

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
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Medication Policy Manual

Policy No: dru127

Topic: Revlimid[®], lenalidomide

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Next Review Date: July 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Lenalidomide (Revlimid[®]), a derivative of thalidomide, is used in the treatment of patients with transfusion-dependent anemia resulting from myelodysplastic syndrome (MDS) or for patients with multiple myeloma.

Policy/Criteria

I. Most contracts require prior authorization approval of lenalidomide prior to coverage. Lenalidomide may be considered medically necessary when the following criteria are met:

A. A diagnosis of myelodysplastic syndrome (MDS) when criteria 1, 2, and 3 below are met:

1. The patient is transfusion-dependent (defined as administration of 2 or more units of red blood cells [RBCs] in the previous 8 weeks).

AND

2. The patient has an absolute neutrophil count (ANC) of at least 500 cells/mm³.

AND

3. The patient has a platelet count of at least 50,000/mm³.

OR

B. A diagnosis of multiple myeloma (MM) when criteria 1, 2, and 3 below are met:

1. Lenalidomide is used in combination with a corticosteroid such as dexamethasone (unless documentation is provided that a corticosteroid is not tolerated).

AND

2. The patient has an absolute neutrophil count (ANC) of at least 1,000 cells/mm³.

AND

3. The patient has a platelet count of at least 30,000/mm³.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence considers lenalidomide to be a self-administered medication.

B. When prior authorization is approved, lenalidomide may be authorized in quantities of up to thirty capsules (any combination of 5 mg, 10 mg, 15 mg, or 25 mg dosage strengths) per month.

C. Authorization periods are defined as follows:

1. Myelodysplastic syndrome (MDS):

Initial authorization: Initial authorization shall be for up to three months when criteria are met.

Continuing authorization: Continuing authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and the medication is effective in significantly decreasing the number of red blood cell transfusions (RBCs) required.

2. Multiple myeloma (MM):

Authorization shall be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

III. Lenalidomide is considered investigational when used in combination with bortezomib (Velcade).

IV. Lenalidomide is considered investigational when used for all other conditions, including but not limited to:

- A.** Chronic lymphocytic leukemia (CLL).
- B.** Crohn's disease.
- C.** Malignant melanoma.
- D.** Metastatic prostate cancer.
- E.** Metastatic renal cell carcinoma (RCC).
- F.** Non-Hodgkin's Lymphoma (NHL).
- G.** Solid tumors.

Position Statement

Summary

- Lenalidomide is used:
 - * For treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. ^[4]
 - * In combination with dexamethasone for the treatment of multiple myeloma (MM) in patients who have received at least one prior therapy. ^[4]
- The efficacy of lenalidomide in MDS was evaluated based on its ability to decrease the need for RBC transfusions in patients with low- to intermediate-1 risk disease.
- In MM, lenalidomide plus dexamethasone was observed to decrease the time to progression of disease when compared with dexamethasone alone.
- Patients with ANC and platelet levels below prespecified limits were not included in clinical trials because of the potential for lenalidomide to further lower these counts putting patients at risk for life-threatening infections and bleeding.
- Lenalidomide has not been proven to be effective for other types of cancer.

Clinical Efficacy in Myelodysplastic Syndrome (MDS)

- Some patients with MDS have anemia that requires red blood cell (RBC) transfusions.
- Chronic RBC transfusions can lead to iron overload and other clinical complications.
- Lenalidomide is used in MDS to eliminate the need for RBC transfusions.
- Lenalidomide has not been shown to provide any other benefit(s) in this population.
- In an unreliable clinical trial, 63% of patients with MDS 5q- syndrome who were treated with lenalidomide 10 mg daily achieved transfusion independence. ^[2, 4, 9] Transfusion independence was defined as absence of transfusions with RBCs during any consecutive "rolling" 56 days during the treatment period.
 - * The trial is of open-label, single arm design (no placebo or active control).

- * Patients had transfusion-dependent anemia (received 2 or more units of RBCs within 8 weeks of study treatment).
- * Patients were excluded for the following lab abnormalities:
 - absolute neutrophil count (ANC) < 500/mm³
 - AST or ALT > 3 times upper limit of normal
 - serum creatinine > 2.5 mg/dl
 - platelet count < 50,000/mm³
 - serum direct bilirubin > 2.0 mg/dl
- * Hematopoietic growth factors (e.g., filgrastim [Neupogen[®]], epoetin alfa [Procrit[®]]) were not allowed within 7 days of the first lenalidomide dose.
- * Only 96 (64.9%) of the 148 patients enrolled in the trial were evaluated for the endpoint, which greatly compromises the quality of the results. However, if a patient experiences transfusion independence on lenalidomide, this “all or none response” is a good indication that it is working.
- The National Comprehensive Cancer Network (NCCN) MDS treatment guideline supports the use of lenalidomide in patients with transfusion dependence who have MDS with deletion 5q genetic abnormalities based on the evidence from this trial and expert consensus.^[3]

Clinical Efficacy in Multiple Myeloma (MM)

- Primary induction in MM is based on whether a patient is a candidate for a bone marrow transplant. Some combinations of medications are more toxic to the bone marrow and may make harvest of viable cells more difficult.^[8]
- Primary induction therapy for transplant candidates may include:^[8]
 - * lenalidomide/dexamethasone
 - * bortezomib/dexamethasone
 - * bortezomib/doxorubicin/dexamethasone
 - * bortezomib/thalidomide/dexamethasone
- Primary induction therapy for non-transplant candidates may include:^[8]
 - * lenalidomide/low-dose dexamethasone
 - * melphalan/prednisone/bortezomib (MPB)
 - * melphalan/prednisolone/thalidomide (MPT)

- The goal of induction is to reduce the number of cancer cells before performing stem cell transplantation or beginning maintenance therapy.
- In two clinical trials using lenalidomide/dexamethasone in MM: ^[4, 15, 16]
 - * failure of at least one prior MM therapy was required before patients were eligible to receive lenalidomide.
 - * progression of disease was studied as the endpoint in the trials.
 - * the median time to progression was increased by approximately 17 weeks in the lenalidomide/dexamethasone group (versus dexamethasone alone).
- Two additional studies in the treatment of MM have investigated different doses of lenalidomide ^[10], as well as lenalidomide in combination with other chemotherapy agents ^[14].
- There is no evidence that therapy with lenalidomide/dexamethasone is superior to primary conventional MM therapy.
- The National Comprehensive Cancer Network (NCCN) MM treatment guideline lists lenalidomide (in combination with dexamethasone) as one of several treatment options for patients who have received at least one prior therapy based on these studies and expert consensus. ^[8]
- There is recent interest in adding lenalidomide to a combination of bortezomib and dexamethasone for induction prior to bone marrow transplant. Preliminary response rates from an ongoing, uncontrolled study in patients with relapsed/refractory MM look promising. ^[23] A larger, controlled, phase III ECOG study comparing bortezomib/dexamethasone with bortezomib/lenalidomide/dexamethasone is in progress to evaluate the safety and effectiveness of this combination. ^[24]

OTHER CANCERS

- There are small published clinical studies using lenalidomide in chronic lymphocytic leukemia (CLL) ^[11, 26], metastatic renal cell carcinoma ^[12, 27], non-Hodgkin's Lymphoma ^[25], and in combination with other agents in treatment-naïve patients with MM. ^[20-21] Well-controlled trials in larger numbers of patients are necessary to establish the safety and efficacy of lenalidomide in these cancers.
- There are ongoing studies of lenalidomide in metastatic prostate cancer, solid tumors, and other cancers ^[22]; however, it is too early to draw conclusions regarding its potential benefit in these populations.
- Two trials studying lenalidomide in malignant melanoma were halted early by an independent

data monitoring committee due to lack of benefit. ^[18] In addition, two small trials of lenalidomide in Crohn's disease and Waldenstrom's macroglobinemia did not demonstrate any benefit. ^[19, 28]

Safety

- Boxed warnings on lenalidomide package labeling include (1) potential for human birth defects, (2) hematologic toxicity, and (3) risk of deep venous thrombosis and pulmonary embolism.
 - * Lenalidomide is a thalidomide derivative and has all of the same warnings regarding pregnancy and potential for severe life-threatening birth defects. ^[4]
 - * Significant neutropenia and thrombocytopenia are associated with lenalidomide when used in the treatment of MDS. In clinical trials, 80% of patients required dose delays and reductions due to hematologic toxicity. ^[4]
 - * Product labeling warns of an increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients treated with lenalidomide based on observations from clinical trials that used a combination of lenalidomide and dexamethasone in the treatment of multiple myeloma. ^[4, 6]
- The risk of toxicity with lenalidomide is greater in patients with impaired renal function as the drug is extensively excreted by the kidneys. ^[4]
- A restricted distribution program (RevAssistSM) is in place to prevent accidental fetal exposure to lenalidomide. ^[7]

Dosing and Administration in Myelodysplastic Syndrome (MDS)

- The recommended starting (and maximum) dose of lenalidomide in MDS is 10 mg orally once-a-day. ^[4]
- Dosing in MDS is modified based on platelet and neutrophil counts. ^[4]
- When treating MDS, interruption of lenalidomide therapy is recommended when:
 - * The absolute neutrophil count (ANC) drops below 500 cells/mm³ to 750 cells/mm³ within 4 weeks of initiating therapy. ^[4]
 - * The platelet count drops below 30,000/mm³ to 50,000/mm³ within 4 weeks of the start of therapy. ^[4]

Dosing and Administration in Multiple Myeloma (MM)

- The usual dose of lenalidomide in MM is 25 mg orally daily given in conjunction with dexamethasone pulse therapy. ^[4]
- Sequential dose reductions to 15 mg daily, 10 mg daily, and 5 mg daily may be necessary if toxicity occurs. ^[4]
- When treating MM, interruption of lenalidomide therapy is recommended when then absolute neutrophil count drops below 1000 cells/mm³ or the platelet count drops below 30,000/mm³. ^[4]

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Cross References
None

Codes	Number	Description
HCPCS	J8499	Prescription drug, oral, non-chemotherapeutic, Not otherwise specified