BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINES	
SECTION: DRUGS	
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REVLIMID® (lenalidomide) oral

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

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

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

  2. Individual is 18 years of age or older

  3. 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. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     a. Complete blood count
     b. Comprehensive metabolic panel
     c. Thyroid function tests
     d. Negative pregnancy test in a woman of child bearing 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 (linalidomide) is enrolled in the REMS
     f. Eastern Cooperative Oncology Group (ECOG) Performance Status is 0-2

  5. There are **NO** FDA-label contraindications, such as:
     a. Pregnancy

  6. There are no significant interacting drugs

  Initial approval duration: 6 months

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Criteria for continuation of coverage (renewal request): Revlimid (lenalidomide) is considered ***medically necessary*** and will be approved with documentation of **ALL** of the following:

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

2. Individual's condition responded while on therapy
    a. Response is defined as:
        i. No evidence of disease progression
        ii. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or significant adverse drug effects that may exclude continued use
    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. Allergic reaction (angioedema, skin exfoliation, bullae, anaphylaxis)
        iv. Liver failure
        v. Tumor lysis syndrome
        vi. Severe cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms

5. There are no significant interacting drugs

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 a Non-cancer Medications**

    2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

Description:

Revlimid (lenalidomide) 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**

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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). Revlimid (lenalidomide), in combination with a rituximab product, is also indicated for **previously treated follicular lymphoma** and for **previously treated marginal zone lymphoma**. Revlimid (lenalidomide) 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 Revlimid (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. 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 Revlimid (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 Revlimid (lenalidomide), even if they have undergone a successful vasectomy.

Definitions:

Revlimid (lenalidomide) 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

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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

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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

Resources:

Revlimid (lenalidomide) product information, revised by Celgene Corporation 10-2019. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on June 25, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Multiple Myeloma Version 7.2021 – Updated April 26, 2021. Available at https://www.nccn.org. Accessed on June 24, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Myelodysplastic Syndromes Version 3.2021 – Updated January 15, 2021. Available at https://www.nccn.org. Accessed on June 25, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): B-Cell Lymphomas Version 4.2021 – Updated May 05, 2021. Available at https://www.nccn.org. Accessed on June 25, 2021.

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.