Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2289

lenalidomide 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg and 25mg hard capsules (Revlimid®)

Celgene Ltd

04 September 2020

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

lenalidomide hard capsules (Revlimid®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation (ASCT).

In phase III, randomised studies, lenalidomide maintenance treatment improved progression-free survival in patients with newly diagnosed multiple myeloma who had undergone ASCT compared with placebo or observation. Median overall survival data were supportive of lenalidomide maintenance treatment.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/list price that is equivalent or lower.

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

Chairman
Scottish Medicines Consortium

Indication

As monotherapy for the maintenance treatment of adult patients with newly diagnosed multiple myeloma who have undergone autologous stem cell transplantation.[1]

Dosing Information

The recommended starting dose is lenalidomide 10mg orally once daily continuously (on days 1 to 28 of repeated 28-day cycles) given until disease progression or intolerance. After three cycles of lenalidomide maintenance, the dose can be increased to 15mg orally once daily if tolerated. The capsules should be swallowed whole, preferably with water, either with or without food.

Lenalidomide maintenance should be initiated after adequate haematologic recovery following ASCT in patients without evidence of progression. Lenalidomide must not be started if the absolute neutrophil count (ANC) is $<1.0 \times 10^9$/L, and/or platelet counts are $<75 \times 10^9$/L.

Lenalidomide treatment should be supervised by a physician experienced in the use of anti-cancer therapies.

The Summary of Product Characteristics (SPC) gives recommendations for dose reductions, interruptions and discontinuations due to toxicity.[1]

Product availability date

16 February 2017
Lenalidomide meets SMC orphan criteria for this indication.

Summary of evidence on comparative efficacy

Lenalidomide is a thalidomide derivative, which acts as an immunomodulator with anti-neoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Lenalidomide has marketing authorisation for maintenance treatment of newly diagnosed multiple myeloma patients who have undergone autologous stem cell transplant (ASCT).[1]

This marketing authorisation was supported by two double-blind, randomised, phase III studies: CALGB 100104 and IFM 2005-02. Both studies used the licensed dose of lenalidomide: 10mg daily continuously, increased to 15mg daily after three 28-day cycles if there were no dose-limiting toxicities.[1, 2]

CALGB 100104 compared maintenance treatment with lenalidomide against placebo in 460 patients aged 18 to 70 years with active multiple myeloma within 90 to 100 days after undergoing ASCT in the United States. The primary outcome was progression-free survival (PFS; defined as the time from randomisation to progression or death, whichever occurred first). Overall survival was a

secondary outcome but the study was not powered for this. At an interim PFS analysis (December 2009; median follow-up of 15.5 months), a statistically significant improvement in PFS in the lenalidomide group compared with the placebo group led to unblinding and patients randomised to placebo were able to crossover to lenalidomide before disease progression. After a median follow-up of 34 months (cut off date October 2011), median PFS was 46 months in the lenalidomide group compared with 27 months in the placebo group; hazard ratio 0.48 (95% CI: 0.36 to 0.63). Overall survival data were immature with only 15% and 23% of patients respectively having died; hazard ratio 0.62 (95% CI: 0.40 to 0.95). At an updated analysis (October 2016) after a median follow up of 91 months, median PFS was 57.3 months in the lenalidomide group compared with 28.9 months in the placebo group; hazard ratio 0.57 (95% CI: 0.46 to 0.71) and median overall survival, based on deaths in 38% and 52% of patients respectively, was 113.8 months versus 84.1 months; hazard ratio 0.61 (95% CI: 0.46 to 0.80).[1-4]

The second study, IFM 2005-02, compared maintenance treatment with lenalidomide or placebo in 614 patients aged 18 to 65 years with multiple myeloma within 6 months of ASCT. Patients received two cycles of consolidation treatment with lenalidomide (25 mg daily on 21 days of a 28-day cycle) before starting maintenance treatment which differs from Scottish clinical practice. At an interim PFS analysis (July 2010 after a median of 31.4 months follow up), there was a statistically significant improvement in the primary outcome, PFS, in the lenalidomide group compared with the placebo group: 40.1 months versus 22.8 months respectively; hazard ratio 0.52 (95% CI: 0.41 to 0.66). The study was unblinded and patients randomised to placebo were able to crossover to lenalidomide after disease progression. In January 2011, an increased incidence of second primary cancers was observed in the lenalidomide group and the safety monitoring committee recommended stopping lenalidomide maintenance treatment with follow-up continued. After a median follow-up of 96.7 months (cut-off date February 2016), median PFS, was 44.4 months in the lenalidomide group versus 23.8 months in the placebo group (hazard ratio 0.57 [95% CI: 0.47 to 0.68]) and median overall survival was 105.9 months versus 88.1 months (hazard ratio 0.90 [95% CI: 0.72 to 1.13]).[1, 2, 5]

A more recent UK study (Myeloma XI) compared lenalidomide with observation in patients aged ≥18 years with newly diagnosed, symptomatic multiple myeloma. The study included transplant-eligible and ineligible patents. The company considered this the most relevant evidence for their submission. Myeloma XI is an ongoing, open-label, randomised, phase III study of adaptive design intended to compare standard induction chemotherapy with or without carfilzomib and then lenalidomide maintenance treatment or not. Sufficiently young and fit patients were eligible to receive high-dose melphalan and an ASCT. Patients eligible for randomisation to maintenance treatment had completed assigned induction treatment, achieved a maximal response and, in the intensive regimen, received ≥100mg/m^2 of melphalan and had no worsening of myeloma. Maintenance treatment comprised lenalidomide, lenalidomide plus vorinostat or observation only. The lenalidomide plus vorinostat group of the study was subsequently discontinued. Therefore only the lenalidomide and observation groups are discussed here. Eligible patients were randomised to receive lenalidomide 10mg daily on days 1 to 21 of each 28-day cycle (n=1,137) or observation (n=834) which was continued until disease progression. In patients who had

undergone ASCT, maintenance treatment commenced approximately 100 days later and only when the neutrophil count was ≥1.0 x 10^9/L and the platelet count was ≥100 x10^9/L. The lenalidomide dose could be temporarily discontinued or reduced to manage toxicity. It was recommended that all patients receive bisphosphonates until disease progression and thromboprophylaxis for the first 3 months of the study. Randomisation to maintenance treatment was stratified according to the induction regimen, use of intensification and study centre. [6, 7]

The maintenance treatment phase of Myeloma XI had two primary outcomes: PFS (defined as the time from randomisation to maintenance treatment to disease progression or death from any cause) and overall survival (defined as the time from randomisation to maintenance treatment to death from any cause or last follow-up). Disease progression was assessed according to the modified International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma by local assessors and (where available) centrally by a blinded expert panel. Efficacy analyses of maintenance treatment were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation to lenalidomide or observation. The overall ITT population includes patients who were transplant-eligible and transplant-ineligible. Pre-specified subgroup analyses included a subgroup of patients eligible for ASCT (n=1,248).[7] The company also presented unpublished, post hoc subgroup analysis results for a cohort of patients of the ASCT-eligible subgroup who had been randomised to lenalidomide 10mg daily or placebo (excluding patients randomised to lenalidomide 25mg daily [from an early protocol version] or to lenalidomide plus vorinostat). The company considered this cohort of patients was the most representative group for clinical practice.

Results have been published after a median duration of follow-up of 31 months (cut-off date October 2017). In the ITT population of Myeloma XI (including both ASCT-eligible and ineligible patients), lenalidomide maintenance treatment compared with observation significantly improved PFS (median PFS of 39 months versus 20 months respectively, hazard ratio 0.46 [95% CI: 0.41 to 0.53), p<0.001]) and non-significant improvement in overall survival (median overall survival not reached in either group, hazard ratio 0.87 [95% CI:0.73 to 1.05]). The results of the pre-specified subgroup of ASCT eligible patients and the relevant cohort also favoured treatment with lenalidomide. Details are presented in table 1 below.

Table 1: Primary outcomes results for the maintenance phase of Myeloma XI in the ITT population, ASCT-eligible subgroup and cohort reflecting practice (unconfirmed)[7]

	Lenalidomide	**Observation**	**Hazard ratio (95% CI)**
ITT population (centrally assessed)	**(n=1,137)**	**(n=834)**	
PFS			
Number of PFS events	456	533	
Median PFS (months)	39	20	0.46 (0.41 to 0.53), p<0.001

Overall survival			
Number of deaths	234	226	
Median overall survival	Not reached	Not reached	0.87 (0.73 to 1.05), p=0.15
KM estimates 3-year overall survival	79%	76%	
KM estimates 5-year overall survival	61%	57%	
Pre-specified ASCT-eligible subgroup (centrally assessed)	(n=730)	(n=518)	
PFS			
Number of PFS events	199	264	
Median PFS (months)	57	30	0.48 (0.40 to 0.58), p<0.001
Overall survival			
Number of deaths	84	98	
Median overall survival	Not reached	Not reached	0.69 (0.52 to 0.93), p=0.014
KM estimates 3-year overall survival	88%	80%	

ITT=intention to treat; CI=confidence interval; PFS=progression-free survival, KM=Kaplan Meier

The secondary outcome was PFS 2 (defined as time from maintenance randomisation to the date of second progressive disease, start of third anti-myeloma treatment or death from any cause). In the ITT population, median PFS 2 was 64 months in the lenalidomide group and 45 months with observation; hazard ratio 0.65 (95% CI:0.56 to 0.77). In the pre-specified ASCT-eligible subgroup, median PFS 2 was not reached in the lenalidomide group compared with 59 months in the observation group; hazard ratio 0.57 (95% CI: 0.44 to 0.73).[7] The company did not present results for PFS 2 for the cohort reflecting practice. Time to improved response was also a secondary outcome but has not been reported.

Health Related Quality of Life (HRQoL) was not assessed in Myeloma XI.[7]

A published meta-analysis of the CALGB 100104, IFM 2005-02 and the GIMEMA studies (a smaller Italian/Israeli study which included lenalidomide consolidation before randomisation to a maintenance dose of lenalidomide 10mg daily on days 1 to 21 of each 28-day cycle) comprised 605 patients randomised to lenalidomide and 603 to placebo/observation. The results found that median PFS was 52.8 months with lenalidomide and 23.5 months with placebo/observation (hazard ratio 0.48 [95% CI: 0.41 to 0.55]) and after a median follow-up of 79.5 months, that median overall survival was not reached and 86.0 months respectively (hazard ratio 0.75 [95% CI: 0.63 to 0.90]).[8]

The published MYELOMA XI maintenance study included brief results of a summary meta-analysis of transplant-eligible patients from MYELOMA XI and the three studies included in the published meta-analysis above. This comprised 3,179 patients and found a hazard ratio for PFS of 0.47 (95% CI: 0.41 to 0.54) and for overall survival of 0.72 (95% CI: 0.56 to 0.91).[7]

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

Summary of evidence on comparative safety

Based on safety data from CALGB 100014 and IFM-2005-02, the European Medicines Agency (EMA) noted that the safety results for patients with newly diagnosed multiple myeloma treated with lenalidomide were generally consistent with the known safety profile for lenalidomide. However, a risk of increase in second primary malignancy was associated with lenalidomide maintenance. Based on pooled data from these studies, according to lenalidomide exposure, the incidence rate of haematologic malignancies (most notably acute myeloid leukaemia, myelodysplastic syndromes and B-cell malignancies) was 1.31 per 100 person-years for the lenalidomide arms and 0.58 per 100 person-years for the placebo arms (1.02 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT). The incidence rate of solid tumour second primary malignancy was 1.36 per 100 person-years for the lenalidomide arms and 1.05 per 100 person-years for the placebo arms (1.26 per 100 person-years for patients exposed to lenalidomide after ASCT and 0.60 per 100 person-years for patients not-exposed to lenalidomide after ASCT).[1, 2]

At the time of the publication of Myeloma XI (cut-off date October 2017), patients in the lenalidomide group had received a median of 18 x 28-day cycles (interquartile range: 6 to 30). Details of safety data are limited to the following: in the safety population of the maintenance phase of Myeloma XI (n=1,931), serious adverse events were reported by 45% (494/1097) of lenalidomide patients and 17% (150/874) of observation patients. In the lenalidomide group, 15% (167/1097) of patients discontinued treatment due to an adverse event. In the ITT population, 69% (781/1,137) of patients treated with lenalidomide had dose modifications.[7] The overall incidences of patients reporting any grade of adverse event or of treatment-related adverse events were not reported.[2, 7]

In the overall study safety population, the most frequently reported adverse events of any grade reported in the lenalidomide group (n=1,097) were: neutropenia (71%), anaemia (64%), thrombocytopenia (51%), fatigue or lethargy (34%), upper or lower respiratory infection (33%), peripheral sensory neuropathy (30%), constipation (29%), back pain (16%), rash (15%), nausea (13%), cough (13%), myalgia (12%), other infections and infestations (12%), and arthralgia (11%). With the exception of neutropenia, most of these adverse events were of grade 1 or 2 severity. The most common grade 3 or 4 adverse events in the lenalidomide group were neutropenia (33%), thrombocytopenia (6.6%) and anaemia (3.8%). Infections were the most commonly reported serious adverse events in both treatment groups (42% and 7.6%, respectively). The 3-year

cumulative incidence of second primary malignancies was 5.3% in the lenalidomide group compared with 3.1% in the observation group (2.4 per 100 patient-years versus 1.4 per 100 patient-years respectively).[7]

The company presented safety data for the cohort of patients from Myeloma XI considered to represent use in practice and the incidence of adverse events appeared similar to those reported in the overall safety population. These data are currently unconfirmed.

Summary of clinical effectiveness issues

Multiple myeloma is a form of blood cancer in which plasma cells undergo transformation in the bone marrow resulting in an accumulation of clonal plasma cells in the bone marrow. These cells produce abnormal antibody, paraprotein, and they suppress the development of other normal blood cells, including white blood cells to fight infection, red blood cells to carry oxygen and platelets for blood clotting. Multiple myeloma is a disease of the elderly with an overall median age at manifestation of approximately 70 years. However in Scotland, 22% (98/454) cases were in patients aged <65 years in 2017.[9] Prognosis depends on various factors at the time of diagnosis. Treatment aims to prolong survival and maintain quality of life. Current guidelines recommend induction therapy followed by high-dose therapy with ASCT for younger, fitter patients. Following ASCT, patients are monitored and offered supportive care. Active maintenance treatment may help to control the growth of cancer cells and delay the time to disease progression and current European and American guidelines recommend lenalidomide for maintenance treatment in these patients.[10, 11] Lenalidomide is the only medicine licensed for the maintenance treatment of newly diagnosed multiple myeloma after ASCT.[1,] Clinical experts consulted by SMC considered that there is an unmet need for treatments that maintain remission after ASCT in newly diagnosed patients with multiple myeloma. Lenalidomide meets SMC orphan criteria.

The main evidence to support the licence for lenalidomide monotherapy as maintenance treatment in newly diagnosed multiple myeloma patients after ASCT came from two studies (CALGB 100104 and IFM 2005-02) using the licensed dosing regimen of lenalidomide. The more recent Myeloma XI study compared lenalidomide with observation in transplant-eligible and transplant-ineligible patients. It was performed in the UK and the company considered this the most relevant evidence for their submission. PFS was a primary outcome in all three studies and lenalidomide significantly improved PFS compared with placebo/observation in all studies. Overall survival was a secondary outcome in CALGB 100104 and IFM 2005-02 and a co-primary outcome in Myeloma XI and was longer in the lenalidomide-treated patients than control across all studies. In Myeloma XI, there was no statistically significant improvement in overall survival between lenalidomide and observation in the ITT population but a survival benefit was observed in the ASCT-eligible subgroup and the relevant cohort. Further subgroup analyses indicated that the treatment effect was consistent across cytogenetic risk in transplant-eligible patients but these results should be interpreted with caution since not all patients were assessed for cytogenetics and the numbers are smaller. A summary meta-analysis of available studies in ASCT-eligible

patients, including the results of the Myeloma XI study, has indicated a survival benefit for lenalidomide (hazard ratio 0.72 [95% CI: 0.56 to 0.91]). There were a number of differences between the studies including patient baseline characteristics, induction therapy regimen (and whether this contained lenalidomide), number of permitted ASCTs, dose of lenalidomide maintenance, rules around crossover and subsequent treatment, and durations of follow-up. However all studies found a consistent treatment effect favouring lenalidomide.[2, 4, 5, 7, 8]

There were a number of limitations with the Myeloma XI study. The lenalidomide maintenance dose used (10mg daily on days 1 to 21 of each 28-day cycle) was different from the licensed dosing regimen (10mg daily continuously) and may affect the generalisability of both the efficacy and safety study results to the Scottish population treated with the licensed dose.[1, 7] The company considered the lenalidomide dose used in Myeloma XI most closely reflected the dose that would be used in Scottish clinical practice and this was supported by clinical experts consulted by SMC.

The company presented results of an unpublished post hoc subgroup analysis of a cohort of transplant-eligible patients as they considered this evidence most closely reflected the use of lenalidomide in Scottish clinical practice. Although results for the cohort of patients favoured lenalidomide over observation, the study was not planned or powered for these analyses. Reported baseline characteristics appeared to be well-matched in this cohort of patients but details of cytogenetic risk have not been presented and it is unclear if there were any imbalances in this unplanned cohort. Therefore these unpublished results should be treated with caution.

Other limitations of the Myeloma XI study include its open-label design which may introduce the potential for bias when efficacy and safety outcomes were assessed by investigators. In addition, lenalidomide maintenance treatment was compared with observation only and was not placebo-controlled. The study is ongoing and is expected to complete in December 2022. Overall survival results are currently immature and results after a longer follow-up are awaited but may be confounded by subsequent treatment. The Myeloma XI study did not assess quality of life which may be important when considering long-term maintenance treatment.[7]

Lenalidomide has been associated with an increased risk of second primary malignancies. The SPC notes that this increased risk is also relevant to newly diagnosed multiple myeloma patients after ASCT. Although this risk is not yet fully characterised, it should be kept in mind when considering and using lenalidomide in this setting. It advises that the risk of occurrence of haematologic second primary malignancy must be taken into account before initiating treatment with lenalidomide either in combination with melphalan or immediately following high-dose melphalan and ASCT. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.[1]

The introduction of lenalidomide as maintenance treatment for newly diagnosed patients following ASCT would offer the only licensed treatment option for these patients and was considered to be a therapeutic advancement by clinical experts consulted by SMC. Lenalidomide is

associated with improved PFS and overall survival. It is administered orally which offers convenience for patients and the service. Patients may require monitoring more regularly than they would under observational follow-up but this would not be expected to have major service implications. The potential benefits of maintenance treatment should be balanced against the risk of second primary malignancy in the individual patient.

Patient and clinician engagement (PACE)

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 NHSScotland.

The key points expressed by the group were:

- Multiple myeloma is an incurable, relapsing, remitting disease. Symptoms are recurrent and debilitating, and include bone disease, pain, fatigue and recurrent infections. The diagnosis and significant symptoms have a huge impact on the quality of life of patients, families and carers. Newly diagnosed patients who have undergone an ASCT are often younger/fitter and are more likely to have dependents and/or be working. They, therefore, face particular challenges in living with myeloma and its treatments.
- There is currently no cure for myeloma and treatment aims to halt its progression and improve quality of life. The first remission is often the deepest and longest and this stage of treatment provides the best opportunity to prolong first relapse and maintain patients in good quality of life. There is currently no maintenance treatment used after ASCT and this is a high unmet need.
- Lenalidomide maintenance may substantially improve progression-free and overall survival and delay next progression compared with observation.
- Lenalidomide maintenance treatment is very well tolerated and the clinical benefits may be achieved with no detrimental effect on quality of life. Patients may be able to return to normal life, enjoy time with family and holidays and return to work.
- Lenalidomide is orally administered which is convenient for patients and their carers and has minimal service implications.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 8% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from Myeloma UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis of lenalidomide maintenance monotherapy versus observation in newly diagnosed adult patients with multiple myeloma who have undergone ASCT and have not progressed. The time horizon of the model was 40 years.

The analysis used a partitioned survival model with three health states: progression-free, progressed and dead. The area under the curve approach was used for the calculation of proportion of patients in each health state at different time points. The cycle length was 28 days. The perspective for the analysis was that of NHS Scotland.

In the company's base case analysis, patients received 10 mg of lenalidomide daily on days 1-21 of each 28-day cycle until treatment discontinuation due to progression or intolerance. As discussed above, this is inconsistent with the licensed dosage regimen. A relative dose adjustment was applied and treatment discontinuation was modelled based on data from the Myeloma XI study. Time on treatment data were further extrapolated using the exponential parametric model which was selected due to its best statistical fit. The company provided two analyses using the licensed dose on request, as discussed below.

PFS and overall survival data for lenalidomide maintenance and observation were obtained from a sub-group of patients in the Myeloma XI study. Overall survival data were immature in the lenalidomide arm and were extrapolated using parametric survival distributions. It should be noted that due to the short follow-up in the Myeloma XI study, the majority of parametric models fit the K-M PFS and overall survival data reasonably well. For the extrapolation of PFS data in both arms, the Weibull distribution had the best statistical fit (lowest AIC and BIC) in both joint and independently fitted models and also had a good visual fit to the PFS K-M data from the main clinical study. However, the exponential distribution was selected due to its better fit to PFS K-M curve from the CALGB 100104 study. Generalized gamma (independent models) had the best statistical fit in both arms based on overall survival data from the Myeloma XI study but did not fit well to data from the CALGB 100104 study. Thus, Weibull was selected in the observation arm and log-logistic in the lenalidomide arm. The latter was associated with a substantially longer tail.

Baseline utility values for the pre and post-progression health states were obtained from a cross-sectional postal study of patients with multiple myeloma in the UK and are shown in table 2. Utilities were further adjusted for age in both arms and for adverse events as a one-off utility decrement in the lenalidomide treatment arm only.

Table 2: Base case health state utility values

State	Utility value: mean	95% CI
Pre-progression	0.72	0.69, 0.75
Progressive disease	0.67	0.64, 0.70
Abbreviations: CI, confidence interval		

Apart from medicines costs, other costs considered in the analysis included treatment of adverse events in the maintenance arm only (grade 3 or greater in at least 2% of patients treated with lenalidomide in Myeloma XI) and medical resource use costs for follow-up monitoring and two lines of subsequent therapy costs upon first progression of disease in both arms. The proportions of people receiving each type of healthcare resource in the model were obtained from a survey conducted by the submitting company. Equal pre and post-progression health care resource use was assumed in both observation and lenalidomide maintenance arms.

A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price of lenalidomide.

The company's base case analysis resulted in an incremental cost-effectiveness ratio (ICER) of £40,312. The cost-effectiveness results using the licensed dosage regimen of lenalidomide are presented in table 3.

Table 3: Cost-effectiveness results: licensed dosage regimen of lenalidomide

Dose/ToT	**Treatments**	**ICER (£/QALY)**
Licence/CALGB ToT	Observation	-
	Lenalidomide	£38,174
Licence (no increase after 3 months)/ Myeloma XI ToT	Observation	-
	Lenalidomide	£53,074
Abbreviations: ToT, time on treatment; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio		

The company provided two analyses using the licensed dosage regimen of lenalidomide.
The first analysis uses the licensed regimen but time on treatment from the CALGB study which resulted in a lower than base case ICER. This was due to the shorter time on treatment in the study, presumably due to higher toxicity associated with the higher lenalidomide dose. The second analysis uses the licensed regimen and time of treatment from the Myeloma XI study. However, the analysis does not account for dose escalation of lenalidomide after 3 months.

Other key scenario analyses of lenalidomide maintenance compared to observation are presented in table 4 below. The most substantial ICER changes resulted from using different parametric models for the extrapolation of PFS and OS data.

Table 4: Other selected scenario analyses

	Scenario	Base case	ICER
0	Base case	-	£40, 312
1	Time horizon: 20 years	40 years	£43,330
2	Using Weibull for the extrapolation of OS for both observation (currently the base case) and lenalidomide (best statistical fit to	Using Weibull for the extrapolation of OS in the observation arm and log-logistic in the lenalidomide arm (long tail) (independent models based on visual fit to the CALGB K-M data).	£65,941

	Myeloma XI data and good visual fit) (joint models).		
3	Using Weibull for the extrapolation of PFS for both observation and lenalidomide (best statistical fit to Myeloma XI data and good visual fit)	Using the exponential for the extrapolation of PFS for both observation and lenalidomide (based on visual fit to the CALGB K-M data)	£44,012
4	Using lenalidomide dose which corresponds to the licensed dose for maintenance treatment: 10mg daily ***continuously*** (increased after 3 months to 15 mg daily if tolerated) and using time on treatment from the CALGB100104 study, using Weibull for the extrapolation of OS for both observation (currently the base case) and lenalidomide, using Weibull for the extrapolation of PFS for both observation and lenalidomide.	10 mg of lenalidomide daily on days 1-21 of each 28-day cycle until treatment discontinuation due to progression or intolerance Using Weibull for the extrapolation of OS in the observation arm and log-logistic in the lenalidomide arm (long tail) (independent models based on visual fit to the CALGB K-M data). Using the exponential for the extrapolation of PFS for both observation and lenalidomide (based on visual fit to the CALGB K-M data)	£68,145
5	Using Weibull for the extrapolation of OS for both observation (currently the base case) and lenalidomide and using Weibull for the extrapolation of PFS for both observation and lenalidomide	Using Weibull for the extrapolation of OS in the observation arm and log-logistic in the lenalidomide arm (long tail) (independent models based on visual fit to the CALGB K-M data). Using the exponential for the extrapolation of PFS for both observation and lenalidomide (based on visual fit to the CALGB K-M data)	£71,786
6	Assuming 100% RDI for maintenance lenalidomide	Using RDI as observed in the Myeloma XI study for lenalidomide	£51,907
7	Subsequent treatment pathway: Myeloma XI	Survey conducted by the submitting company	£35,027
8	Subsequent treatment pathway: UKCS	Survey conducted by the submitting company	Dominant

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity UKCS, UK Clinician's Survey.

The main limitations with the analysis were:

- Dose and treatment duration of lenalidomide in the company base case analysis (10mg administered orally once a day on days 1-21 in 28 day cycles until progression or intolerance) are lower than the licensed regimen. The company provided analyses on request using the licensed dosage regimen (table 3 scenarios) and these results are relevant for SMC decision-making as SMC remit requires medicines to be assessed according to their marketing authorisation. Using the continuous lenalidomide dose and

time on treatment from the Myeloma XI study without accounting for potential dose increase as per the licence can potentially underestimate the ICER. The lower than base case ICER when using the shorter time on treatment in the CALGB study does not account for the potential increased toxicity and longer term safety issues associated with the higher dose.

- There is uncertainty around long term PFS and OS outcomes. Parametric curve selection for the extrapolation of PFS and OS from the Myeloma XI study were heavily influenced by visual fit to the K-M data from a US-based study where differences in treatment protocol and comparator were present. Parametric models with reasonably good statistical and visual fit to data from the Myeloma XI study have been excluded on the basis of poor fit to the data from CALGB 100104 study. Although the OS K-M from Myeloma XI visibly tended to overlap with the K-M from the CALGB 100104 study in the observation/placebo arm, this did not appear to be the case in the lenalidomide arm where the two curves appeared to have started to diverge.

- Insufficient justification was provided for fitting different types of models (monotonic vs. non-monotonic hazards) to the observation and lenalidomide arm for the extrapolation of OS. As a result, the model potentially overestimates life years gained in the lenalidomide arm. Model projections in terms of PFS and OS have not been validated by clinical experts.

- The model assumed the costs of two lines of subsequent therapy upon first progression which might potentially overestimate the costs in the observation arm due to its higher first progression rates. The mix of subsequent treatments after first and second relapse in the two arms was obtained from 1 surveyed Scottish clinician and was not validated. Clinical experts contacted by SMC suggested alternative subsequent treatment regimens (e.g. increasing the lenalidomide dose upon progression if tolerated in the maintenance arm). As presented in table 4, scenario analyses 7 and 8, the choice of subsequent therapies has an impact on the ICER.

- The model assumed equal pre-progression monitoring and testing healthcare resource use in the observation and lenalidomide arms. However, it is reasonable to expect higher resource use rates in an active treatment population due to the need to monitor for toxicity.

- There was some sensitivity to the chosen base case time horizon. This is appropriate if the substantially higher survival projected in the lenalidomide arm is an accurate prediction. All patients in the observation arm are expected to die within approximately 20 years.

The Committee also considered the benefits of lenalidomide in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission and the absence of other treatments of proven benefit. In

addition, as lenalidomide is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted lenalidomide for use in NHSScotland.

Additional information: guidelines and protocols

The National Comprehensive Cancer Network (NCCN) published multiple myeloma guidelines in 2019.[11] This guidance recommends lenalidomide as "one of the preferred maintenance regimens" following ASCT. However, the guideline also states that "*the benefits of improved PFS with lenalidomide maintenance must be weighed against the increased rate of severe (grade 3 and 4) neutropenia, risk of secondary cancers, and other toxicities*".[11]

The European Myeloma Network (EMN) published guidance in 2018 for multiple myeloma.[12] This guidance recommends lenalidomide, thalidomide, bortezomib for the maintenance treatment of multiple myeloma and states that:

- Lenalidomide use is supported by a better toxicity profile than thalidomide, which favours the long-term administration
- Bortezomib use is supported by a better toxicity profile than thalidomide, and a potentially higher efficacy.
- immunomodulators alone could be suboptimal in high-risk patients and patients with renal failure, who may benefit from bortezomib.

The EMN guidance states that treatment choice should be based on patients' characteristics and expected toxicity of the proposed regimen. The guidance also highlights limited available data and specifically states that randomised comparative data are lacking.[12]

The European Society for Medical Oncology (ESMO) published an updated version of multiple myeloma: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up in 2017.[10] The guidance notes that the immunomodulators, thalidomide and lenalidomide, prolongs PFS and that a meta-analysis has shown that lenalidomide maintenance following ASCT is associated with an overall survival benefit of more than two years. The guidance also highlights that lenalidomide was approved by the EMA and is recommended by ESMO for the maintenance treatment of multiple myeloma following ASCT.[10]

Additional information: comparators

None.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
lenalidomide	**10mg orally daily continuously, increased to 15mg orally daily after three cycles if tolerated**	**65,502**

Costs from BNF online on 9 June 2020. Cost based on 10mg daily continuously. Costs do not take patient access schemes into consideration.

Additional information: budget impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

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

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This assessment is based on data submitted by the applicant company up to and including 20 July 2020.

**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*

Medicine 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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.