MM is treated with HSCT. However, many patients with MM are not eligible for the high intensity chemotherapy required

for HSCT because of advanced age, co-morbidities or poor performance status. In this group of patients standard treatments include MPT or the bortezomib, melphalan and prednisolone regimen (VMP). A dose attenuated regimen of cyclophosphamide, thalidomide and dexamethasone (CTDa) has also been used.[11,12]

The submitting company initially requested that the Scottish Medicines Consortium (SMC) consider lenalidomide when positioned for use in patients who are unable to tolerate or have contraindications to thalidomide. After discussion with the submitting company, SMC was asked to consider lenalidomide when positioned for use in patients who are unsuitable for thalidomide containing regimens.

The pivotal study, MM020, compared continuous Rd with MPT. The primary outcome of PFS is of benefit to patients. Continuous Rd, compared with MPT, significantly improved PFS, with a HR of around 0.60 and increased median PFS by about 4 months. Advantages were also observed in overall survival, with a HR of 0.75 and increase in median OS of about 10 months relative to MPT. Survival data are immature with only interim analyses available to date. There were benefits in response rate and duration of response.[3,5] However, within the proposed positioning for use in patients unsuitable for thalidomide MPT is not a relevant comparator. Treatment regimens that may be used in these patients include VMP, melphalan plus prednisolone or bortezomib plus dexamethasone.

There are some points to note in relation to the design of MM020. The criteria for ineligiblity for HSCT included age >65years, but also younger patients were recruited who were ineligible for HSCT for non-clinical reasons, i.e. patient choice or cost.[3] It is possible that some of these patients may have been physically fit enough to undergo transplant. The company submitted data which provided reassurance that the younger group of patients ineligible for HSCT for non-clinical reasons did not constitute a significant proportion of the study population. The open-label design may affect assessment of subjective outcomes, such as quality of life measures, and adverse events. Also the differing duration of treatment (until disease progression in continuous Rd versus 72 weeks in 18-cycle Rd and MPT) may have affected the rates of adverse events reported.

In both the pivotal and supportive studies administration of anti-myeloma therapies after disease progression, which were at the discretion of the investigator, may have confounded the analysis of OS. A significant effect on PFS with lenalidomide maintenance was observed in the supportive MM015 study, but no effect was observed in OS. In this study 60% of patients in the control group, MP, received lenalidomide after disease progression and this may affect to some extent the OS outcome.[8]

Continuous Rd was compared with VMP in patients with newly diagnosed MM unsuitable for HSCT using Bayesian network meta-analysis (NMA) in terms of PFS and OS. The primary base case analysis had five studies, including the pivotal studies supporting the licensed indications for lenalidomide (MM020) and bortezomib (VISTA[15]) plus three studies comparing MPT and MP. The analysis indicated that continuous Rd was likely to be superior to MP, MPT and VMP for PFS and OS. The NMA did not assess relative adverse event profiles and the study populations may not be representative of patients specified in the proposed positioning, i.e. those not suitable for thalidomide. The extent to which heterogeneity across the studies limits the validity of results is unclear. There were differences in the inclusion criteria relating to eligibility for HSCT. In some studies age was the only criterion, whereas others included patient choice or cost as reasons for ineligibility for HSCT.

There was also variation in the dose schedules for MPT and MP across the studies and differences in duration of treatment, from six 4-week cycles to nine 6-week cycles. Outcomes in the common control groups, MPT and MP, varied across the studies. Finally, there was heterogeneity across the studies in maturity of data for the outcomes input to the NMA.

There are no direct or indirect comparative data with any of the other regimens that may be used in treatment-naïve patients who are not eligible for transplant and who are unsuitable for thalidomide (e.g melphalan plus prednisolone).

Continuous Rd has practical advantages compared with VMP in terms of administration as it is administered orally, whereas VMP required attendance at out-patient clinic for administration of intravenous or subcutaneous bortezomib twice week for the first four 6-week cycles then once weekly for the next five 6-week cycles.

Summary of patient and clinician engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of lenalidomide, as an orphan medicine, in the context of treatments currently available in NHS Scotland.

The key points expressed by the group were:

- Myeloma is an incurable, relapsing and remitting cancer associated with a range of symptoms and complications which have a major impact on quality of life. The uncertain relapsing, remitting nature of the disease is particularly difficult for patients and their families.

- Older patients ineligible for transplantation have less effective treatment options alongside co-morbidities that can further limit choice.

- Clinicians advised that oral lenalidomide may provide the opportunity for a deep initial response and a delayed relapse alongside manageable toxicity leading to anticipated improvements in quality of life compared to alternative treatments.

- Alternative non-thalidomide options are limited to subcutaneous or intravenous bortezomib regimens requiring regular trips to hospital, or considerably less effective oral regimens such as mephalan and prednisolone.

- Clinicians stated that they would wish to use lenalidomide as a first-line treatment for all MM patients ineligible for transplant. However, they were able to identify patients who would fit within the company's positioning e.g. those at greatest risk of, or who already have severe peripheral neuropathy on the basis of clinical experience that indicates that lenalidomide is associated with a lower risk of peripheral neuropathy compared to both thalidomide and bortezomib.

- The PACE group felt strongly that this medicine should be made available in NHS Scotland. This was particularly the case in the small group of patients who are not suitable for treatment with thalidomide containing regimens and in whom alternative treatment options are extremely limited and undesirable as they are challenging to deliver and increase the risk of severe quality of life issues.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis of Rd compared to VMP in patients with previously untreated multiple myeloma who are not eligible for transplant and are unable to tolerate or have contradictions to thalidomide. SMC clinical experts have highlighted that there are also other appropriate comparators for this patient population that could have been considered.

The company submitted a cohort survival partition model. Patients at the beginning of the model enter in the progression free (PF) state and then after each 28-day cycle can remain in PF or transition to post-progression (PP) or death. The analysis was conducted over a lifetime time horizon equating to 38 years, with patients assumed to be age 40 years at the start of the model. The main data sources were the NMA and MM-020 study described above. To estimate PFS for the Rd arm the data from the Rd arm of the MM-020 trial were used. For the comparator arm the company used the HR for VMP compared to MPT from the NMA, then fitted a Weibull parametric function to both arms to extrapolate the PFS data. To estimate OS, the company used the OS data from the Rd arm in the MM-020 trial as the reference case and for the VMP arm OS estimates the VMP HR from the NMA was used, and then again a Weibull distribution was fitted to the data to extrapolate over the time horizon of the model. The company has included first-line and second-line progression rates from the MM-020, MM-010 and MM-009 studies in order to estimate the proportion of patients who survived and will thus receive further lines of therapy. Treatment discontinuations were also modelled. The company modelled discontinuations on the time to treatment failure (TTF) data from the MM-020 study for the Rd arm. TTF data are taken from the VISTA study.

The utility values for the Rd arm were derived from EQ-5D data collected in the MM-020 study, and for the VMP arm HRQoL data from the VISTA study were used based on the EORTC QLQ-C30 mean functional and symptom scores mapped to the EQ-5D using a published mapping algorithm. The utility value for patients at baseline was 0.53 and for the PP state the utility score was 0.59. Disutilities were not included as the company assumed any disutility from adverse events would be captured in the quality of life data collected in the studies.

Medicines cost and resource use covered medicine acquisition and administration costs and on-going care costs associated with advanced myeloma . Patient access schemes (PAS) are in place for both pomalidomide and bortezomib (second-line only), which were included in the analysis as subsequent lines of treatment. The analysis includes the estimated PAS prices of these medicines. The submission also included a decision tree model to capture the cost of PP myeloma treatments for patients who continued on treatment.

The company estimated a base case cost per quality adjusted life year (QALY) for the comparison Rd vs. VMP of £26,800. This is based upon an incremental cost of £33,343 and an incremental QALY gain of 1.24. The main driver of the incremental cost is the higher drug costs accrued in first-line treatments. The majority of the QALY gain is derived in the PF health state.

The company provided a scenario analysis and also a variety of deterministic analyses which showed the model was most sensitive to changes in the following parameters:

- Applying the Gompertz parametric function to the extrapolation of OS. This increased the ICER to £36k, and the QALY gain falls to 0.89.
- Truncating the time horizon to 10 years increased the ICER to £40k.
- Applying the lower bounds of the 95% CI of the HR for OS increased the ICER to £79k.
- Assuming 100% relative dose intensity on all medicines – increased the ICER to £36k.

- Excluding PP treatment costs, increased the ICER to £46k.
- Assuming there would be vial sharing for bortezomib first-line increased the ICER to £33k.
- As many of the ICERs are around £30k the company was asked to provide a probabilistic sensitivity analysis at willingness to pay thresholds of £20k and £30k. This showed that Rd compared to VMP is cost-effective 22.2% of the time at a willingness to pay threshold of £20k. Rd compared to VMP is cost-effective 54.6% of the time at a willingness to pay threshold of £30k.

The main weaknesses with the analysis are;

- A lack of clinical data for patients in the proposed positioning who are unable to tolerate or contraindicated to thalidomide for use in the economic evaluation has uncertain implications for the cost-effectiveness.
- SMC clinical experts suggested a possible comparator for these patients would be MP. The company provided a supplementary scenario analysis using MP as a comparator. This resulted in a cost per QALY of £34,759 based on an incremental cost of £78,365 and a QALY gain of 2.25.
- There were no direct study data available to inform the economic model and thus a NMA was required. There were potential weaknesses with the NMA which underpins the economic evaluation, which led to uncertainties in the base case cost-effectiveness results regarding treatment outcomes. The sensitivity analysis noted above indicated that using an alternative function (which was also a good fit to the available data) to extrapolate OS resulted in a higher ICER of £36k. The company also provided a sensitivity analysis with a conservative estimate of the OS HR assuming almost no benefit with Rd; applying this increased the ICER to £79k and decreased the QALY gain to 0.38.
- The utility values were elicited from patients in the clinical study and were comparatively low compared to what would be expected for these patients given they are previously untreated. In the previous SMC submission of Rd for patients who have had previous lines of treatment the utility values used in the economic evaluation were higher. The company supplied additional analysis applying the utility values from the Rd submission where patients have been previously treated, using utility values as follows; stable disease 0.81, stable after 2 years 0.77 and progressed disease 0.64.This lowered the ICER to £24k and increased the QALY gain to 1.24. The ICER falls as there is a bigger difference between the PF and PP utilities and assumes with Rd treatment more patients are PF for longer.

The Committee considered the benefits of lenalidomide in the context of its decision modifiers that can be applied when encountering high cost-effectiveness ratios and where there is increased uncertainty due to the orphan status of the medicine and concluded that the criterion for a substantial improvement in survival was met.

After considering all the available evidence, the output from the PACE process, and after application of the appropriate modifiers, the Committee was able to accept lenalidomide for restricted use in NHS Scotland.

Summary of patient and public involvement

The following information reflects the views of the specified Patient Groups.

- Submissions were received from Leukaemia CARE and Myeloma UK, which are both registered charities.

- Both Leukaemia CARE and Myeloma UK have received pharmaceutical company funding in the past two years, with both having received funding from the submitting company.

- Myeloma is an incurable, complex and destructive cancer of plasma cells. Patients may experience a range of symptoms including – bone pain, severe fatigue, unexplained weight loss, frequent and persistent infections etc. These symptoms can collectively and individually impact hugely on patients' quality of life. Treatment can halt its progress for periods of time and improve quality of life. The incurable nature of myeloma can have a profound effect on the emotional well-being of patients. Reduction in mobility and perceived increase in reliance on carers and family members, also impacts on patients' sense of control.

- Lenalidomide may be a particularly relevant drug for older/frailer myeloma patients, due to the much reduced side-effect profile, its oral formulation and the fact that it is given in a two-drug combination.

- In this setting lenalidomide may improve quality of life by reducing the symptoms of myeloma (treating the underlying disease) and may also substantially increase progression free and overall survival – these are outcomes patients greatly value. The approval of lenalidomide would improve treatment options for this group of patients and allow doctors to choose treatments suited to the clinical situation at hand.

Additional information: guidelines and protocols

In February 2014 the British Committee for Standards in Haematology (BCSH) published guidelines for the diagnosis and management of MM. For older and/or less fit patients in whom high-dose therapy is not planned, these recommend that induction therapy should consist of either a thalidomide-containing regimen in combination with an alkylating agent and steroid such as MPT [melphalan, prednisolone, thalidomide] or CTDa [cyclophosphamide, thalidomide, dexamethasone regimen attenuated]; or bortezomib in combination with melphalan and prednisolone. It was noted that patients receiving MPT in clinical studies "experienced increased incidences of side effects, notably cytopenias, thrombosis, fatigue and peripheral neuropathy. Given the historical equivalence of cyclophosphamide to melphalan, UK investigators developed an alternative regimen to MPT comprising cyclophosphamide, thalidomide and dexamethasone (CTD), which is given to older less fit patients in attenuated doses (CTDa). CTDa was used in the non-intensive arm of the Myeloma IX trial and early results from this study demonstrated superior response rates for CTDa over MP and suggested similar efficacy to MPT although PFS and overall survival data are not yet available."[11]

In August 2013 the European Society of Medical Oncology (ESMO) published clinical practice guidelines for diagnosis, treatment and follow-up of MM. These note that standards of care in Europe for elderly patients not suitable for transplant are oral combinations of melphalan and prednisone (MP) plus novel agents. MPT VMP were both recommended options based on phase III study data and it was noted that both regimens are approved in this setting by the EMA. Bendamustine plus prednisone

was also mentioned as another regimen that is approved by the EMA in patients who have clinical neuropathy at time of diagnosis precluding the use of thalidomide according to the MPT regimen or bortezomib according to the VMP regimen. It was noted that in the [MM015] study of MPR versus MP, the triplet therapy, MPR, was not superior to MP over a fixed number of cycles, therefore, this triplet combination is not approved and cannot be considered as a standard of care. A comparison of CTD with MP was noted to show superiority in for response rates, but no clear survival advantage over MP. Lenalidomide combined with low-dose dexamethasone was recognised to be widely used in US centres and to yield important response and overall survival rates but was [at that time] not approved in Europe. This regimen was being compared with MPT in a large randomised phase III trial (MM020).[12]

In July 2011 the National Institute for Health and Clinical Excellence (NICE) published a multiple technology appraisal number 228: bortezomib and thalidomide for the first-line treatment of MM. This recommends thalidomide in combination with an alkylating agent and a corticosteroid as an option for the first-line treatment of MM in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of MM if high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide.[13] Healthcare Improvement Scotland issued advice that this guidance is considered valid in NHS Scotland.[14]

On 27 July 2011 NHS Healthcare Improvement Scotland issued advice that the NICE appraisal, bortezomib and thalidomide for the first-line treatment of multiple myeloma, published today has been considered by Healthcare Improvement Scotland through its procedure of processing of NICE appraisals. This guidance states that thalidomide in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate. Bortezomib in combination with an alkylating agent and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if high-dose chemotherapy with stem cell transplantation is considered inappropriate and the person is unable to tolerate or has contraindications to thalidomide. NHS Scotland should note that:

1. No important differences were identified for this NICE appraisal and Healthcare Improvement Scotland advises that the recommendations are as valid for Scotland as for England and Wales.

2. The Scottish Medicines Consortium (SMC) has previously issued guidance to NHS Scotland on the use of thalidomide in this indication (525/08). This NICE MTA guidance supersedes the SMC advice. There is no material difference between the NICE and the SMC guidance.

3. NHS Scotland should take account of the NICE appraisal and this Healthcare Improvement Scotland email in its planning, funding and provision of services to ensure that recommended drugs or treatments are made available to meet clinical need.

4. Copies of the NICE appraisal can be downloaded from http://www.nice.org.uk. Also on the website are tools (a costing template and audit criteria) that NICE has developed to help organisations implement this guidance. NICE MTA costing templates now include the NHS Scotland boards. However, please note that the care pathway described in the costing tool may not completely reflect practice in NHSScotland.

   Finally, an easy to read summary of the appraisal, called "understanding NICE guidance" is published on the NICE website to provide information for patients and the public.

5. Healthcare Improvement Scotland advice represents the evidence-based view of Healthcare Improvement Scotland.

6. This advice does not override or replace the individual responsibility of health professionals to make appropriate decisions in the circumstances of their individual patients, in consultation with the patient and/or guardian or carer.

7. No other publications on the NICE appraisal will be issued by Healthcare Improvement Scotland.[14]

Additional information: comparators

Current treatment options for the first-line treatment of MM in patients unsuitable for HSCT and thalidomide containing regimens include VMP or melphalan plus prednisolone.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per course (£)
Lenalidomide* Dexamethasone	**25mg orally once daily on days 1 to 21 40mg orally once daily on days 1, 8, 15, 22**	**4,431**	**88,620**
Melphalan** Prednisolone Bortezomib	9mg/m^2 orally once daily on days 1 to 4 60mg/m^2 orally once daily on days 1 to 4 1.3mg/m^2 IV on days 1, 4, 8, 11, 22, 25, 29, 32 of cycles one to four, then on days 1, 8, 22, 29 of cycles five to nine.	6,157 (cycle 1- 4) 3,108 (cycle 5-9)	40,167
Melphalan*** Prednisolone	0.18mg/kg orally once daily on days 1 to 4 of a 28-day cycle 2mg/kg orally once daily on days 1 to 4 of a 28-day cycle	42	378

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 3 July 2015, except lenalidomide and bortezomib, which are from MIMS. IV = intravenous injection. Costs based on body surface area of 1.8m^2.

* 28-day cycles continued until disease progression or unacceptable toxicity. The median duration of treatment at cut-off 24 May 2013 in the lenalidomide and dexamethasone (Rd) group of study MM020 of 80 weeks (i.e. 20 cycles) has been assumed for the cost per course. The annual cost is £57,603.

** 42-day cycles continued to a maximum of 9 cycles

*** assumes 9 cycles; other dosage regimens may be used in Scotland but the costs are expected to be similar.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 61 patients in year 1 rising to 62 in year 5 to which confidential estimates of treatment uptake were applied. The company has assumed a 39% discontinuation rate each year.

The company estimated the gross medicines budget impact to be £689k in year 1 and £1.1m in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £288k in year 1 and £467k in year 5. The estimates do not take account of any effects on the use of subsequent lines of treatment.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Celgene, Summary of product characteristics for lenalidomide, last updated 02 April 2015

2. European Medicines Agency. Orphan drug designation for lenalidomide, EMA/COMP/388/2004 Rev.4, 17 June 2011.

3. Benboubker L, Dimopoulos MA, Dispenzieri A et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014; 371: 906–17.

4. Celgene. Clinical study report for MM020

5. European Medicines Agency. European public assessment report for lenalidomide

6. European Medicines Agency. Guideline on the evaluation of anticancer medicinal products in man. EMA/CHMP/205/95/ Rev.4, 13 December 2012

7. 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, prednisolone, thalidomide. Haematologica 2015; 100: 826-33.

8. Palumbo A, Hajek R, Delforge M et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012; 366: 1759–69.

9. Celgene. Clinical study report for MM015

10. NHS National Service Scotland. Cancer registration data for 2013, multiple myeloma and malignant plasma cell neoplasms.

11. Bird JM, Owen RG, D'Sa S et al. Guidelines for the diagnosis and management of multiple myeloma 2014. http://www.bcshguidelines.com/4_HAEMATOLOGY_GUIDELINES.html

12. Moreau P, San Miguel J, Ludwig H et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 (suppl 6):vi133-vi137.

13. National Institute for Health and Clinical Excellence (NICE) pub lished a multiple technology appraisal (No. 228): Bortezomib and thalidomide for the first-line treatment of multiple myeloma, July 2011.

14. NHS Healthcare Improvement Scotland. Advice on NICE MTA 228, Bortezomib and thalidomide for the first-line treatment of multiple myeloma, 27 July 2011.

15. San Miguel JF, Schlag R, Khuageva NK et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008; 359: 906–17.

This assessment is based on data submitted by the applicant company up to and including 11 September 2015.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.