



Medication Policy Manual

Policy No: dru127

Topic: Revlimid®, lenalidomide

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IMPORTANT REMINDER

This Medication 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 medication policy is to provide a guide to coverage. Medication 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 an orally administered medication used in the treatment of patients with transfusion-dependent anemia resulting from myelodysplastic syndrome (MDS) or for patients with multiple myeloma (MM).

Policy/Criteria

- I. Most contracts require prior authorization approval of lenalidomide prior to coverage. Lenalidomide may be considered medically necessary when criteria A, B, or C below are met:
- A. A diagnosis of myelodysplastic syndrome (MDS) when criteria 1 and 2 below are met:
1. The diagnosis has been established by a specialist in hematology or oncology.
- AND**
2. The patient is transfusion-dependent (defined as administration of 2 or more units of red blood cells [RBCs] in the previous 8 weeks).
- OR**
- B. A diagnosis of multiple myeloma (MM) when used in combination with a corticosteroid such as dexamethasone (unless used as maintenance or documentation is provided that a corticosteroid is contraindicated or is not tolerated).
- OR**
- C. A diagnosis of Mantle cell lymphoma (MCL) when criteria 1 and 2 below are met:
1. Prior treatment with bortezomib (Velcade) was ineffective or not tolerated.
- AND**
2. Prior treatment with at least one other therapy listed in *Appendix 1* for MCL has been ineffective, unless all are contraindicated or not tolerated.
- II. Administration, Quantity Limitations, and Authorization Period
- A. OmedaRx 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 2.5 mg, 5 mg, 10 mg, 15 mg, 20 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 may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

3. Mantle cell lymphoma (MCL): Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.
- III. Lenalidomide is considered not medically necessary for the treatment of the following conditions:
 - A. Metastatic castration-resistant prostate cancer
- IV. Lenalidomide is considered investigational when used for all other conditions, including but not limited to:
 - A. Acute myeloid leukemia (AML)
 - B. Chronic lymphocytic leukemia (CLL).
 - C. Colorectal cancer (CRC).
 - D. Crohn's disease.
 - E. Malignant melanoma.
 - F. Prostate cancer.
 - G. Metastatic renal cell carcinoma (RCC).
 - H. Non-Hodgkin's Lymphomas (NHLs), other than Mantle cell lymphoma (MCL).
 - I. Solid tumors.
 - J. Systemic light chain amyloidosis (AL) in the absence of multiple myeloma.
 - K. Myelofibrosis.
 - L. Waldenström's macroglobulinemia.

Position Statement

Summary

- Lenalidomide, an orally administered immunomodulator, has been found to be safe and effective when used in the treatment of transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS), for multiple myeloma (MM), and for Mantle cell lymphoma (MCL).
- 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. Evaluation of therapy after 3 months is prudent to assure that therapy is effective (the medication has resulted in a decreased need for blood transfusions) prior to continuation.
- In MM, lenalidomide in combination with dexamethasone was observed to decrease the time to progression of disease when compared with dexamethasone alone.
- After stem cell transplant, lenalidomide may be used alone as a maintenance therapy.
- 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.
- A durable tumor response to lenalidomide has been observed in patients with MCL. The usefulness of this data is limited due to a lack of comparator group in clinical trials.

- Lenalidomide has been found to be safe and effective at the following doses:
 - * MM: 25 mg orally daily.
 - * MDS: 10 mg orally once daily.
 - * MCL: 25 mg orally once daily on Days 1-21 of repeated 28-day cycles.
- Lenalidomide has not been proven to be effective for other types of cancer.

Clinical Efficacy

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. ^[1] 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. ^[2]

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. ^[3]

- Conventional primary induction therapy for transplant candidates may include lenalidomide/dexamethasone (Rd), bortezomib/dexamethasone (Vd), bortezomib/doxorubicin/dexamethasone, or bortezomib/thalidomide/dexamethasone (VTD). [3]
- Conventional primary induction therapy for non-transplant candidates may include lenalidomide/low-dose dexamethasone, melphalan/prednisone/bortezomib (MPB), melphalan/prednisone/lenalidomide (MPL), or melphalan/prednisone/thalidomide (MPT). [3]
- 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, 5]
 - * 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).
- Several additional studies in the treatment of MM have investigated different doses of lenalidomide, as well as lenalidomide in combination with other chemotherapy agents [6-8].
- 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. It may also be used as monotherapy after stem cell transplant. [3]

Mantle Cell Lymphoma (MCL)

- A single-arm, open-label trial evaluated the efficacy of lenalidomide in 134 patients with MCL who had relapsed after or were refractory to bortezomib or a bortezomib-containing regimen. [9]
 - * All included patients were required to have received prior treatment with an anthracycline or mitoxantrone, cyclophosphamide, rituximab, and bortezomib, alone or in combination.
 - * The efficacy endpoints evaluated were overall response rate (ORR) and duration of response. Thirty-four patients (26%) achieved ORR (9 complete responses, 25 partial responses) with a median duration of response of 16.6 months.
 - * The extent of benefit with lenalidomide in patients with MCL cannot be accurately estimated due to the absence of a control group.
- NCCN treatment guidelines for MCL recommend multi-drug chemotherapy regimens for induction therapy (Category 2A). Lenalidomide with or without rituximab is listed among many second-line treatment options for MCL (Category 2A). [108]
- It is unknown how the safety and efficacy of lenalidomide compare to other treatment options for MCL.
- One small Phase 2 trial (n=38) evaluated the efficacy of lenalidomide in combination with rituximab as initial therapy for MCL. [11] However, there is no evidence to establish efficacy relative to the other multi-drug first-line treatment options. Additional trials are needed.

OTHER CANCERS AND DISEASES

- There are small, poor quality published clinical studies using lenalidomide in chronic lymphocytic leukemia (CLL) [12-15], metastatic renal cell carcinoma (RCC) [16,17], other non-Hodgkin's Lymphomas [18-20], acute myeloid leukemia (AML) [21], prostate cancer [22], and myelofibrosis. [23,24] 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 solid tumors and other cancers [25]; however, it is too early to draw conclusions regarding its potential benefit in these populations.
- A randomized, double-blind, phase 3 study evaluated docetaxel plus either lenalidomide or placebo for the treatment of chemotherapy-naïve metastatic castration-resistant prostate cancer. After a median follow-up of 8 months, 129 had died in the lenalidomide group and 92 had died in the placebo group. Median overall survival was 17.7 months (95% CI 14.8 to 18.8) in the lenalidomide group and not reached in the placebo group (hazard ratio [HR] 1.53, 95% CI 1.17 to 2.00, p=0.0017). The trial was subsequently closed early due to futility. Rates of serious adverse events, including febrile neutropenia and pulmonary embolism, were also higher in the lenalidomide group compared to placebo. [26]
- Two trials studying lenalidomide in malignant melanoma were halted early by an independent data monitoring committee due to lack of benefit. [27-29] In addition, two small trials of lenalidomide in Crohn's disease and Waldenström's macroglobulinemia (WM) did not demonstrate any benefit. [30,31] A second small trial (n=17) in WM demonstrated some disease activity, but a low overall response rate (29%). Additional trials are needed. [32]
- A phase 2 open-label study evaluated lenalidomide in combination with cetuximab in KRAS-mutant metastatic colorectal cancer. This study was terminated early due to lack of efficacy. [33]
- One small Phase 2 trial (n=28) evaluated lenalidomide in combination with dexamethasone and cyclophosphamide for systemic light chain amyloidosis (AL). Overall hematologic response rate was 46%. [34] Additional trial are needed to clarify the efficacy for AL. Lenalidomide in combination with dexamethasone with or without cyclophosphamide is one of many potential treatment regimens listed in the NCCN AL guidelines; however, the guidelines state that optimal therapy for AL remains unknown and treatment in the context of a clinical trial is strongly encouraged when possible. Other listed treatment options include, but are not limited to, bortezomib, cyclophosphamide/thalidomide/ dexamethasone, dexamethasone/alpha-interferon, oral melphalan/dexamethasone, and thalidomide/dexamethasone. [35]

OmedaRx performs independent analyses of oncology medications. The OmedaRx analysis and coverage policy may differ from NCCN guidelines.

Safety [9]

- 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.
- * 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.
- * 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.
- The risk of toxicity with lenalidomide is greater in patients with impaired renal function as the drug is extensively excreted by the kidneys.
- A restricted distribution program (Revlimid REMS™) is in place to prevent accidental fetal exposure to lenalidomide. [36]

Dosing and Administration [9]

- The recommended starting (and maximum) dose of lenalidomide in MDS is 10 mg orally once-a-day.
- The usual dose of lenalidomide in MM is 25 mg orally daily given in conjunction with dexamethasone pulse therapy. The usual dose of lenalidomide in MCL is 25 mg orally daily on Days 1-21 of repeated 28-day cycles.
- Dosing is modified (or interrupted) based on platelet and neutrophil counts.
- Lenalidomide is available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg capsules to allow for dosing flexibility.

Appendix 1: First-line therapy options for mantle cell lymphoma [10]

- CHOP/RCHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab (Rituxan) – various regimens, including sequential and alternating
- CALGB (rituximab, methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone)
- R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with rituximab plus high-dose methotrexate and cytarabine) (or modified)
- NORDIC (rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone alternating with rituximab + high-dose cytarabine)
- Alternating RCHOP/RDHAP [rituximab (Rituxan), dexamethasone, cisplatin, cytarabine]
- Sequential RCHOP/RICE [rituximab (Rituxan), ifosfamide, carboplatin, etoposide]
- Rituximab + EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- Bendamustine ± rituximab (Rituxan)
- VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone)
- Cladribine ± rituximab (Rituxan)

Cross References
Darzalex®, daratumumab, Medication Policy Manual, Policy No. 452
Empliciti®, elotuzumab, Medication Policy Manual, Policy No. 453
Farydak®, panobinostat, Medication Policy Manual, Policy No. 397
Kyprolis®, carfilzomib, Medication Policy Manual, Policy No. 282
Ninlaro®, ixazomib, Medication Policy Manual, Policy No. 455
Pomalyst®, pomalidomide, Medication Policy Manual, Policy No. 293
Velcade®, bortezomib, Medication Policy Manual, Policy No. 190

Codes	Number	Description
HCPCS	J8499	Prescription drug, oral, non-chemotherapeutic, Not otherwise specified
ICD-10	C83.10-C83.19, Z85.72	Mantle Cell Lymphoma
ICD-10	C92.10, D46.0, D46.1, D46.20, D46.21, D46.4, D46.9, D46.A, D46.B, D46.C, D46.Z	Myelodysplastic Syndrome (MDS)
ICD-10	C90.00, C90.01, C90.02, C90.10, C90.12, C90.20, C90.22, C90.30, C90.31, C90.32, Z85.79	Multiple Myeloma

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Revision History

Revision Date	Revision Summary
7/15/2016	- No changes to criteria with this update.
6/10/2016	- Remove the combination of Velcade/Revlimid from “Not Medically Necessary”