BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/01/16**
SECTION: DRUGS	**LAST REVIEW DATE: 11/16/17**
	LAST CRITERIA REVISION DATE: 11/16/17
	ARCHIVE DATE:

THALOMID® (thalidomide) oral capsule

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.**

THALOMID® (thalidomide) oral capsule (cont.)

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.

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

THALOMID® (thalidomide) oral capsule (cont.)

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).

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

National Comprehensive Cancer Network (NCCN) version 2.2018 (Oct 2, 2017)
NCCN 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:

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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

Thalomid (thalidomide)

Medication class:
Angiogenesis inhibitor, antineoplastic agent, immunomodulator

FDA-approved indication(s):
- Treatment of newly diagnosed multiple myeloma (MM) in combination with dexamethasone
- Acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL)
- Maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence

Limitations of use:
- Thalidomide is not indicated as monotherapy for acute ENL treatment in the presence of moderate to severe neuritis, corticosteroids may be started simultaneously with thalidomide

Recommended Dose:
- MM:
  - 200 mg once daily with dexamethasone 40 mg daily on days 1-4, 9-12, 17-20 every 28 days
- ENL:
  - 100-300 mg once daily for an episode of cutaneous ENL, up to 400 mg once daily for severe cutaneous ENL
  - Dosing is continued until signs & symptoms of active reaction subside (usually 2 weeks)
  - Patients may be tapered off using increments of 50 mg every 2-4 weeks
  - For those who need maintenance, use lowest dose that controls reaction, tapering off should be attempted every 3-6 months using increments of 50 mg every 2-4 weeks

Maximum dosage
- 400 mg/day

Available Dosage Forms:
- 50 mg, 100 mg, 150 mg, and 200 mg capsules

Warnings, Precautions, and other Clinical Information:
- Use is associated with a REMS requirement detailing avoidance of pregnancy
- Pregnancy must be ruled out before use (done via REMS) proven by 2 negative pregnancy tests before starting, then routinely as outlined in the REMS
- Immediately discontinue if a woman discovers she is pregnant
- Woman of child bearing potential must use 2 forms of effective contraception
- Woman who is breast feeding an infant or child should stop breast feeding
- Male, even if has undergone a successful vasectomy, on Thalomid with female partner of reproductive potential must use condoms
- Thalomid should not be initiated with an absolute neutrophil count of < 750 mm^3
- Dose reduction, delay, or discontinuation may be required for thrombocytopenia associated with Thalomid

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- Patients are at increased risk for venous and arterial thromboembolism (DVT, PE, cardiac ischemia, MI, stroke), some patients may need thromboprophylaxis
- Thalidomide is known to cause nerve damage that may be permanent, Thalomid should be discontinued if peripheral neuropathy occurs
- Dose reduction or discontinuation may be required for bradycardia and syncope associated with Thalomid
- Permanently discontinue if a rash that is exfoliative, purpuric, or bullous or if Stevens-Johnson syndrome or toxic epidermal necrolysis occurs
- Tumor lysis syndrome may occur in those with a high tumor burden
- The drug has not been studied in patients with hepatic impairment
- Avoid use of opioids, antihistamines, antipsychotics, antianxiety agents, or other CNS depressing agents including alcohol due to additive sedative effects

Criteria:

- **Criteria for initial therapy:** Thalomid (thalidomide) is considered ***medically necessary*** when **ALL** of the following criteria are met:

  1. Prescriber is an Oncologist

  2. Individual is 13 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Multiple myeloma (MM) **AND** individual is receiving concurrent dexamethasone
     - 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
     - Maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence

  4. There are **NO** contraindications:
     - Contraindications include:
       - Pregnancy
       - Demonstrated hypersensitivity to thalidomide or any product components

  Initial approval duration: 6 months with initial fills of 14 days per fill for first 3 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 an Oncologist

  2. Individual's condition has not worsened while on therapy
     - Worsening is defined as:

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- Disease progressed while on Thalomid

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use such as:
   - Contraindications as listed in the criteria for initial therapy section
   - Significant adverse effect:
     - Arterial thromboembolic events
       - Signs and symptoms may include: chest pain that spreads to arms, neck, jaw, back, or stomach, sweating, sudden weakness or numbness on one side of body, headache, confusion, difficulty with speech, vision, or balance, fatigue
     - Venous thromboembolic events
       - Signs and symptoms may include: shortness of breath, chest pain, or arm or leg swelling, leg pain
     - Peripheral neuropathy
       - Signs and symptoms may include: numbness, tingling, pain, burning sensation in hands, legs, or feet
     - Skin reaction
       - Signs and symptoms may include: skin rash, hives, blistering, oral ulcers
     - Thrombocytopenia
       - Signs and symptoms may include: unusual bleeding or bruising, nose bleeds, red or purple spots on body
     - Tumor lysis syndrome
       - Signs & symptoms may include: nausea, vomiting, shortness of breath, irregular heartbeat, flank pain, blood in urine, weakness, lethargy, edema, seizure

5. There are no significant interacting drugs

Renewal duration: 12 months

Resources:

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.

Thalomid. Package Insert. Revised by manufacturer 8/2015. Accessed 09-04-2015, 10-23-2016

UpToDate: Epidemiology, microbiology, clinical manifestations of leprosy. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/epidemiology-microbiology-clinical-manifestations-and-diagnosis-of-leprosy?source=search_result&search=erythema%20nodosum%20leprosum&selectedTitle=1~36

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UpToDate: Treatment and prevention of leprosy. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-and-prevention-of-leprosy?source=see_link&sectionName=Type%202%20reaction%20(T2R,%20erythema%20nodosum%20leprosum,%20ENL)&anchor=H310298210#H310298210

NCCN Clinical Practice Guidelines in Oncology: Multiple myeloma. Version 2.2018, Oct 2, 2017. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

UpToDate: Treatment of relapsed or refractory multiple myeloma. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/treatment-of-relapsed-or-refractory-multiple-myeloma?source=search_result&search=multiple%20myeloma&selectedTitle=5~150

UpToDate: Overview of the management of multiple myeloma. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/overview-of-the-management-of-multiple-myeloma?source=search_result&search=multiple%20myeloma&selectedTitle=2~150

UpToDate: Clinical feature, laboratory manifestations, and diagnosis of multiple myeloma. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/clinical-features-laboratory-manifestations-and-diagnosis-of-multiple-myeloma?source=search_result&search=multiple%20myeloma&selectedTitle=1~150

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.