09-J1000-56

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Revised: 07/15/19

Subject: Thalidomide (Thalomid®) Capsules

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Thalidomide (Thalomid) was approved by the U.S. Food and Drug Administration (FDA) in July 1998 for the treatment of erythema nodosum leprosum (ENL) and later in May 2006 for newly diagnosed multiple myeloma (MM). Celgene, the manufacturer of thalidomide, previously received orphan drug designation from the FDA for the approved indications (ENL – 1995, MM – 1998), and also received designations for several off-label indications (treatment of primary brain malignancies - 1998, Crohn's disease – 1999, Kaposi's sarcoma - 1998, HIV-associated wasting syndrome - 1996, myelodysplastic syndrome (MDS) – 2004, severe recurrent aphthous stomatitis in severely, terminally immunocompromised patients - 1995, and treatment of mycobacterium infections – 1993). While the mechanism of action of thalidomide is not completely understood, it is known that the agent selectively reduces levels of tumor necrosis factor alpha by accelerating degradation of messenger RNA encoding protein.

National Comprehensive Cancer Network (NCCN) Guidelines for AIDS-Related Kaposi Sarcoma (Version 2.2019), B-cell Lymphomas (Version 3.2019), Multiple Myeloma (Version 2.2019), and Myeloproliferative Neoplasms (Version 2.2019) include category 1 and/or 2A recommendations for use of thalidomide in some capacity in each disease state and/or disease subtypes.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an

outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

The initiation of thalidomide **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions ("1" to "10"), **ALL** associated criteria are met, **AND** thalidomide will **NOT** be used in combination with another immunomodulatory drug [i.e., lenalidomide (Revlimid) or pomalidomide (Pomalyst)]:

1. Behcet's syndrome
    a. The member has severe, refractory disease with either widespread involvement, or disease involvement of the eye, brain, large blood vessels, and/or other major organs
    b. Member has had an inadequate response to an adequate trial (at least 60 days), had persistent intolerable adverse effects, or has a contraindications to **ALL** of the following ("i", "ii", and "iii" - the specific adverse effects and/or contraindications must be provided):
        i. Azathioprine
        ii. Systemic corticosteroid
        iii. At least one of the following immunosuppressant drugs:
            - Cyclophosphamide
            - Cyclosporine
            - Methotrexate
    c. Member's dosage does not exceed 400 mg daily obtained using the fewest number of capsules possible
2. Chronic graft-versus-host disease (cGVHD)
    a. The member is diagnosed with cGVHD following an allogenic hematopoietic stem cell (bone marrow) transplant
    b. Member's disease is refractory to an adequate trial of combination therapy with a systemic corticosteroid **AND** a calcineurin inhibitor (i.e., cyclosporine or tacrolimus). Corticosteroid monotherapy is acceptable for members who have an intolerance or contraindication to a calcineurin inhibitor (the specific intolerance or contraindication must be provided)
    c. Member's dosage does not exceed 800 mg daily obtained using the fewest number of capsules possible
3. Erythema nodosum leprosum (ENL)
    a. **ONE** of the following ("i" or "ii"):
        i. Member is currently having acute cutaneous manifestations of moderate to severe ENL
        ii. Thalidomide is for maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence
    b. Member's dosage does not exceed 400 mg daily obtained using the fewest number of capsules possible
4. Lupus erythematosus
    a. Member has moderate to severe cutaneous manifestations resulting in impaired quality of life

b. Member has had an inadequate response to a sufficient trial (at least 60 days), had persistent intolerable adverse effects, or has a contraindications to **ALL** of the following ("i", "ii", and "iii" - the specific adverse effects and/or contraindications must be provided):
    i. Hydroxychloroquine
    ii. At least **TWO** immunosuppressant drugs (i.e., azathioprine, cyclosporine, leflunomide, methotrexate, or mycophenolate)
    iii. An oral retinoid (i.e., acitretin or isotretinoin)
c. Member's dosage does not exceed 200 mg daily obtained using the fewest number of capsules possible

5. Multicentric Castleman's disease (CD)
    a. Thalidomide is used as monotherapy or in combination with rituximab (Rituxan)
    b. Treatment is used as third-line or later therapy for relapsed, refractory, or progressive disease
    c. Member's dosage does not exceed 200 mg daily obtained using the fewest number of capsules possible
6. Multiple myeloma (MM)
    a. Member has active (symptomatic) multiple myeloma
    b. The member's baseline (i.e., within 90 days prior to initiating treatment with thalidomide) serum monoclonal protein (M-protein) level, as detected by serum protein electrophoresis (SPEP), is provided*
    c. Member's dosage does not exceed 200 mg daily obtained using the fewest number of capsules possible

    **If the M-protein is undetectable by SPEP, baseline serum free light chain (SFLC) levels (kappa and lambda), as detected by serum free light chain assay (SFLCA), must also be provided*

7. Myelofibrosis-associated anemia
    a. Member has symptomatic anemia requiring red blood cell (RBC) transfusion
    b. Thalidomide will be used as a single agent or in combination with prednisone
    c. **EITHER** of the following ('i" or "ii"):
        i. Serum erythropoietin level >500 mU/mL (laboratory documentation must be submitted)
        ii. Serum erythropoietin level ≤500 mU/mL (laboratory documentation must be submitted), **AND** no response after 3 months (or response followed by loss of response) with, or contraindication to erythropoiesis stimulating agent (ESA) treatment [e.g., epoetin (Procrit)] (the specific contraindication must be provided)
    d. Member's dosage does not exceed 200 mg daily obtained using the fewest number of capsules possible
8. Prurigo nodularis
    a. The diagnosis of prurigo nodularis has been confirmed by skin biopsy
    b. Thalidomide is prescribed by, or in consultation with, a dermatologist
    c. Member has refractory disease with an inadequate response to a sufficient trial (at least 60 days), persistent intolerable adverse effects, or contraindications to **ALL** of the

following ("i", "ii", and "iii" - the specific adverse effects and/or contraindications must be provided):

i. Phototherapy in combination with topical corticosteroid treatment

ii. Methotrexate

iii. Cyclosporine

d. Member's dosage does not exceed 400 mg daily obtained using the fewest number of capsules possible

9. Relapsed or refractory AIDS-related Kaposi sarcoma when **ALL** of the following criteria are met ("a" to "e"):
    a. Thalidomide will be used as third-line or later systemic therapy
    b. Member has had disease progression or lack of response to separate lines of systemic treatment with **BOTH** liposomal doxorubicin **AND** paclitaxel
    c. Thalidomide will **NOT** be used in combination with another immunomodulatory agent (i.e., thalidomide or lenalidomide) or in combination with systemic chemotherapy
    d. Treatment will be given in combination with appropriate antiretroviral therapy (ART)
    e. The dosage does not exceed 800 mg daily and will be obtained using the fewest number of capsules possible
10. Other FDA-approved or NCCN supported diagnosis (not previously listed above), and **BOTH** of the following ("a" and "b"):
    a. **EITHER** of the following is met:
        i. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
        ii. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
    b. The dosage of thalidomide does not exceed the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Duration of approval: 6 months

Continuation of thalidomide (Thalomid) **meets the definition of medical necessity** when **ALL** of the following are met ("1" to "4"):

1. Authorization or reauthorization for thalidomide has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of multiple myeloma, multicentric Castleman's disease, chronic GVHD, Behçet's syndrome, myelofibrosis-associated anemia, prurigo nodularis, lupus erythematosus with cutaneous manifestations, erythema nodosum leprosum, or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria.
2. **ANY** of the following based on the indication for use:
    a. Multiple myeloma:

i. If less than18 months of treatment – a serum M-protein level decrease of 25% or more* compared to baseline, or M-protein is undetectable, **AND** no increase in the size or number of lytic bone lesions after at least two cycles of treatment with thalidomide[†,#]

ii. 18 or more months of treatment - provider attestation that the member has not had disease progression during thalidomide treatment

**If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a decrease of 25% or more in the difference between the light chain produced by the myeloma cells (lambda or kappa) and the other light chain must be achieved*

[†]*If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a follow-up SFLC level must be provided*

[#]*An exception is permitted if a baseline M-protein level AND SFLC level are unavailable. In these cases the physician may provide an attestation of a beneficial clinical response which must include no increase in the size or number of lytic bone lesions.*

b. All other indications – The member has had a beneficial response to treatment per physician attestation

3. Thalidomide is **NOT** used in combination with another immunomodulatory drug [i.e., lenalidomide (Revlimid) or pomalidomide (Pomalyst)]
4. The member's dosage does not exceed the following depending on the indication for use:
    a. Multicentric Castleman's disease, lupus erythematosus, myelofibrosis-associated anemia, or multiple myeloma– 200 mg daily obtained using the fewest number of capsules possible
    b. Erythema Nodosum Leprosum (ENL), Behçet's syndrome, or prurigo nodularis – 400 mg daily obtained using the fewest number of capsules possible
    c. AIDS-related Kaposi sarcoma, or chronic graft-versus-host disease (GVHD) – 800 mg daily obtained using the fewest number of capsules possible
    d. Other FDA-approved or NCCN-supported diagnosis (not previously listed above or an orphan indication) - the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

Thalidomide **meets the definition of medical necessity** when used for **ANY** of the following designated orphan indications, the members has previously failed first-line treatment, the dosage does not exceed 400 mg daily (obtained using the fewest number of capsules possible), **AND** thalidomide will **NOT** be used in combination with another immunomodulatory drug (i.e., lenalidomide or pomalidomide):

1. Treatment of HIV-associated wasting syndrome
2. Treatment of severe recurrent aphthous stomatitis in severely, terminally immunocompromised members (e.g., members with AIDS)
3. Treatment of primary brain malignancies (e.g. glioblastoma multiforme, hemangioblastomatosis, etc.)
4. Treatment of Crohn's disease
5. Treatment of the clinical manifestations of mycobacterial infection caused by Mycobacterium tuberculosis and non-tuberculous mycobacteria

6. Treatment of myelodysplastic syndrome (MDS)

Duration of approval: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Thalidomide is indicated for: (1) the treatment of patients with newly diagnosed multiple myeloma in combination with dexamethasone, (2) acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL), and (3) as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. Thalidomide is **NOT** indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.

- Multiple myeloma: 200 mg once daily. The recommended dose of dexamethasone is 40 mg/day on days 1-4, 9-12, and 17-20 every 28 days.
- Erythema nodosum leprosum: 100 to 300 mg/day for an episode of cutaneous ENL. Patients weighing less than 50 kilograms should be started at the low end of the dose range. Up to 400 mg/day for severe cutaneous ENL. In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids may be started concomitantly and eventually tapered and discontinued when the neuritis has ameliorated. Dosing should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering should be maintained on the minimum dose necessary to control the reaction. Tapering off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.

Dosage Adjustments

- Renal impairment: no dosage adjustment is needed
- Hepatic impairment: no clinical studies have been conducted in patients with hepatic impairment
- Toxicity: No specific dosage recommendations are given in the package insert. Consider dose reduction, delay, or discontinuation in patients who develop NCI CTC (National Cancer Institute Common Toxicity Criteria) Grade 3 or 4 adverse reactions and/or based on clinical judgment.

Drug Availability

- Capsules: 50 mg, 100 mg, 150 mg and 200 mg

PRECAUTIONS:

Boxed Warning

- **Embryo-fetal toxicity**: If thalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Even a single dose [1 capsule (regardless of strength)] taken by a pregnant woman during her pregnancy can cause severe birth defects. Pregnancy must be excluded before start of treatment. Prevent pregnancy thereafter by the use of two reliable methods of

contraception. Thalidomide is only available through a restricted distribution program, the THALOMID REMS program (formerly known as the System for Thalomid Education and Prescribing Safety (S.T.E.P.S.) program).

- **Venous thromboembolism**: Significant increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving thalidomide with dexamethasone. Ischemic heart disease (including myocardial infarction) and stroke have been observed. Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of thromboembolism. Consider thromboprophylaxis based on an assessment of individual patients' underlying risk factors.

Contraindications

- Pregnancy
- Hypersensitivity to thalidomide

Precautions/Warnings

- **Thrombocytopenia**: including Grade 3 or 4 occurrences, has been reported in association with the clinical use of thalidomide. Monitor blood counts, including platelet counts. Dose reduction, delay, or discontinuation may be required.
- **Increased Mortality**: Observed in patients with MM when pembrolizumab was added to dexamethasone and a thalidomide analogue.
- **Tumor lysis syndrome**: Monitor patients at risk (e.g., those with high tumor burden prior to treatment) and take appropriate precautions.
- **Peripheral neuropathy**: Examine patients at monthly intervals for the first 3 months of thalidomide therapy and periodically thereafter for signs or symptoms of peripheral neuropathy. Consider electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter every 6 months in an effort to detect asymptomatic neuropathy.
- **Increased HIV viral load**: Measure viral load after the first and third months of treatment and every 3 months thereafter
- **Bradycardia**: Monitor patients for bradycardia and possible syncope. Dose reduction or discontinuation may be required.
- **Seizures**: Monitor patients with a history of seizures or at risk for the development of seizures closely for clinical changes that could precipitate acute seizure activity.
- **Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis**: Do NOT resume thalidomide following discontinuation for these reactions.
- **Neutropenia**: Patients may require dose interruption and/or dose reduction.
- **Dizziness and Orthostatic Hypotension**: Advise patients to sit upright for a few minutes prior to standing up from a recumbent position
- **Drowsiness and Somnolence**: Instruct patients to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness.
- **Drug Interactions**: Use caution if other drugs which have sedative and hypnotic properties, slow cardiac conduction and/or cause peripheral neuropathy must be used.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY)
J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

A30.0 – A30.9	Leprosy [Hansen's disease]
A31.0	Pulmonary mycobacterial infection
A31.1	Cutaneous mycobacterial infection
A31.8	Other mycobacterial infections
A31.9	Mycobacterial infection, unspecified
B20	Human immunodeficiency virus [HIV] disease (must be billed in combination with K12.0 or R64)
C46.0 – C46.9	Kaposi's sarcoma
C70.0 – C70.9	Malignant neoplasm of meninges
C71.0 – C71.9	Malignant neoplasm of brain
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.11	Plasma cell leukemia in remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.21	Extramedullary plasmacytoma in remission
C90.22	Other immunoproliferative neoplasms, in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.31	Solitary plasmacytoma in remission
C90.32	Solitary plasmocytoma in relapse
C94.40 – C94.42	Acute panmyelosis with myelofibrosis
D46.0	Refractory anemia without sideroblasts, so stated
D46.1	Refractory anemia with sideroblasts
D46.20 – D46.22	Refractory anemia with excess of blasts
D46.9	Myelodysplastic syndrome, unspecified
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ringed sideroblasts
D46.C	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
D46.Z	Other myelodysplastic syndromes
D47.4	Osteomyelofibrosis
D47.Z2	Castleman disease
D47.Z9	Neoplasm of uncertain behavior of plasma cells
D75.81	Myelofibrosis
D89.811	Chronic graft-versus-host disease
D89.812	Acute on chronic graft-versus-host disease
K12.0	Recurrent oral aphthae
K50.00 – K50.919	Crohn's disease (regional enteritis)
L28.1	Prurigo nodularis
L52	Erythema nodosum

L93	Lupus erythematosus
M35.2	Behçet's disease
R64	Cachexia

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT.**

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Common Terminology Criteria for Adverse Events (CTCAE): standardized definitions for adverse events published by the National Cancer Institute to describe the severity of organ toxicity for patients receiving cancer therapy. Toxicity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the organ system involved.

Heavy chain: the larger component of an immunoglobulin. There are five types: IgG, IgA, IgM, IgD, and IgE.

Immunoglobulins (a.k.a., antibodies): proteins made by normal plasma cells that have an important role in fighting infection as part of the humoral immune response. Antibodies are composed of two heavy chains and two light chains that form a larger complex. Each plasma cell produces only one type of heavy chain and one type of light chain.

Light chain: the smaller component of an immunoglobulin. There are two types: kappa and lambda.

Myeloma Protein (M-Protein): a nonfunctional immunoglobulin protein or protein fragment produced by malignant plasma cells (or myeloma cells). Since myeloma cells are monoclonal, the M-proteins for a given patient are structurally identical. Both portions of an immunoglobulin (the heavy chain and light chain) can be found in the serum, while only light chains can be found in the urine.

Plasma cell: a fully differentiated B lymphocyte (a type of white blood cell) that is specialized for immunoglobulin production and is found primarily in bone marrow.

Plasmacytoma: a discrete tumor consisting of neoplastic, monoclonal (originating from a single cell) plasma cells in either bone or soft tissue (extramedullary).

Serum Protein Electrophoresis (SPEP) – a test that detects and quantifies the amount of M-protein in the serum. An serum M-protein of greater than 30 g/L is consistent with a diagnosis of MM.

Smoldering (Asymptomatic) myeloma: defined as M-protein in serum of 30 g/dL or more **AND/OR** bone marrow clonal plasma cells of 10% or more and no related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms.

RELATED GUIDELINES:

Autologous Bone Marrow and Stem Cell Transplantation 02-38241-01

Bortezomib IV 09-J0000-92

Carfilzomib (Kyprolis) IV, 09-J1000-81

Daratumumab (Darzalex) IV, 09-J2000-49

Doxorubicin HCl Liposome (Doxil) IV 09-J0000-91

Elotuzumab (Empliciti) IV, 09-J2000-50

Ixazomib (Ninlaro), 09-J2000-51

Lenalidomide (Revlimid) 09-J0000-80

Panobinostat (Farydak), 09-J2000-37

Pomalidomide (Pomalyst) Capsule, 09-J1000-95

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/12/19.

GUIDELINE UPDATE INFORMATION:

01/01/12	New Medical Coverage Guideline.

12/15/12	Review and revision to guideline; consisting of updating position statement, dosage and administration, contraindications, precautions and warnings, exceptions and references.
11/15/13	Review and revision to guideline; consisting of revision and reformatting position statement, dosage/administration, precautions, and references.
11/15/14	Review and revision to guideline; consisting of description and references.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/15	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, definitions, related guidelines, and references.
10/01/16	Revision: ICD-10 code updates.
11/15/16	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, definitions, related guidelines, and references.
02/16/17	Revision: Update to Position Statement.
12/15/17	Review and revision of guidelines consisting of updating the description, position statement, dosage/administration, precautions, billing/coding, and references.
07/15/18	Review and revision to guidelines consisting of updating the description section, position statement, precautions, billing/coding information, definitions, and references.
07/15/19	Review and revision to guidelines consisting of updating the description section, position statement, related guidelines, and references.