BlueCross BlueShield Arizona

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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/1/2016**
SECTION: DRUGS	**LAST REVIEW DATE: 11/18/2021**
	LAST CRITERIA REVISION DATE: 11/18/2021
	ARCHIVE DATE:

THALOMID® (thalidomide)

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:** Thalomid (thalidomide) is considered ***medically necessary*** when **ALL** of the following criteria are met:

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

  2. Individual is 12 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     a. Multiple myeloma (MM) **AND** individual is receiving concurrent dexamethasone and other standard chemotherapy agents as either primary therapy for symptomatic MM or for previously treated MM relapse or progressive disease

     b. Acute cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) **AND** if moderate to severe neuritis is present will not be used as monotherapy

     c. Maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence

     d. 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:
     a. Individual is participating in the Thalomid REM program
     b. When used in cancer, Eastern Cooperative Oncology Group (ECOG) performance status 0-2

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

  6. Will not be used in a patient with hepatic impairment

  7. There are no significant interacting drugs

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Thalomid (thalidomide) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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

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2. Individual's condition has not worsened while on therapy
    a. Worsening is defined as:
        i. Disease progressed while on Thalomid

3. Individual has been adherent with the medication

4. Individual is participating in the Thalomid REM program

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use such as:
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect:
        i. Arterial thromboembolic events
        ii. Venous thromboembolic events
        iii. Peripheral neuropathy
        iv. Neutrophil count is < 750 mm^3
        v. Thrombocytopenia
        vi. Symptomatic bradycardia and syncope
        vii. Severe skin reaction such as is exfoliative, purpuric, or bullous or if Stevens-Johnson syndrome or toxic epidermal necrolysis
        viii. Tumor lysis syndrome
        ix. Angioedema
        x. Anaphylaxis

6. 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:

Thalomid (thalidomide) is indicated, in combination with dexamethasone, for the treatment of newly diagnosed multiple myeloma (MM); it is also indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL), Thalomid (thalidomide) is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.; and it is indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

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Thalomid (thalidomide) is an immunomodulatory agent. The mechanism of action is not fully understood. Thalidomide possesses immunomodulatory, anti-inflammatory and antiangiogenic properties. Available data from *in vitro* studies and clinical trials suggest that the immunologic effects of this compound may be related to suppression of excessive tumor necrosis factor-alpha (TNF-a) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration. For example, administration of thalidomide has been reported to decrease circulating levels of TNF-a in patients with ENL. Other anti-inflammatory and immunomodulatory properties of thalidomide may include suppression of macrophage involvement in prostaglandin synthesis, and modulation of interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. Thalidomide treatment of multiple myeloma patients is accompanied by an increase in the number of circulating natural killer cells, and an increase in plasma levels of interleukin-2 and interferon-gamma (T cell-derived cytokines associated with cytotoxic activity). Thalidomide was found to inhibit angiogenesis, the cellular processes of angiogenesis inhibited by thalidomide may include the proliferation of endothelial cells.

Use of Thalomid (thalidomide) 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.

MM is a malignancy of plasma cells in the bone marrow. Malignant monoclonal plasma cells accumulate in the bone marrow and produce a monoclonal protein (usually IgG or IgA which are often referred to as M or myeloma proteins) that causes disruption of normal bone marrow function, destruction and invasion of bone surrounding the bone marrow cavity, production and release of M-proteins from the myeloma cells into the blood stream and/or into the urine, and a reduction of normal immune function. MM makes up 10-15% of all hematologic malignancies.

MM is a genetically complex disease that develops through several steps over time and as a result has various clinical presentations or phases. The earliest phase is monoclonal gammopathy of undetermined significance (MGUS). The next phase is smoldering multiple myeloma (SMM), distinguished from MGUS by a greater tumor cell content of >10% and an average risk of progression to myeloma of 10% per year for the first five years. The myeloma phase is recognized when malignant clones cause clinically relevant end-organ damage such as the features of CRAB (hypercalcemia, renal dysfunction, anemia, and bone lesions, including bone pain and fractures). Other manifestations include infection, neurologic symptoms (lethargy, headaches, confusion, depression and other), clotting abnormalities and hyperviscosity. The final phase is plasma cell leukemia (PCL).

MM is characterized by multiple relapses and progressive refractoriness to available therapies. There is no cure. The choice of primary therapy is based on whether a patient is a candidate for a stem cell transplant. Drug therapy is used to bridge eligible patients to an autologous stem cell transplant (ASCT). Agents from four different classes are combined with one another or with corticosteroids and/or various generic chemotherapy medications to make up a MM drug regimen. Medication drug classes include: *Chemotherapy:* liposomal doxorubicin (Doxil), melphalan, cyclophosphamide, vincristine, etoposide, cisplatin, others; *HDAC inhibitor:* panobinostat (Farydak); *Immunomodulators:* lenalidomide (Revlimid), pomalidomide (Pomalyst), thalidomide (Thalomid); *Proteasome inhibitors:* bortezomib (Velcade) and carfilzomib (Kyprolis).

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The National Comprehensive Cancer Network (NCCN) version 2.2018 (Oct 2, 2017) lists thalidomide as primary therapy for transplant candidates as useful in certain circumstances when used in combination with bortezomib and dexamethasone or in combination with dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide-bortezomib (VTD-PACE). It is also listed as useful in certain circumstances for therapy for previously treated MM in combination with dexamethasone-cisplatin-doxorubicin-cyclophosphamide-etoposide (DT-PACE) with or without bortezomib (VTD-PACE) for aggressive treatment. Both are NCCN Category 2A evidence. NCCN recommends 3-drug regimens over 2-drug regimens as the standard of care for primary treatment of myeloma.

The main treatment options for relapsed or refractory disease are proteasome inhibitors (bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (lenalidomide, thalidomide), monoclonal antibodies (daratumumab, elotuzumab), alkylators, anthracyclines, panobinostat, and corticosteroids, administered alone, or more commonly as part of two- or three-drug combinations.

ENL is an inflammatory painful condition characterized by tender nodules under the skin. The nodules are flat, firm, hot, and red. ENL is an immune-mediated complication of leprosy. There is a variable degree of systemic involvement and includes fever, arthritis, lymphadenitis, neuritis, iridocyclitis, nephritis, hepatitis, and other organ involvement. Drug treatment of leprosy, depending on the leprosy type, includes use of dapsone, rifampin, or clofazimine. Treatment of ENL, an immune complications of leprosy, includes corticosteroids and thalidomide.

Definitions:

Thalomid (thalidomide) REMS items:

- Enrollment and agreement information
- Treatment initiation information
- Treatment maintenance information
- Pharmacy requirements and responsibilities
- Counseling on serious risks, warnings, and precautions for safe use
- Counseling on contraception and avoidance of pregnancy in a woman of child bearing potential
- Pregnancy testing in females of childbearing potential
- Male on Thalomid with a female partner of childbearing potential counseling

Resources:

Thalomid (thalidomide) product information, revised by Celgene Corporation 02-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed September 03, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Multiple myeloma Version 1.2022 – August 16 2021. Available at https://www.nccn.org. Accessed September 03, 2021.

Scollard S, Stryjewska B, Dacso M. Leprosy: Epidemiology, microbiology, clinical manifestations, and diagnosis. In: UpToDate, Fordham von Reyn C, Baron EL (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 03, 2021.

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Scollard S, Stryjewska B, Dacso M. Leprosy: Treatment and prevention. In: UpToDate, Fordham von Reyn C, Baron EL (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed September 03, 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.