Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

lenalidomide 2.5mg, 5mg, and , 10mg, hard capsules (Revlimid®)

SMC No. (942/14)

Celgene Ltd

07 February 2014

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

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

Indication under review: for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Lenalidomide therapy significantly increased the proportion of patients achieving sustained red blood cell transfusion independence compared with best supportive care. However, there was no significant improvement in overall survival.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

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Indication

For the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate.

Dosing Information

Lenalidomide treatment must not be started if the absolute neutrophil counts (ANC) $<0.5 \times 10^9$/L and/or platelet counts $<25 \times 10^9$/L. The recommended starting dose of lenalidomide is 10mg orally once daily on days 1 to 21 of repeated 28 day cycles. Dosing is continued or modified based upon clinical and laboratory findings. The summary of product characteristics (SPC) presents details of recommended dose adjustments during treatment and restart of treatment.

Patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 1g/dL rise in haemoglobin, should discontinue lenalidomide treatment.

The capsules should be swallowed whole, preferably with water, with or without food and at about the same time each day.

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

Product availability date

Designated orphan medicine for treatment of MDS. June 2013, with the exception of the 2.5mg capsule which is expected to become available in quarter 1 2014.

Summary of evidence on comparative efficacy

Myelodysplastic syndromes (MDS) are a heterogeneous group of rare and life-threatening haematological disorders characterised by progressive cytopenias, complications of infection and bleeding and a risk of progression to acute myeloid leukaemia (AML). The disease affects 3 to 4 per 100,000 per year of the general population with the incidence increasing with age, particularly in those greater than 60 years, to reach an incidence of up to 50 per 100,000 per year. The most commonly occurring cytogenetic abnormality in MDS is partial or complete deletion of the long arm of chromosome 5 (deletion 5q) which is documented in 10 to 15% of MDS patients. The majority of MDS patients require red blood cell (RBC) transfusions and this dependency is often severe in patients with deletion 5q cytogenetic abnormality.[1]

Lenalidomide, an analogue of thalidomide, is an immunomodulating agent with a number of mechanisms of action including anti-neoplastic, anti-angiogenic, pro-erythropoietic effects with immunomodulatory properties. Lenalidomide has been designated an orphan medicine for the treatment of MDS.[1]

The key comparative evidence to support the use of lenalidomide in the treatment of MDS comes from the results of one double-blind, placebo-controlled, randomised, phase III study (MDS-004).[2] The study comprised two phases: a double-blind treatment phase and an open-label extension phase. Eligible patients were aged ≥18 years, with RBC transfusion-dependent patients (no consecutive 8 weeks without RBC tranfusions within the 16 weeks before randomisation) and investigator-documented International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS with deletion 5q with or without additional cytogenetic abnormalities. Patients were randomised to receive lenalidomide 10mg/day on days 1 to 21 of a 28 day cycle (n=69); lenalidomide 5mg/day on days 1 to 28 of a 28 day cycle (n=69) or placebo on days 1 to 28 of a 28 day cycle (n=67). Randomisation was stratified by IPSS karyotype score (i.e. isolated deletion 5q versus deletion 5q plus ≥ one additional cytogenetic abnormality).[1,2] At week 16, all patients were assessed for at least a minor erythroid response (≥50% decrease in transfusion requirements from baseline) and, if achieved, double-blind treatment could continue for up to 52 weeks or until erythroid relapse, disease progression or unacceptable toxicity. If not achieved, patients could cross-over to open-label treatment with lenalidomide 5mg (from placebo) or 10mg (from 5mg) daily. Patients completing the double-blind treatment phase without disease progression or erythroid relapse were unblinded and could continue open-label treatment at their current lenalidomide dose for up to week 156 unless a minor erythroid response was not achieved within 16 weeks of open-label treatment. During the study, granulocyte colony-stimulating factors (G-CSF) and granulocyte-macrophage colony-stimulating factors (GM-CSF) were allowed for neutropenia but erythropoiesis-stimulating agents (ESA) and chemotherapy were not allowed.

The primary outcome was RBC-transfusion independence (RBC-TI) for ≥26 weeks in the modified intention to treat (mITT) population (defined as patients who had taken ≥one dose of study drug with a centrally confirmed diagnosis of IPSS low or intermediate-1 risk MDS and del 5q cytogenetic abnormality and RBC transfusion-dependent anaemia). This was achieved in 56% (23/41) lenalidomide 10mg patients, 43% (20/47) lenalidomide 5mg patients and 5.9% (3/51) placebo patients ($p<0.001$ for both comparisons of lenalidomide versus placebo). Results were similar in the ITT population: 55% (38/69) lenalidomide 10mg, 35% (24/69) lenalidomide 5mg and 6.0% (4/67) placebo patients. [1,2] In those who responded (RBC-TI ≥26 weeks), the median times to response were 4.3, 3.0 and 0.3 weeks respectively.[1] The median durations of RBC-TI were not reached in any of the treatment groups but Kaplan Meier estimates suggest medians of ≥2 years in both lenalidomide groups and ≥1 year in the placebo group.[3] In patients from the mITT population who achieved a major erythroid response for ≥8 weeks, there were median increases in haemoglobin of 6.3g/dL, 5.2g/dL and 2.3g/dL in the lenalidomide 10mg, 5mg and placebo group respectively.[2,3]

After median follow-up of 36.9 months, 35.5 months and 35.9 months in the lenalidomide 10mg, 5mg and placebo groups respectively, the median durations of overall survival were 44.5 months, ≥35.5 months and 42.4 months respectively.[2]

After median follow-up of 36.1 months, 31.8 months and 30.9 months in the lenalidomide 10mg, 5mg and placebo groups respectively, AML progression occurred in 22% (15/69) lenalidomide 10mg patients, 23% (16/69) lenalidomide 5mg patients and 36% (4/11) placebo patients who did not crossover to lenalidomide and 30% (17/56) placebo patients who crossed over to lenalidomide 5mg of the ITT population. Results at a later cut-off date showed that progression to AML had occurred in 23% (16/69), 35% (24/69) and 39% (26/67) patients respectively in the lenalidomide 10mg, 5mg and placebo groups.[1]

Quality of life was assessed using the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) questionnaire at baseline and at weeks 12, 24, 36 and 48. In patients who achieved RBC-TI for ≥26 weeks, the absolute change from baseline was greater than the minimal clinically important difference (≥7 points) at each time point.[2]

A post-hoc analysis of the MDS-004 study estimated the 2-year rate of progression to AML in patients with IHC-p53 positivity (used as a surrogate for TP53 mutation) as 28% compared with 3.6% in patients with IHC-p53 negativity (p=0.0038). In patients with IHC-p53 positivity, a lower rate of progression to AML was observed in patients who achieved a RBC-TI response (11%) compared to non-responders (35%).[1,4]

A supporting, single-arm, open-label, phase II study (MDS-003) assessed the efficacy of lenalidomide in 148 RBC-transfusion dependent patients with low or intermediate-1 risk MDS with deletion 5q with or without additional cytogenetic abnormalities.[5] Patients were initially treated with lenalidomide 10mg daily on days 1 to 21 of a 28 day cycle (n=46) and subsequently with lenalidomide 10mg daily continuously (n=102). The primary outcome of RBC-TI (absence of any RBC transfusion during any consecutive 56 days during the treatment period accompanied by ≥1g/dL increase from baseline in haemoglobin) was achieved by 63% (59/94) patients in the mITT population and in 67% (99/148) of the ITT population by week 24.

A retrospective analysis compared lenalidomide-treated patients from studies MDS-003 and MDS-004 (n=295) with similar untreated MDS patients from a large multi-centre registry (n=125).[6] This found cumulative incidences of AML at 2-years of 6.9% and 12% in lenalidomide and untreated patients respectively, and at 5-years of 23% and 20% respectively. In the subgroup of patients with isolated deletion 5q, the respective cumulative incidences of AML were 6.6% versus 7.4% respectively at 2 years and 18% versus 17% respectively at 5 years. There was no significant difference between the groups in the risk of AML. Overall survival probabilities at 2 years were 90% and 74% and at 5 years were 54% versus 41% respectively. In the subgroup of patients with isolated deletion 5q, the respective overall survival probabilities were 94% versus 76% at 2 years and 60% versus 44% at 5 years.

Summary of evidence on comparative safety

In the placebo-controlled study (MDS-004) described above, at least one adverse event was reported in 100% (69/69) lenalidomide 10mg, 100% (69/69) lenalidomide 5mg and 96% (64/67) placebo patients. The majority of adverse events occurred within the first 16 weeks of treatment with lenalidomide. Grade 3 or 4 adverse events were reported in 94% (65/69), 90% (62/69) and 43% (29/67) of patients respectively. Serious adverse events were reported in 46% (32/69), 45% (31/69) and 21% (14/67) of patients respectively and discontinuation from double-blind treatment due to adverse events was reported in 8.7% (6/69), 17% (12/69) and 4.5% (3/67) of patients respectively.[2] The most frequently reported adverse events in the combined lenalidomide groups versus the placebo group were neutropenia (77% versus 18%), thrombocytopenia (46% versus 3.0%), diarrhoea (35% versus 18%), constipation (20% versus 7.5%), nausea (20% versus 9.0%), pruritus (25% versus 4.5%), rash (18% versus 1.5%), fatigue (18% versus 7.5%) and muscle spasm (17% versus 9.0%).[1]

In patients with MDS, lenalidomide was associated with a risk of venous thromboembolism (mainly deep vein thrombosis and pulmonary embolism) but to a lesser extent than in patients who had multiple myeloma. Due to an increase in second primary malignancies during lenalidomide studies in multiple myeloma, the risk should be considered before initiating lenalidomide treatment.[4]

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 patients of childbearing potential, unless the Pregnancy Prevention Programme is followed.

A post-authorisation safety study is to collect further safety data on progression to AML and associated risk factors.[2]

Summary of clinical effectiveness issues

The comparative study (MDS-004) described above, found that lenalidomide was superior to placebo in achieving RBC-TI for ≥26 weeks. This sustained independence was considered clinically relevant. However, a major limitation of the study methodology was that patients who failed to achieve at least a minor erythroid response at week 16 were allowed to crossover from placebo to lenalidomide 5mg (84% [56/67] patients) or from lenalidomide 5mg to lenalidomide 10mg (20% [14/69] patients). This early crossover confounds the results of the primary outcome, as well as longer term outcomes e.g. overall survival and progression to AML. The results found no significant difference between lenalidomide treatments and placebo in overall survival. An observational analysis at 6 months in patients treated with lenalidomide suggested a reduction in the risk of death and of progression to AML in those who achieved RBC-TI for ≥8 weeks versus those who did not. However there is uncertainty around whether this effect can be directly related to treatment with lenalidomide.

The overall study population (ITT) included a proportion of patients who did not meet the inclusion criteria of low or intermediate-1 risk MDS when reviewed centrally (66/205). Therefore the primary analysis was performed in the mITT population (n=139) for which the study was not sufficiently powered.[2] The licence specifies that lenalidomide is for patients with an isolated deletion 5q cytogenetic abnormality when other therapeutic options are insufficient or inadequate. The licence was restricted to use in patients with an isolated deletion 5q abnormality since these patients have a lower risk of progression to AML than patients with additional cytogenetic abnormalities. However, study patients could have deletion 5q with or without additional cytogenetic abnormalities. The proportion of study patients with an isolated deletion 5q cytogenetic abnormality was 66% (135/205) of ITT patients and 76% (106/139) of mITT patients.[1,2] Therefore the statistical power in the subgroup of patients reflecting the licensed population is greatly reduced. The submitting company has used results from the ITT population for the economic analysis since it was believed to more accurately reflect the patients likely to be treated in practice and increased the available data. The results found in the mITT and ITT populations were similar.

The introduction of lenalidomide would provide a licensed treatment option for patients with low or intermediate-1 risk MDS with an isolated deletion 5q cytogenetic abnormality and it is administered orally which is convenient for patients and the service. Clinical experts consulted by SMC considered that lenalidomide is a therapeutic advancement due to its effect on the disease process and that the place in therapy of lenalidomide would be according to its licence.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing lenalidomide with best supportive care (BSC). This was defined as in the main clinical study and mainly consisted of blood transfusion, with chelation as required. A Markov model was used with health states of transfusion dependent, transfusion independent, AML and death and used data from the ITT population. The time horizon was 20 years (age at start of treatment was 67) and the perspective was NHS plus social services.

Data from the main clinical study were used to estimate the following:

- The response rate, reflecting the movement from transfusion dependent to transfusion independent
- The rate of development of AML
- The rate of mortality

In addition, a published study was used to estimate mortality specifically from AML.

A potentially conservative feature was that there were insufficient responders in the BSC arm to use as a basis for extrapolation so the lenalidomide 5mg arm was used instead. This means that the net effect of the 10mg dose of lenalidomide was compared to the 5mg dose, not to BSC as would be appropriate, so any effect of the 5mg dose versus placebo reduces the effect size of the 10mg dose in the economic model.

Utility values for quality of life were taken from a variety of published sources, with key values for transfusion dependence of 0.65 and transfusion independence of 0.85 taken from a time trade-off study of patients with MDS. The costs included medicines and monitoring costs. Blood transfusion and chelation rates were taken from the main clinical study. Costs and disutilities were included from complications such as the development of heart disease, diabetes and hepatic injury.

A patient access scheme (PAS) was proposed by the submitting company. The PAS was not accepted by the Patient Access Scheme Assessment Group (PASAG) therefore the cost-effectiveness estimates based on the PAS were not considered by SMC as part of the economic case.

Without the PAS, lenalidomide cost an additional £51,082, and yielded an additional 0.88 QALYs (3.38 versus 2.49). The life year gain was 1.15 (5.61 versus 4.47). The net cost per QALY gained was £57,930. The model predicted that, on average, a patient would have better quality of life for 0.4 years (utility 0.85 rather than 0.65) and an extra 1.1 years of life when they would otherwise have been dead at a quality of life of 0.85.

In the submitted sensitivity analysis, potentially important variables resulting in upward uncertainty in the without PAS analysis were:

- the utility value for patients who are transfusion independent; the cost per QALY increased up to £64k when a utility value of 0.79 was used;
- the response rate for patients who are transfusion independent on lenalidomide - the cost per QALY increased to £63k; and
- the proportion of patients experiencing a second dose interruption - the cost per QALY increased to £61k when the value reduced to 63% from a base case value of 73%.

The results showed very little sensitivity to changes made to parameters such as response duration, progression to AML or non-AML mortality.

The submitting company responded to a number of requests for clarification and provided extra analysis to show the impact of using a shorter time horizon of 10 years. This increased the cost per QALY slightly to £58,024.

In addition to the comparatively high base case cost-effectiveness ratio, the main issues and limitations with the analysis were as follows:

- As noted above, the sensitivity analysis showed that the result was relatively stable when a range of key parameters were changed e.g. progression to AML. The company asserted that this was due to the majority of patients in the model having died before differences in the rates of AML progression occurred.
- The analysis used the whole ITT population rather than the licensed patient group. The company has argued that the cost-effectiveness would be similar between the two groups and subsequently provided the results in this group. The ICER fell to £55,677.
- There was crossover in the main clinical study which was not accounted for in the analysis and may introduce some uncertainty in the results.

SMC considered the likely range of cost-effectiveness ratios for lenalidomide in this setting and the remaining uncertainties in the economic case. The committee considered the benefits of lenalidomide in the context of the SMC decision modifiers and agreed that the criterion for a substantial improvement in quality of life in the patient population in the submission was satisfied. Although there were some limitations in the economic analysis, the committee agreed that the relatively high cost per QALY was acceptable given the expected benefits of the treatment and in the context of the decision modifiers and the orphan status of the medicine.

Summary of patient and public involvement

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

- A joint submission was received from the MDS UK Patient Support Group which is a registered UK charity and the Leukaemia CARE society which is a registered Scottish and UK charity.

- Both Patient Information Groups have received funding from several pharmaceutical companies in the past two years.

- Patients suffering from myelodysplastic syndromes (MDS) can have a limited survival time with few treatment options. The main symptoms include extreme fatigue and breathlessness. Neutropenia and the risk of developing infections can be complications of MDS. Other symptoms include anxiety and depression.

- Some patients require transfusions which can be tiring and time consuming and affect a patient's ability to continue working. There can be additional complications of transfusions including the need for iron chelation treatment. Transfusion dependent patients need more frequent help with day to day activities and living independently can be more difficult.

- Additional benefits of lenalidomide include the potential for fewer hospital visits as it is given orally and does not require injections.

- Detailed testimonies of the impact of MDS on patients, carers and families, as evidenced by statements of patients and family experiences were included in the submission.

Additional information: guidelines and protocols

The British Committee for Standards in Haematology published guidelines for the diagnosis and management of adult myelodysplastic syndromes in December 2013.[7] This states that:

- "Patients with IPSS low or intermediate-1 MDS with del(5q), symptomatic anaemia and who fulfil the criteria for a high or intermediate predictive score for response, should be first considered for a trial of therapy with ESAs.
- For transfusion dependent patients unsuitable for a trial of ESA, or for non-responders / patients losing their response to ESA, who have IPSS low or intermediate-1 MDS with del(5q), consider treatment with lenalidomide 10 mg daily for 21 days repeated every 28 days. A careful discussion with patients about the risk and benefit is mandatory.
- Selected MDS patients with del(5q) and IPSS low or intermediate-1 may be candidates for allogeneic stem cell transplantation. These include lenalidomide-treated patients who fail to achieve transfusion independence, those losing their response, or patients with transfusion dependence not considered suitable for lenalidomide.
- Lenalidomide is not currently recommended for patients with del(5q) and bone marrow blasts >5%, multiple (complex) cytogenetic abnormalities in addition to del(5q), patients with IPSS intermediate-2/High or with a known mutated *TP53* gene."

The National Comprehensive Cancer Network (NCCN) published "Myelodysplastic syndromes. Clinical practice guidelines in oncology" and an updated version (2.2014) published in May 2013 is available on their website.[8] This guideline states that patients with IPSS low or intermediate-1 MDS with del(5q) ± other cytogenetic abnormalities should receive lenalidomide. An alternative approach to lenalidomide in patients with del(5q) and symptomatic anaemia may be an initial trial of erythropoietic stimulating agents in cases where serum erythropoietin levels are ≤500mU/mL.

Additional information: comparators

There are no other medicines licensed for the treatment of low to intermediate-1 risk MDS. Therefore the most relevant comparator for lenalidomide is best supportive care, comprising RBC transfusions, iron chelation and possibly erythropoiesis stimulating agents. Azacitidine is indicated for treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with intermediate-2 and high-risk myelodysplastic syndrome (MDS) and therefore not an appropriate comparator.

Cost of relevant comparators

Drug	Dose Regimen	Cost per cycle (£)	Cost per year (£)
Lenalidomide	**10mg daily on days 1 to 21 of a 28 day cycle**	**3,780**	**49,140**

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eMIMs on 4 December 2013.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 4 in year 1 rising to 15 patients being treated in year 5. The gross impact on the medicines budget was estimated to be £114k in year 1 and £171k in year 5. These estimates take account of new patients starting treatment in years 2 to 5 (4 in year 2, 3 in year 3 and 2 in years 4 and 5) plus treatment discontinuations and mortality in the cohort over time. As no other drugs were assumed to be displaced, this is also the net medicines budget impact. Transfusions and chelation may be avoided but these are not easy to convert into cash terms.

References

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

1. European Medicines Agency, European Public Assessment Report for Revlimid® EMEA/H/C/000717/II/0056 25 April 2013. www.ema.europa.eu [accessed 9 October 2013]

2. Fenaux P, Giagounidis A, Selleslag D et al. A randomised phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del5q. Blood 2011;118:3765-76.

3. Celgene Ltd. A multicenter, randomized, double-blind, placebo-controlled, 3-arm study of the efficacy and safety of 2 doses of lenalidomide versus placebo in red blood cell (RBC) transfusion-dependent subjects with low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion (del) 5q[31] cytogenetic abnormality. (Clinical Study Report; CC-5013-MDS-004). 20 October 2010.

4. Celgene Ltd. Revlimid® summary of product characteristics 27 June 2013.

5. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355:1456-65.

6. Kuendgen A, Lauseker M, List AF, et al. Lenalidomide does not increase AML progression risk in RBC transfusion-dependent patients with Low- or Intermediate-1-risk MDS with del(5q): a comparative analysis. Leukemia. 2013;27:1072-79.

7. British Committee for Standards in Haematology. Guidelines for the diagnosis and management of adult myelodysplastic syndromes. www.bcshguidelines.com [accessed 9 December 2013]

8. National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology: Myelodysplastic syndromes version 2.2014 www.nccn.org [accessed 25 November 2013].

This assessment is based on data submitted by the applicant company up to and including 10 January 2014.

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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug 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 NHS Scotland 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 NHS Scotland 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.