BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

Lenalidomide oral
REVLIMID® (lenalidomide) oral

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Revlimid (lenalidomide) and generic lenalidomide are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Treatment of multiple myeloma (MM) used in combination with dexamethasone

    b. Maintenance of MM after autologous hematopoietic stem cell transplantation (auto-HSCT)

c. Transfusion-dependent anemia in low- or intermediate-1-risk myelodysplastic syndrome (MDS) associated with 5q deletion abnormality with or without additional cytogenetic abnormalities

d. Mantle cell lymphoma (MCL) that has relapsed or progressed after two prior therapies, one of which included Velcade (bortezomib)

e. Used in combination with a rituximab product for previously treated follicular lymphoma (FL)

f. Used in combination with a rituximab product for previously treated marginal zone lymphoma (MZL)

g. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Complete blood count
   b. Comprehensive metabolic panel
   c. Thyroid function tests
   d. Negative pregnancy test in a woman of childbearing potential as required by the Risk Evaluation and Mitigation Strategy (REMS) [Note: This is waved if it is verified that Provider, Patient, and Pharmacy are enrolled in the REMS]
   e. Verification that male individual on Revlimid (lenalidomide) is enrolled in the REMS
   f. Eastern Cooperative Oncology Group (ECOG) Performance Status is 0-2

5. **For brand Revlimid (lenalidomide)**: Individual has documented failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic lenalidomide** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. There are **NO** FDA-label contraindications such as:
   a. Pregnancy
   b. Severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Revlimid (lenalidomide) and generic lenalidomide are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual's condition has responded while on therapy with response defined as there is no evidence of disease progression or unacceptable toxicity

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Venous thromboembolism (DVT, PE)
        ii. Arterial thromboembolism (MI, CVA)
        iii. Grade 4 rash, exfoliative or bullous rash, or for other severe cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms
        iv. Liver failure
        v. Tumor lysis syndrome
        vi. Neutropenia and thrombocytopenia

5. **For brand Revlimid (lenalidomide)**: Individual has documented failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for **generic lenalidomide** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Lenalidomide (Revlimid brand or generic) is a thalidomide analogue used **in combination with dexamethasone, is indicated for the treatment of patients with multiple myeloma (MM) and as maintenance following autologous hematopoietic stem cell transplantation (auto-HSCT); it is also indicated for the 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; and it is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included Velcade (bortezomib).** Lenalidomide (Revlimid brand or generic), in combination with a rituximab product, is also indicated for **previously treated follicular lymphoma** and for **previously treated marginal zone lymphoma**. Lenalidomide (Revlimid brand or generic) is not indicated for the treatment of a patient with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

Lenalidomide has immunomodulatory, antiangiogenic, and antineoplastic properties. It inhibits proliferation and induces apoptosis of certain hematopoietic tumor cells including MM, MCL, and del (5q) MDS *in vitro*. Lenalidomide causes a delay in tumor growth in some *in vivo* nonclinical hematopoietic tumor models including

MM. The immunomodulatory properties of lenalidomide include activation of T-cells and natural killer (NK) cells, increased numbers of NKT cells, and inhibition of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. In MM cells, the combination of lenalidomide and dexamethasone synergizes the inhibition of cell proliferation and the induction of apoptosis.

Use of lenalidomide is subject to a Risk Evaluation and Mitigation Strategies (REMS) program that requires provider, patient, and dispensing pharmacy be enrolled into the program. Only providers and Pharmacies enrolled into the REMS may prescribe and dispense the drug, respectively, to individuals who are also in the program. A REMS program attempts to manage known or potentially serious risks associated with a drug product and is required by the Food and Drug Administration (FDA) for some drugs to ensure that the benefits of a drug outweigh its risks.

To avoid embryofetal exposure to Revlimid (lenalidomide) is only available through a restricted distribution program, the REVLIMID REMS program or the LENALIDOMIDE REMS program. Patients must sign a Patient-Physician agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements. Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles or every 2 weeks in females with irregular menstrual cycles. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking Revlimid (lenalidomide) and for up to 4 weeks after discontinuing lenalidomide, even if they have undergone a successful vasectomy.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Lenalidomide (Revlimid brand or generic) REMS items:

- Enrollment and agreement information
- Treatment initiation information
- Treatment maintenance information
- Pharmacy requirements and responsibilities
- Counseling on contraception and avoidance of pregnancy
- Pregnancy testing in females of childbearing potential
- Counseling on serious risks, warnings, and precautions and safe use

International Prognostic Scoring System (IPSS) in myelodysplastic syndrome:

Survival and AML evolution					
	Score value				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone Marrow Blast percentage	< 5	5-10		11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			
Prognosis					

Score	IPSS Group	Median Survival (Years)	25% AML progression (years) in absence of therapy
0	Low	5.7	9.4
0.5-1.0	Intermediate-1	3.5	3.3
1.5-2.0	Intermediate-2	1.1	1.1
> 2.5	High	0.4	0.2

* Cytogenetic definitions:
Good = normal, -Y alone, del(5q) alone, del(20q) alone
Poor = complex (≥3 abnormalities) or chromosome 7 anomalies
Intermediate = other abnormalities (excludes karyotypes t(8;21), inv16, and 5(15;17)
Cytopenias: neutrophil count < 1,800mcL, platelets < 100,000 mcL, Hg < 10 g/dL

Revised international prognostic scoring system (IPSS-R) in myelodysplastic syndrome:

Prognostic variable	Score value						
	0	0.5	1.0	1.5	2.0	3.0	4.0
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (percent)	≤ 2		> 2 to < 5		5 to 10	> 10	
Hemoglobin (g/dL)	≥ 10		8 to < 10	<8			
Platelets (cells/microL)	≥ 100	50 to 100	< 50				
Absolute neutrophil count (cells/microL)	≥ 0.8	< 0.8					

This scoring system was applied to an initial group of 7012 patients with primary MDS by the French-American-British classification who had at least two months of stable blood counts, ≤ 30 percent bone marrow blasts and ≤19 percent peripheral blood blasts, and who were observed until progression to AML transformation or death (did not receive disease-modifying agents for MDS). Patients could be stratified into five groups with the following estimated overall survival and progression to AML.

Risk group	IPSS-R score	Median overall survival (years)	Median time to 25 percent AML evolution (years)
Very low	≤ 1.5	8.8	> 14.5
Low	> 1.5 to 3.0	5.3	10.8
Intermediate	> 3 to 4.5	3.0	3.2
High	> 4.5 to 6	1.6	1.4
Very high	> 6	0.8	0.7

The prognostic value of the IPSS-R was validated in an external cohort of 200 patients with MDS

AML: acute myeloid leukemia; MDS: myelodysplastic syndrome.
* Cytogenetic definitions:
Very good: -Y, del(11q).
Good: Normal, del(5q), del(12p), del(20q), double including del(5q).
Intermediate: del(7q), +8, +19, i(17q), any other single, double not including del(5q) or -7/del(7q), or independent clones.

Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities.
Very poor: Complex: > 3 abnormalities

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Resources:

Revlimid (lenalidomide) product information, revised by Celgene Corporation 03-2013. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 03, 2024.

Lenalidomide product information, revised by Exelan Pharmaceuticals, Inc. 06-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 03, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Multiple Myeloma Version 4.2024. Updated April 26, 2024. Available at https://www.nccn.org. Accessed July 03, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myelodysplastic Syndromes Version 2.2024. Updated May 22, 2024. Available at https://www.nccn.org. Accessed July 03, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-Cell Lymphomas Version 2.2024. Updated April 30, 2024. Available at https://www.nccn.org. Accessed July 03, 2024.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.