

## Lenalidomide (for myelodysplastic syndrome)

### Product:

LENALIDOMIDE (Revlimid®)  
5mg, 10mg capsules

### Class of drugs:

Immunomodulatory/anti-neoplastic agent

### Indication:

Treatment of anemia due to myelodysplastic syndrome

### Manufacturer:

Celgene

## CED Recommendation

The CED recommended that lenalidomide (Revlimid) not be funded unless the price was reduced. The CED noted that current evidence for the use of lenalidomide (Revlimid) in the treatment of myelodysplastic syndrome is promising but further data is required to fully determine its clinical benefit and value for money. The CED also indicated that if funding were to be considered, eligibility should be clearly limited to patients who will most likely benefit from treatment.

## Executive Officer Decision

Based on the CED's recommendation and a subsequent listing agreement, the Executive Officer decided to fund lenalidomide (Revlimid) through the Exceptional Access Program according to specific criteria.

## Status

Funding available through the Ontario Public Drug Programs via the Exceptional Access Program.

### Highlights of Recommendation:

- ◆ Lenalidomide (Revlimid) is an oral treatment for patients who require ongoing blood transfusions for anemia as a result of myelodysplastic syndrome (MDS), a bone marrow disorder.
- ◆ More specifically, lenalidomide (Revlimid) is indicated in patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS that is associated with a particular genetic mutation called 5q deletion.
- ◆ There is some preliminary evidence to support the efficacy of lenalidomide (Revlimid) in the management of MDS, but confirmatory data is needed. Two small, single-arm open-label studies reported that lenalidomide (Revlimid) decreases the need for blood transfusions. A better quality study is underway and is expected to provide further information on the efficacy and safety of lenalidomide (Revlimid) in the management of MDS.
- ◆ The Committee recognized that regular, ongoing blood transfusions could adversely affect patients' quality of life and that available data, although incomplete, support that lenalidomide (Revlimid) reduces the need for transfusions.
- ◆ It was also noted that current treatment options for MDS are limited and lenalidomide (Revlimid) is targeted to a small number of patients with lower risk disease associated with 5q deletion.
- ◆ In terms of side effects, lenalidomide (Revlimid) is associated with high rates of neutropenia (low white cell count) and thrombocytopenia (low platelet count).
- ◆ Lenalidomide (Revlimid) costs \$361 per day, at a dose of 10mg daily. Because its clinical value has not been firmly established, the Committee indicated that the high cost of treatment could not be justified.
- ◆ **Overall, the Committee noted that current evidence for the use of lenalidomide (Revlimid) in patients with MDS is promising, but further data is required to fully determine its clinical benefit and value for money.**

### Background:

Myelodysplastic syndrome (MDS) is a group of disorders that affect the ability of the bone marrow to produce healthy, mature red blood cells, white blood cells, and platelets. MDS primarily affects older patients, with approximately 80 to 90% of cases diagnosed in patients over the age of 60.

The course of the disease is chronic in a majority of cases, with patients experiencing gradual worsening of the disease. Approximately one-third of patients with MDS progress to develop acute myelogenous leukemia (AML), a type of cancer of the blood and bone marrow.

There are various subtypes of MDS. A rare subtype is characterized by a unique genetic mutation, called 5q-deletion. MDS patients with 5q-deletion have a tendency to develop refractory anemia and a greater need for transfusion of blood products.

Patients with MDS are further separated into low-, intermediate-, or high-risk groups, depending upon the number of abnormal immature blood cells that are seen, the characteristics of the abnormality, and how the disease is affecting the normal number of healthy blood cells. In low-risk MDS, the disease develops slowly. In patients with high-risk disease, the bone marrow is more widely affected and the disease can progress more quickly to AML.

The only proven cure for MDS is stem cell transplantation; however, this is generally offered to a small number of patients, usually those who are younger and have high-risk disease. Most patients rely on supportive treatments aimed at improving symptoms and quality of life. MDS patients often require regular red blood cell transfusions to help them with fatigue and anemia. Erythropoietin, a drug used to stimulate the production of red blood cells, may also be used to reduce the number of blood transfusions in some patients.

Lenalidomide (Revlimid) is only available through a controlled distribution program called RevAid. Only prescribers and pharmacists registered with this program are able to prescribe and dispense lenalidomide (Revlimid). In addition, patients must be registered and meet all the conditions of the program in order to receive the product.

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## Detailed Discussion:

- ◆ The Committee considered the funding of lenalidomide (Revlimid) for the treatment of MDS on two occasions, initially in April 2008 and again in October 2008.
- ◆ Lenalidomide (Revlimid) for the treatment of MDS was approved by Health Canada on the basis of a Notice of Compliance with conditions (NOC/c). Approval was based on a surrogate marker of transfusion independence and is conditional upon the manufacturer completing additional clinical trials to verify clinical benefit.
- ◆ Current evidence for the use of lenalidomide (Revlimid) in MDS comes from two small, open-label, single-arm trials. (*Open-label, single-arm studies are not as rigorous as double-blind, randomized controlled trials. Please see glossary for details: [http://www.health.gov.on.ca/english/providers/program/drugs/dr\\_glossary/glossary\\_mn.html](http://www.health.gov.on.ca/english/providers/program/drugs/dr_glossary/glossary_mn.html).)*)
- ◆ The two studies reported that a significant number of MDS patients with 5q-deletion taking lenalidomide (Revlimid) achieved transfusion independence (defined as not requiring red blood cell transfusions for any consecutive 56-day period).
- ◆ In the main study, 148 transfusion-dependent patients with low- or intermediate-1-risk MDS associated with a 5q-deletion abnormality were treated with either lenalidomide (Revlimid) 10mg daily or a cyclic regimen of 10mg daily for 21 days and 7 days off treatment, for 24 weeks. The study reported that, of the 148 patients who received lenalidomide (Revlimid), 112 (76%) had a hematologic response (a reduction in transfusion requirements), 99 (67%) achieved transfusion independence. Of the 85 patients who could be evaluated for cytogenetic response (reduction in the number of abnormal bone marrow cells), 38 (45%) had complete cytogenetic remission and 24 patients (28%) had a partial cytogenetic response.
- ◆ One of the major limitations to the studies was that there was no control group (a group of patients who are given no treatment, for comparison purposes, to determine whether it was the drug that caused the observed effect).
- ◆ Given the lack of a control group in the studies and the short duration of the trials, it is unknown whether lenalidomide (Revlimid) impacts survival or progression of the disease to AML.
- ◆ Because there were no placebo controlled arms in the studies, the side effect of lenalidomide (Revlimid) could not be fully characterized. The studies reported that a very high percentage of patients on lenalidomide (Revlimid) experienced severe neutropenia and thrombocytopenia, necessitating a dosage reduction or delay.
- ◆ There are data to suggest that MDS patients with 5q-deletion may be more sensitive to the side effects of lenalidomide (Revlimid); therefore, lower doses may be required in this patient population.
- ◆ The Committee indicated that data on the optimal dose and duration of treatment, as well as long-term efficacy and safety are required to establish the therapeutic role of lenalidomide (Revlimid) in the treatment of MDS. A randomized controlled trial is currently underway. This study may provide some of the required information to better assess the clinical value of treatment.
- ◆ The Committee did however acknowledge that transfusion dependence is associated with poor quality of life and that lenalidomide (Revlimid) has been shown to provide hematologic and cytogenetic response, important clinical improvements.
- ◆ At the currently recommended dose of 10mg daily, lenalidomide (Revlimid) costs \$361 per day. The high cost of treatment could not be justified largely because the clinical value remains uncertain.
- ◆ Overall, the Committee noted that current evidence for the use of lenalidomide (Revlimid) in patients with MDS is promising but that further data is required to fully determine its clinical benefit and value for money. The Committee indicated that if funding were to be considered, eligibility should be clearly limited to patients who will most likely benefit from treatment.
- ◆ The CED worked jointly with a subcommittee involving cancer experts to review this cancer drug, as is done for all other cancer drug treatments.

## EAP Criteria:

Funding for lenalidomide (Revlimid) is considered through the Exceptional Access Program (EAP) for patients who meet all of the following clinical criteria:

- *Demonstrated diagnosis of MDS on bone marrow aspiration*
- *Presence of 5-q deletion documented by standard cytogenetic or fluorescence in situ hybridization*
- *International Prognostic Scoring System (IPSS) risk category low or intermediate-1*
- *Presence of symptomatic anemia (defined as transfusion-dependent)\**

*\*Requests for patients who are NOT transfusion-dependent will be considered on a case-by-case basis. The physician should provide clinical evidence of symptomatic anemia affecting the patient's quality of life and the rationale for why transfusions are not being used.*

### Renewals

For patients who were transfusion-dependent:

- *Demonstration of at least a 50% reduction in transfusion requirements (a transfusion record both pre- and post-lenalidomide should be provided).*

*Renewal requests for all other patients will be considered on a case-by-case basis. The following documentation should be provided: serial CBC (pre- and post-lenalidomide) and any other objective evidence of response.*



Ministry of  
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