



# CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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Coverage Policy Number ..... 6120

Subject **Lenalidomide (Revlimid®)**

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## Hyperlink to Related Coverage Positions

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

## Coverage Policy

**CIGNA covers lenalidomide (Revlimid®) as medically necessary for treatment ANY of the following:**

- **myelodysplastic syndromes (MDS) including ANY of the following:**
  - transfusion-dependent anemia due to Low- or Intermediate-1-risk associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities
  - initial use in lower risk individuals with symptomatic anemia with no del(5q) and serum erythropoietin levels greater than 500 mU/mL and a low probability of response to immunosuppressive therapy
  - lower risk individuals with symptomatic anemia with no del(5q) and no response to initial treatment with epoetin alfa or darbopoetin alfa, hypomethylating agents, or immunosuppressive therapy
- **multiple myeloma as a single agent or when used in combination with dexamethasone**
- **non-Hodgkin lymphoma (NHL)**

## **FDA Approved Indications**

### **Myelodysplastic Syndromes (MDS)**

Revlimid (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

### **Multiple Myeloma**

Revlimid in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.

## **FDA Recommended Dosing**

### **Myelodysplastic Syndromes (MDS)**

For the management of myelodysplastic syndromes (MDS), the recommended initial dosage in adults is 10 mg once daily.

### **Multiple Myeloma**

For the management of multiple myeloma in adults who have received at least one prior therapy, the recommended initial dosage of lenalidomide is 25 mg once daily (as a single 25-mg capsule) on days 1–21 of repeated 28-day cycles.

## **Drug Availability**

Revlimid 5 mg, 10 mg, 15 mg and 25 mg capsules will be supplied through the RevAssist program and are available as follows: white opaque capsules imprinted “REV” on one half and “5 mg” on the other half in black ink in bottles of 28 or 100; blue/green and pale yellow opaque capsules imprinted “REV” on one half and “10 mg” on the other half in black ink in bottles of 28 or 100; powder blue and white opaque capsules imprinted “REV” on one half and “15 mg” on the other half in black ink in bottles of 21 or 100; and white opaque capsules imprinted “REV” on one half and “25 mg” on the other half in black ink in bottles of 21 or 100.

## **General Background**

### **Disease Overview**

Myelodysplastic syndromes (MDS) are a collection of disorders in which the bone marrow does not function normally and the body does not make enough normal blood cells. Patients with MDS may need blood and platelet transfusions and antibiotic therapy for infections. MDS includes but is not limited to: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-t), chronic myelomonocytic leukemia (CMML).

Deletion 5q is one of the most common cytogenetic abnormalities found in MDS. Patients who have del 5q can be grouped into 3 distinct categories, with variable prognoses:

- isolated del 5q and no additional cytogenetic abnormalities - prognosis is generally favorable, with up to a 9-year or longer median survival and a very low rate of AML progression
  - subgroup of isolated deletion 5q patients have a distinct clinical profile, called "5q-syndrome". This includes isolated deletion 5q, anemia, <5% blasts, normal to elevated platelets, and mononuclear megakaryocytes
- del 5q plus 1 additional cytogenetic abnormality - prognosis is worse than for isolated deletion 5q with a median survival usually <4 years
- complex cytogenetics: del 5q plus 2 or more additional cytogenetic abnormalities - poor prognosis

### **Pharmacology**

Lenalidomide, chemically similar to thalidomide, is an immunomodulatory agent with antiangiogenic properties. In the laboratory tests, it has been shown to be more potent but appears to lack some of the more common side effects of thalidomide. It has multiple mechanisms of action that affect both the cancer cell and its microenvironment. Lenalidomide inhibits the secretion of pro-inflammatory cytokines and increases the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. It also inhibits cell proliferation in some but not all cell lines.

## **Guidelines**

The National Comprehensive Cancer Network (NCCN) recommended guidelines for Revlimid's use is as follows:

### **Multiple Myeloma**

Grade 1- Induction chemotherapy for progressive solitary plasmacytoma or smoldering myeloma (asymptomatic) that has progressed to active (symptomatic) myeloma in combination with dexamethasone with or without bortezomib for transplant candidates; combination with low-dose dexamethasone for nontransplant candidates. Salvage therapy on or off clinical trials for disease relapse or for progressive or refractory disease as a single agent or in combination with dexamethasone with or without bortezomib or cyclophosphamide

Grade 2A - Maintenance therapy as a single agent for active (symptomatic) myeloma responding to primary induction therapy; stable or responsive disease following stem cell transplant. Primary treatment in combination with dexamethasone.

### **MDS**

Grade 2A - Initial treatment in lower risk patients with del(5q) chromosomal abnormalities with clinically significant cytopenia(s) and symptomatic anemia. If there is a response, continue lenalidomide treatment

Initial treatment in lower risk patients with symptomatic anemia with no del(5q) and serum erythropoietin levels greater than 500 mU/mL and a low probability of response to immunosuppressive therapy.

Treatment in lower risk patients with symptomatic anemia with no del(5q) and no response to initial treatment with epoetin alfa or darbopoetin alfa, hypomethylating agents, or immunosuppressive therapy.

### **Non-Hodgkin Lymphoma (NHL)**

#### **Grade 2A**

#### **Diffuse large B-cell lymphoma**

Second-line therapy as a single agent for relapsed or refractory disease in noncandidates for high-dose therapy with autologous stem cell rescue.

#### **Follicular lymphoma and Nodal marginal zone lymphoma**

Second-line therapy as a single agent for refractory or progressive disease.

#### **Gastric MALT lymphoma**

Second-line therapy as a single agent for recurrent or progressive disease in patients with the indications for treatment.

#### **Mantle cell lymphoma**

Second-line therapy as a single agent for relapsed, refractory, or progressive disease.

#### **Nongastric MALT lymphoma**

Second-line therapy as a single agent for recurrent stage I-II disease or for progressive disease in patients with the indications for treatment.

#### **Primary cutaneous B-cell lymphoma**

Second-line therapy for primary cutaneous marginal zone or follicle center B-cell refractory generalized cutaneous disease or relapsed generalized extracutaneous disease. Second-line therapy as a single agent for relapsed or refractory primary cutaneous diffuse large B-cell lymphoma, leg type in noncandidates for high-dose therapy with autologous stem cell rescue.

#### **Splenic marginal zone lymphoma**

Second-line therapy as a single agent for progressive disease in patients with the indications for treatment.

### **Clinical Efficacy**

The Mayo Clinic myeloma experts published a consensus statement (Dispenzieri, et al., 2007) to offer a simplified, evidence-based algorithm of decision-making for patients with newly diagnosed myeloma. Based on results of a phase 2 clinical study conducted at the Mayo Clinic [(Rajkumar, et al., 2005) and other clinical trials

published in abstracts [(Lacy, et al., 2006), (Rajkumar, et al., 2006)], lenalidomide plus low-dose dexamethasone is a highly effective regimen in patients with newly diagnosed myeloma, with response rates exceeding 90%, and a more favorable toxicity profile compared to thalidomide plus dexamethasone.

An open-label, single-center trial evaluated the safety and efficacy of lenalidomide in 43 patients with myelodysplastic syndromes who had symptomatic anemia. Three oral dosing schedules were sequentially evaluated: 25 mg daily, 10 mg daily, and 10 mg daily for 21 days of every 28-day cycle. All patients either had no response to recombinant erythropoietin or had a high endogenous erythropoietin level with a low probability of benefit from such therapy. The final response was assessed after 16 weeks. Twenty-four patients (56%) had a response; 20 of 32 transfusion-dependent patients (63%) achieved independence from transfusion. Of 11 patients who required no transfusions, one had an increase in the hemoglobin level of more than 2 g per deciliter, and three had more than a 50% reduction in the need for transfusions. Patients with a major response reached a median hemoglobin level of  $13.2 \pm 1.4$  g per deciliter, with a corresponding median increase in hemoglobin from baseline of 5.3 g per deciliter. The response rate was highest among patients with a clonal interstitial deletion involving chromosome 5q31.1 (83%, as compared with 57% among those with a normal karyotype and 12% among those with other karyotypic abnormalities;  $p=0.007$ ) and patients with lower prognostic risk. After an 81-week median follow-up, the median duration of transfusion independence had not been reached, and the median hemoglobin level was 13.2 g/dl. The most common adverse events reported were neutropenia (65%) and thrombo-cytopenia 74%. Other adverse events were mild and infrequent.

Two multicenter, multinational, double-blind, randomized, placebo-controlled studies were conducted to compare the addition of lenalidomide to dexamethasone, a standard steroid treatment for multiple myeloma, to dexamethasone alone. The primary efficacy endpoint in both studies was time to disease progression. One of the studies was conducted in the United States that included patients with refractory multiple myeloma; 170 were treated with lenalidomide plus dexamethasone (Rev-Dex) and 170 were treated with dexamethasone only. After more than 15 months' follow-up, time to cancer progression and overall anti-cancer response rates were significantly improved in the group of patients treated with the combination therapy, Rev-Dex, compared to those treated with dexamethasone alone. Anti-cancer response rates were achieved in 51.3% of patients treated with lenalidomide plus dexamethasone, compared to 22.9% of patients treated with dexamethasone only. The second study, conducted in Europe, compared Rev-Dex to dexamethasone only in patients with refractory multiple myeloma. This trial included 176 patients treated with Rev-Dex and 176 patients treated with dexamethasone only. Overall anti-cancer response rates and time to cancer progression was significantly improved in the group of patients treated with Rev-Dex (47.6%) compared to the group treated with dexamethasone only (18.9%).

Rajkumar et al. (2005) evaluated the efficacy of combination therapy with 25 mg lenalidomide plus 40 mg dexamethasone for newly diagnosed myeloma in a phase 2 trial in 34 patients. Lenalidomide was given on days 1–21 of a 28-day cycle and dexamethasone was given on days 1–4, 9–12, and 17–20 of each cycle. Each cycle was repeated every four weeks, and patients were allowed to discontinue treatment to pursue stem cell transplant (SCT). Objective response was defined as a decrease in serum monoclonal (M) protein level by 50% or greater and a decrease in urine M protein level by at least 90% or to a level less than 200 mg/24 hours, confirmed by two consecutive determinations at least four weeks apart. Out of 34 patients, 91% (31) responded to the combination therapy and achieved an objective response. Of the 31 patients, two patients (6%) achieved complete response (CR); 11 patients (32%) achieved a very good partial response (VGPR); and 18 patients achieved a partial response. Overall, 47% of patients experienced grade III or higher non-hematologic toxicity. The most common side effects reported were fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). Further, Lacy et al. (2007) evaluated the long-term effects of the combined regimen of Rev-Dex on time to progression, progression-free survival, and overall survival (OS) in these patients. The complete response plus very good partial response among the 21 patients who received Rev-Dex without SCT was 67%. The two-year progression-free survival rates for patients proceeding to SCT and patients remaining on Rev-Dex were 83% and 59%, respectively. At two and three years, the OS rates were 92% and 90%, respectively. The three-year OS rate for the whole cohort was 88%. The author concluded that the randomized trials are needed to determine if this and other combination regimens are better used early in therapy or should be reserved for later interventions.

### **Ongoing Studies**

Lenalidomide is currently under investigation for the following indications: treatment of complex regional pain syndrome type I – Phase III; treatment of painful lumbar radiculopathy – Phase III; treatment of chronic

lymphocytic leukemia (CLL) – Phase II; treatment of myelofibrosis, as monotherapy and in combination with prednisone – Phase II; treatment of non-Hodgkin's lymphoma – Phase II; treatment of prostate cancer - Phase II; treatment of radioiodine-unresponsive papillary and follicular thyroid carcinomas – Phase II; and treatment of solid tumors – Phase II.

### **Contraindications**

Lenalidomide therapy includes a Black Box Warning for Potential for Human Birth Defects (Pregnancy Category X) due to its structural similarities to thalidomide, known to cause severe birth defects. Lenalidomide is contraindicated in pregnant women and women capable of becoming pregnant. Females of childbearing potential should be advised to avoid pregnancy while on lenalidomide. Due to this potential toxicity and to avoid fetal exposure to lenalidomide, the manufacturer, Celgene, has made lenalidomide available only under a restricted distribution program called "RevAssist." Prescribers and pharmacists registered with this program can only prescribe and dispense lenalidomide. In addition, lenalidomide can only be dispensed to patients who are registered and meet all of the conditions of the RevAssist program.

### **Adverse Reactions**

The safety profile for lenalidomide has shown that neutropenia and/or thrombocytopenia were the most common adverse events and that patients may require a dose adjustment. Significant risks of DVT and PE have been reported in patients with multiple myeloma. The most common reported adverse events include neutropenia, thrombocytopenia diarrhea, pruritis, rash, and fatigue.

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## **Coding/Billing Information**

**Note:** This section is not in use.

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## Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	11/15/2007	6120	Lenalidomide (Revlimid®)
Great-West Healthcare	8/2007	P06.102.1	Revlimid

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