Scottish Medicines Consortium

Resubmission

lenalidomide, 5mg, 10mg, 15mg and 25mg capsules (Revlimid®)
No. (441/08)

Celgene Ltd

09 April 2010

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 re-submission

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

Licensed indication under review: in combination with dexamethasone, for the treatment of multiple myeloma patients who have received at least one prior therapy.

SMC restriction: use in patients who have received at least two prior lines of therapy.

Lenalidomide plus dexamethasone significantly increased the time to progression compared with dexamethasone alone in multiple myeloma patients who had been treated with at least one prior therapy.

The health economic case was demonstrated only for a sub-population of patients within the licensed indication.

Taking into account the orphan drug status of lenalidomide and the substantial survival benefit it appears to offer SMC concluded that the economic case was demonstrated.

Overleaf is the detailed advice on this product.

Advice must be treated in strict confidence until published on the SMC website (www.scottishmedicines.org.uk) on **10 May 2010.**

Chairman
Scottish Medicines Consortium

Indication

In combination with dexamethasone for the treatment of multiple myeloma patients who have received at least one prior therapy.

Dosing information

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

Treatment with lenalidomide must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma. Lenalidomide capsules should be taken at about the same time each day and should not be broken or chewed but swallowed whole, preferably with water.

Product availability date

June 2007

Summary of evidence on comparative efficacy

Lenalidomide, an analogue of thalidomide, is a novel immunomodulatory agent. It has a number of mechanisms of action including anti-neoplastic, anti-angiogenic, pro-erythropoietic effects with immunomodulatory properties.

The Scottish Medicines Consortium (SMC) has previously not recommended lenalidomide for the treatment of multiple myeloma in patients who have received at least one prior therapy. In this resubmission the company has indicated that they wish the SMC to consider lenalidomide use in a narrower patient population: lenalidomide in combination with dexamethasone for the treatment of patients who have received more than one prior therapy (i.e. at second relapse).

The licence is based on two, double-blind, randomised, placebo-controlled, phase lll studies, of similar design, in a total of 704 patients (aged >18 years) with relapsed or refractory multiple myeloma after at least one prior therapy, Durie-Salmon stage II or III disease, measurable levels of myeloma (M)-paraprotein in serum or urine and a performance score of 0, 1, or 2. Patients were randomised equally to lenalidomide 25mg daily on days 1 to 21 of a 28-day cycle or placebo. Randomisation was stratified by baseline serum β_2-microglobulin level, prior therapy with high-dose chemotherapy supported by stem cell transplantation and the number of prior anti-myeloma regimens (1 versus >1). All patients were treated with dexamethasone 40mg on days 1 to 4, 9 to 12 and 17 to 20 of each 28 day cycle for the first 4 cycles, then on days 1 to 4 every 28 days thereafter. Treatment continued until disease progression or withdrawal because of unacceptable toxicity. Dose adjustments could be made for each patient based on tolerability. Concomitant therapies allowed included bisphosphonates, antibiotics, growth factors, erythropoietin and transfusions.

The primary efficacy outcome was the time to progression (TTP), defined as the time from randomisation to the first documentation of progressive disease (based on the myeloma response criteria), discontinuation or death due to progressive disease in the intention to treat (ITT) population. Secondary analyses of the primary outcome were conducted for the stratified groups. Secondary outcomes included response rate and overall survival (OS),

defined as time from randomisation to death from any cause. Both TTP and OS were estimated using Kaplan-Meier analyses.

An interim analysis was planned when 50% of the patients had reached the primary endpoint. The TTP was censored for patients who had not progressed at the time of analysis, withdrew from treatment before documented progression, received another antimyeloma therapy without documented progression or suffered intolerable adverse events. The interim analysis found that the median TTP was significantly longer in both studies for patients treated with lenalidomide plus dexamethasone than with dexamethasone alone (41 weeks versus 20 weeks and median not reached versus 20 weeks, respectively). Patients in the dexamethasone monotherapy group were three times more likely to have progressed than those in the combination group. After reviewing the interim analysis, an independent data monitoring committee recommended that the study be unblinded. Patients in the dexamethasone only group were given the option of receiving open-label lenalidomide, while remaining assigned to the dexamethasone group.

Further analyses of TTP were undertaken at the time both studies were unblinded and are presented in table 1. These show a significantly longer time to disease progression in the lenalidomide plus dexamethasone group.

Table 1. Analysis of time to progression (TTP) at the unblinding of the two pivotal Phase III placebo-controlled studies

	Study 1		**Study 2**	
Outcome	len/dex	dex	len/dex	dex
No. of patients	177	176	176	175
Median TTP (months)	11.1	4.7	11.3	4.7
(Hazard ratio (95% CI)	2.82 (2.15 to 3.70)		2.85 (2.16 to 3.76)	

len=lenalidomide, dex=dexamethasone CI=confidence interval

Secondary analyses of the primary endpoint, for the pooled results of studies 1 and 2, comparing the TTP in patients having received one prior therapy with those having received more than one prior therapy are presented in table 2.

Table 2. Sub-group analysis of time to progression (TTP) for patients with one versus more than one prior therapy using pooled data from the two pivotal Phase III placebo-controlled studies

	1 prior regimen		**>1 prior regimen**	
	len/dex	dex	len/dex	dex
No. of patients	120	121	226	225
Median TTP (months)	15.5	4.7	10.2	4.7
(Hazard ratio (95% CI)	2.86 (2.04 to 4.01)		2.66 (2.10 to 3.37)	

len=lenalidomide, dex=dexamethasone CI=confidence interval

Results of the secondary outcomes supported the primary outcome. The response rate in the lenalidomide plus dexamethasone group was significantly greater than for dexamethasone alone and was similar between studies, 61% and 60%, compared with 20% and 24%, respectively.

In a pooled update of the two pivotal studies, after a median follow-up of 48 months for surviving patients, 199 patients (56%) had died in the lenalidomide plus dexamethasone group and 219 patients (62%) had died in the dexamethasone monotherapy group. There was a significant benefit in OS (median of 38.0 versus 31.6 months) despite 48% of patients who were randomised to dexamethasone alone receiving lenalidomide-based treatment after disease progression or study unblinding.

In an analysis of pooled data to January 2007, treatment with lenalidomide plus dexamethasone compared with dexamethasone alone significantly improved median OS in patients who received two or more prior therapies: 32.4 versus 27.3 months, respectively. In patients with one prior therapy median OS had not yet been reached in the lenalidomide plus dexamethasone group and was 35.3 months in the dexamethasone alone group, a non-significant difference.

Summary of evidence on comparative safety

Anaemia, neutropenia, thrombocytopenia, constipation, pneumonia, decreased weight, hypokalaemia, hypocalcaemia, tremor, rash, and deep vein thrombosis (DVT) were reported significantly more frequently in the lenalidomide plus dexamethasone group than in the dexamethasone monotherapy group. The most common adverse events (AEs) with lenalidomide treatment were haematological; principally neutropenia and thrombocytopenia, and these were the primary reasons for dose reductions. Cardiac adverse events were reported more frequently for lenalidomide plus dexamethasone than for dexamethasone only (18% versus 11%). Lenalidomide plus dexamethasone increased the risk of DVT and pulmonary embolism, with serious DVT occurring in 7% versus 3% of dexamethasone only patients.

Pooled results from both studies found pulmonary embolism and neutropenia were the primary reasons for discontinuation in the lenalidomide plus dexamethasone group compared with anaemia and thrombocytopenia in the dexamethasone only group.

Owing to the structural similarities between lenalidomide and thalidomide, a risk management programme has been developed to provide data on potential teratogenicity risk and to restrict use in women of childbearing potential, unless the Pregnancy Prevention Programme is followed.

The neurotoxic potential of lenalidomide associated with long-term use is not fully resolved and is subject to post-marketing follow up and therefore cannot at present be ruled out.

Data from a recently published expanded access programme, comprising 1,438 patients with multiple myeloma, confirmed the safety results of the pivotal studies.

Summary of clinical effectiveness issues

The significant benefit in TTP was maintained over time. The sensitivity analyses around the primary endpoint calculated the more conservative endpoint of progression-free survival (a similar endpoint to TTP but including death from any cause). This confirmed the results of the primary TTP analysis.

An advantage in OS was also demonstrated, although the true benefit attributable to lenalidomide is confounded by a significant number of patients, who had progressed on dexamethasone alone, being subsequently treated with open-label lenalidomide, in addition to those receiving lenalidomide after the unblinding of the study (170 of 351 patients in total). These patients remained assigned to the dexamethasone group and therefore the measure of OS in the dexamethasone group includes patients treated with lenalidomide.

Although time to first worsening of performance status was reported as a secondary outcome, quality of life measures were not reported.

Subgroup analysis showed that the benefit of lenalidomide plus dexamethasone versus dexamethasone alone remained statistically significant in subgroups that received prior treatment with thalidomide or bortezomib.

In this resubmission, the company wishes SMC to consider a subset of the study populations and licensed indication: use in those patients who have already received at least two prior therapies. This subset, which constituted 65% (n=456) of the pooled study population, demonstrated superiority in TTP of lenalidomide plus dexamethasone over dexamethasone alone. However, as may be expected, the results in this more refractory population are poorer than in the whole study population. The secondary analysis of the primary endpoint found that TTP was significantly shorter for patients who received lenalidomide plus dexamethasone after at least two prior regimens than after only one: 10.2 months versus 15.5 months, respectively.

A recently published subset analysis of the effect of prior antimyeloma therapy in the pivotal studies redefined the term “prior therapy” and retrospectively assessed the number of prior lines of therapy. The analysis, which only reported results for the lenalidomide plus dexamethasone group, found a significant reduction in TTP in patients who had received at least two prior therapies compared with one, 10.6 months versus 17.1 months, respectively, a greater difference than reported in the original studies. This recent analysis also found that the updated OS (data to December 2008) was significantly shorter in patients who had received at least two prior lines of therapy compared with one: 35.8 versus 42.0 months, respectively.

From the baseline demographics, the populations in both studies were at the younger end of the spectrum for this disease; the median age in the studies was between 62 and 64 years. The British Committee for Standards in Haematology reports that the median age of patients presenting with multiple myeloma in the UK is around 70 years. They were also a fit population with 80-90% of patients having a performance status of 0 or 1. This population may not be entirely representative of the population likely to be treated with this therapy in Scotland.

Advances in research and the availability of newer drugs have changed the treatment choices for multiple myeloma in recent years. Recent guidance from the European Society for Medical Oncology in 2008 and from the UK Myeloma Forum in 2009 does not include dexamethasone monotherapy as a treatment option for relapsed multiple myeloma.

Summary of comparative health economic evidence

The manufacturer presented a lifetime cost-utility analysis of lenalidomide plus high dose dexamethasone (HDD) to HDD alone. This comparator seemed reasonable given the recent SMC decision on the use of bortezomib following first relapse and variation in treatment at this later stage of disease. The patient group of interest was multiple myeloma patients who had received at least two prior lines of therapy. A discrete event simulation model was used

based on patient level data from the pivotal trials, sampling patients who would have the characteristics of patients who were the subject of the economic model. The model structure dealt with the time periods from treatment initiation to progression and then an extrapolation to estimate the period of survival post-progression. As crossover occurred for patients in the HDD arm of the trial the manufacturer used an estimate of the median overall survival seen in the MRC multiple myeloma trials to help estimate the likely survival for HDD patients.

Utility values were taken from a published study, but assumed a relatively flat structure across the responder categories i.e. a value of 0.81 for complete responders as well as for partial responders and patients with stable disease. Disutilities were also included to account for adverse events. Costing was comprehensively covered, based on the findings from a survey of Scottish clinicians, and included costs for tests and procedures to monitor patients, costs of disease management and costs of adverse events.

The results showed an incremental cost of £62,401 and incremental QALYs of 1.82 to give an incremental cost per QALY of £34,286. In the range of sensitivity analysis that was provided, the ICER was most sensitive to the use of Scottish test and procedure costs instead of NHS reference costs. When Scottish costs were used the ICER rose to £41,381.

There were a number of limitations with the analysis, principally concerning the survival benefits predicted by the analysis:

- The model estimated a fairly large survival gain for lenalidomide at this stage of treatment. However, there was uncertainty in the survival benefit caused by the need for extrapolation and also to adjust survival in the HDD arm for the cross-over that occurred in the trials. Only limited testing was carried out on the outcomes of the model but sensitivity analysis using the 95% confidence intervals for overall survival showed that the ICERs could rise by around 14% when the lower limit was used.
- Use of the median rather than mean survival in the calibration of the HDD survival estimate, when it has been suggested by other health technology assessment agencies that the mean survival estimate would have been the correct one to use. While the manufacturer argues that median values were appropriate, the use of the mean has been shown to substantially increase the ICERs, thereby highlighting the impact of uncertainty with the survival estimates derived.

Although there were some limitations in the economic analysis in terms of the likely estimate of overall benefit, the economic case was considered to be demonstrated when the SMC modifiers, in particular those relating to medicines for orphan diseases and the anticipated survival benefit associated with lenalidomide, were applied.

Summary of patient and public involvement

A Patient Interest Group Submission was received from Myeloma UK.

Additional information: guidelines and protocols

The European Society for Medical Oncology published guidance entitled "Multiple Myeloma: Clinical Recommendations for diagnosis, treatment and follow-up" in 2008. It notes that regimens similar to those used initially can induce a second remission. Vincristine, doxorubicin and high-dose dexamethasone (VAD) is no longer considered the standard option for patients in relapse. Thalidomide is mostly used in combination with dexamethasone and/or chemotherapy. (However, it should be noted that in the UK thalidomide is only indicated for first-line therapy). Bortezomib is used either alone or in combination with dexamethasone or with chemotherapy. (It should be noted that bortezomib is licensed in the UK as monotherapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation; and in combination with melphalan and prednisone it is licensed for the treatment of patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with bone marrow transplant).

A recently completed randomised trial shows that bortezomib in combination with pegylated liposomal doxorubicin is superior to bortezomib alone. Lenalidomide has just been approved in Europe for the treatment of relapsed multiple myeloma (in combination with dexamethasone).

The UK Myeloma Forum published a position statement on the use of lenalidomide in multiple myeloma in 2009. It states that the forum believe that lenalidomide in combination with dexamethasone should be available for prescription by UK haematologists according to its licensed indication in patients with relapsed myeloma.

The UK Myeloma Forum, Nordic Myeloma Study Group and British Committee for Standards in Haematology published joint guidelines on the diagnosis and management of multiple myeloma in 2005. These predate the licensing of lenalidomide and other new drugs for multiple myeloma.

Additional information: comparators

Advances in research and the availability of newer drugs have changed the treatment choices for multiple myeloma in recent years. Thalidomide based regimens may be used first-line and bortezomib monotherapy is often used second-line. Regimens similar to those used initially may induce a second remission. Choice of treatment is influenced by the age and performance status of the patient, length of response to previous therapy, relapse after response versus primary refractory disease and initial course of disease management. Vincristine, doxorubicin and high-dose dexamethasone (VAD) is no longer considered the standard option for patients in relapse. Pegylated liposomal doxorubicin (Caelyx®) is not recommended for use within NHS Scotland for multiple myeloma. Treatments at various stages of multiple myeloma include cyclophosphamide, melphalan, dexamethasone, prednisolone, bortezomib or thalidomide based regimens. Treatment options for patients who relapse after two prior therapies are limited.

Cost of relevant comparators

Drug	Dose regimen	Length of cycle	Cost per cycle (£)
Lenalidomide **Dexamethasone**	**25mg orally on days 1- 21** **40mg orally on days 1- 4, 9 - 12, 17-20**	**28 days**	**4,389[#]**
Bortezomib	1.3mg/m^2 iv on days 1,4,8,11	21 days	3,050
Cyclophosphamide[A] Vincristine Doxorubicin Dexamethasone	500mg orally or iv on days 1,8,15 0.4mg iv on days 1-4 9mg/m^2 iv on days 1-4 40mg orally on days 1-4 and 12-15	21 days	(221) to 231
Cyclophosphamide	300 to 500mg/m^2 orally or iv on day 1	7 days	5 to 30*
Dexamethasone monotherapy	40mg orally on days 1-4, 9-12, 17-20	28 or 35 days	21
Melphalan Prednisolone	7mg/m^2 orally on days 1-4 40mg po Day 1-4	28 days	14

Doses are for general comparison and do not imply therapeutic equivalence. Costs from evadis on 18.01.10 and British National formulary 58, September 2009. A=CVAD regimen, based on Medical Research Council Myeloma IX protocol. Costs based on 1.8m^2 body surface area. [#] Lenalidomide treatment is continued until disease progression or unacceptable toxicity and annual cost up to £57,057 * Cyclophosphamide monotherapy costs calculated for 4 weeks (4 cycles). iv=intravenous

Additional information: budget impact

The manufacturer estimated the net drug budget impact as £862k in year one rising to £2.72m by year five, taking account of dose interruptions and dose reductions based on clinical trial data. Accounting for the costs of monitoring, adverse event and medical management costs in addition to the drug costs, the impacts rose to £920k and £2.92m respectively.

The number of eligible patients was estimated at 234 in year one and 370 in year five. Uptake was estimated at 10% in year one rising to 50% in year five to give 23 patients starting treatment in year one and 51 patients starting treatment in year five. These figures may be an underestimate as in practice the rate of uptake may be higher.

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.

This assessment is based on data submitted by the applicant company up to and including **14 March 2010.**

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. 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.

The undernoted references were supplied with the submission.

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European Medicines Agency (EMEA). European public assessment report: lenalidomide (Revlimid®). 12/01/2010, EMEA H-C-717. www.emea.europa.eu

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Stadtmauer EA, Weber DM, Niesvizky R et al. Lenalidomide in combination with dexamethasone at first relapse in comparison with its use as later salvage therapy in relapsed or refractory multiple myeloma. Eur J Haematol 2009; 82: 426–432.