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Subject: Lenalidomide (Revlimid®)

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:

Lenalidomide (Revlimid) is a chemical derivative of thalidomide. While the mechanism of action of lenalidomide is not completely understood, it is known that the agent possesses immunomodulatory properties that result in the inhibition of pro-inflammatory cytokines and cell proliferation of some cell lines. Additionally, lenalidomide inhibits growth factor-induced endothelial cell migration.

Lenalidomide was first approved by the U.S. Food and Drug Administration (FDA) in December 2005 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. Lenalidomide was then FDA-approved for the treatment of multiple myeloma (MM) in patients who have received at least one prior therapy in June 2006 and then mantle cell lymphoma (MCL) in patients whose disease has relapsed or progressed after two prior therapies in June 2013. The MM indication was expanded to include first-line treatment in February 2015. In May 2019, the FDA-approved indications were expanded to include previously treated follicular lymphoma (FL) and marginal zone lymphoma (MZL), in combination with a rituximab product. Lenalidomide was previously granted orphan designation, as sponsored by the innovator drug company, for its FDA-approved indications (MM – 2001, anemia due to MDS – 2004, MCL – 2009, follicular lymphoma – 2013, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) – 2015, and splenic and nodal marginal zone lymphoma - 2017), and also has orphan designations for off-label indications (chronic lymphocytic leukemia – 2007 and diffuse large B-cell lymphoma – 2011).

National Comprehensive Cancer Network (NCCN) Guidelines for B-cell Lymphomas (Version 3.2019), Central Nervous System Cancers (Version 1.2019), Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (Version 5.2019), Hodgkin Lymphoma (Version 1.2019), Multiple Myeloma (Version 2.2019),

Myelodysplastic Syndromes (Version 2.2019), Myeloproliferative Neoplasms (Version 2.2019), Primary Cutaneous Lymphomas (Version 2.2019), Systemic Light Chain Amyloidosis (Version 1.2019), and T-cell Lymphomas (Version 2.2019) include category 1 and/or 2A recommendations for use of lenalidomide 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.

Initiation of lenalidomide (Revlimid) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions ("1" to "11") when **ALL** associated criteria are met, **AND** lenalidomide will **NOT** be used in combination with another immunomodulatory drug [i.e., pomalidomide (Pomalyst) or thalidomide (Thalomid)]:

1. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL), and **ALL** of the following ("a", "b", and "c"):
    a. **ANY** of the following ("i", "ii", or "iii"):
        i. Treatment is used as second-line or later therapy for relapsed or refractory disease
        ii. **ALL** of the following ("1", "2", and "3"):
            1. Treatment is used as post first-line maintenance therapy for a member who obtained a partial response or better after at least 4 cycles of first-line CLL/SLL induction therapy
            2. The member is documented as high-risk for early disease progression [high-risk is defined as either after first-line therapy: (1) a blood minimal residual disease (MRD) level of $\geq 10^{-2}$, or (2) both a blood MDR level of $\geq 10^{-4}$ to $<10^{-2}$ **AND** an unmutated immunoglobulin heavy-chain variable-region (IGVH) gene] – confirmatory laboratory documentation must be submitted
            3. The member does **NOT** have the del(17p)/TP53 mutation - confirmatory laboratory documentation must be submitted
        iii. Treatment is used as post second-line maintenance therapy for a member who obtained a partial response or better after treatment for relapsed or refractory disease
    b. **EITHER** of the following depending on the indication for use:
        i. For post first- or second-line maintenance therapy – lenalidomide will used as monotherapy
        ii. Non-maintenance therapy - lenalidomide will be used as either monotherapy or in combination with rituximab
    c. Member's dosage does not exceed the either of the following depending on the indication for use, and will be obtained using the fewest number of capsules possible:
        i. For post first- or second-line maintenance therapy – 10 mg daily
        ii. Non-maintenance therapy – 25 mg daily
2. Classical Hodgkin Lymphoma (CHL), and **ALL** of the following ("a", "b", and "c"):

a. Indication for use is second-line or later therapy for relapsed or refractory disease

b. Lenalidomide will be used as monotherapy for treatment of the member's disease

c. Member's dosage does not exceed 25 mg daily on days 1 to 21 of a 28-day cycle , and will be obtained using the fewest number of capsules possible

3. Multiple Myeloma (MM), and **ALL** of the following ("a", "b", and "c"):

   a. Member has active (symptomatic) multiple myeloma

   b. The member's baseline (i.e., within 90 days prior to initiating treatment with lenalidomide) serum monoclonal protein (M-protein) as detected by serum protein electrophoresis (SPEP) is provided*

      **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*

   c. **EITHER** of the following ("i" or "ii"):

      i. Maintenance therapy following stem cell transplant or maintenance therapy after primary therapy for non-transplant candidates: member's dosage does not exceed 15 mg daily, and will be obtained using the fewest number of capsules possible

      ii. All other non-maintenance therapies: member's dosage does not exceed 25 mg daily on days 1 to 21 of a 28-day cycle or days 1 to 14 of a 21-day cycle, and will be obtained using the fewest number of capsules possible

4. Myelodysplastic Syndromes (MDS), and **ALL** of the following ("a", "b", "c", and "d"):

   a. Member has symptomatic anemia requiring red blood cell (RBC) transfusion

   b. **ANY** of the following ("i" , "ii", or "iii") – IPSS, IPSS-R, or WPPS score must be provided:

      i. IPSS criteria - The member's MDS is classified as low- or intermediate-1 (INT-1) risk disease defined as an International Prognostic Scoring System (IPSS) score of 1 or less

      ii. IPSS-R criteria - The member's MDS is classified as very low-, low-, or intermediate-risk (3.5 score only) disease defined as a revised International Prognostic Scoring System (IPSS-R) score of 3.5 or less

      iii. WPSS criteria - The member's MDS is classified as very low-, low-, or intermediate-risk disease defined as a WHO-based Prognostic Scoring System (WPSS) score of 2 or less

   c. Member has **EITHER** of the following ("i" or "ii"):

      i. A confirmed deletion 5q chromosome [del(5q)] abnormality (laboratory documentation must be submitted)

      ii. No del(5q) abnormality (or status is unknown) and **EITHER** of the following ("1" or "2"):

         1. **BOTH** of the following ("a" and "b"):

            a. Serum erythropoietin level >500 mU/mL (laboratory documentation must be submitted)

            b. Member has a low probability of response to immunosuppressive therapy (i.e., antithymocyte globulin with or without cyclosporine) as initial treatment

         2. **ALL** of the following ("a", "b", or "c"):

            a. Serum erythropoietin level ≤500 mU/mL (laboratory documentation must be submitted)

            b. 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)

c. Lenalidomide will be used in combination with an ESA (unless use of an ESA is contraindicated)

d. Member's dosage does not exceed 10 mg daily

5. Myelofibrosis-associated anemia, and **ALL** of the following ("a", "b", "c", and "d"):
   a. Member has symptomatic anemia requiring red blood cell (RBC) transfusion
   b. Lenalidomide 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 10 mg daily
6. Non-Hodgkin Lymphoma (NHL), and **ALL** of the following ("a", "b", and "c"):
   a. Treatment is used as second-line or later therapy for relapsed, refractory, or progressive NHL disease [see exceptions for follicular lymphoma, mantle cell lymphoma, and Mycosis Fungoides (MF)/Sézary Syndrome (SS)]
   b. Member is diagnosed with **ANY** of the following subtypes of NHL, and **ALL** associated criteria are met:
      - Adult T-Cell leukemia/lymphoma (ATLL) and **BOTH** of the following ("i" and "ii"):
        i. Lenalidomide is being used for non-responders to first-line therapy for acute disease or lymphoma (**NOT** to be used for chronic/smoldering ATLL)
        ii. Lenalidomide will be used as monotherapy
      - AIDS-related B-cell lymphoma and **ALL** of the following ("i", ii" and "iii"):
        i. The member has **ANY** of the following subtypes:
           - Diffuse large B-cell lymphoma [non-germinal center B-cell (GCB) subtypes only; does not include primary DLBCL of the CNS – see separate primary CNS lymphoma indication]
           - HHV8-positive DLBCL, NOS
           - Primary effusion lymphoma
        ii. Member is **NOT** a candidate for stem cell transplant
        iii. Lenalidomide will be used as either monotherapy or in combination with rituximab
      - Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) – see separate indication #1
      - Diffuse large B-cell lymphoma, non-germinal center B-cell type (i.e., non-GCB DLBCL) including those with histological transformation from follicular lymphoma or marginal zone lymphoma [does not include primary DLBCL of the CNS – see separate primary CNS lymphoma indication] and **BOTH** of the following ("i" and "ii"):
        i. Member is **NOT** a candidate for stem cell transplant
        ii. Lenalidomide will be used as either monotherapy or in combination with rituximab
      - Follicular lymphoma, and **EITHER** of the following ("i" or "ii"):

i. Treatment is used first-line therapy, and **BOTH** of the following ("a" and "b"):

a. Member does **NOT** have limited, non-bulky disease (i.e., stage I or continuous stage II disease with tumor mass <7 cm) that could be treated with involved-site radiation therapy (ISRT)

b. Lenalidomide will be used in combination with rituximab

ii. Treatment is used as second-line or subsequent therapy (if not previously given as first-line) for refractory or progressive disease **AND** lenalidomide will be used as either monotherapy or in combination with rituximab

- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma **AND** lenalidomide will be used as either monotherapy or in combination with rituximab
- Hepatosplenic gamma-delta T-cell lymphoma, and **BOTH** of the following ("i" and "ii"):
  i. Member has refractory disease after two primary treatment regimens
  ii. Lenalidomide will be used as monotherapy
- High-grade B-cell lymphomas (a.k.a,, double-hit/triple-hit lymphomas), and **BOTH** of the following ("i" and "ii"):
  i. Member is **NOT** a candidate for stem cell transplant
  ii. Lenalidomide will be used as either monotherapy or in combination with rituximab
- Mantle cell lymphoma (MCL), and **EITHER** of the following ("i" or "ii"):
  i. Treatment is used as less aggressive induction therapy for previously untreated disease in combination with rituximab
  ii. Treatment is used as second-line or later therapy for relapsed, refractory, or progressive disease **AND** lenalidomide will be used as either monotherapy or in combination with rituximab
- Multicentric Castleman's disease (CD) **AND** lenalidomide will be used as either monotherapy or in combination with rituximab
- Mycosis Fungoides (MF)/Sézary Syndrome (SS), and **BOTH** of the following ("i" and "ii"):
  i. **EITHER** of the following ("1" or "2"):
    1. Lenalidomide is being used as initial primary treatment of EITHER of the following subtypes:
      a. Stage IV non Sezary or visceral disease (solid organ)
      b. Large cell transformation (LCT) with generalized cutaneous or extracutaneous lesions
    2. Lenalidomide is being used an second-line or later treatment for **ANY** of the following subtypes that are relapsed or refractory to prior therapy:
      a. Stage IA, IB, or IIA disease with B1 blood involvement
      b. Stage IIB, IIIA, IIIB, or IV disease
      c. Any stage disease with large-cell transformation (LCT)
  ii. Lenalidomide will be used as monotherapy or in combination with skin-directed therapies (with or without radiation therapy)
- Nodal marginal zone lymphoma **AND** lenalidomide will be used as either monotherapy or in combination with rituximab

- Non-gastric MALT lymphoma **AND** lenalidomide will be used as either monotherapy or in combination with rituximab
- Peripheral T-cell lymphoma and **BOTH** of the following ("i" and "ii"):
    i. The member has **ANY** of the following subtypes:
        - Angioimmunoblastic T-cell lymphoma (AITL)
        - Peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS)
        - Enteropathy-associated T-cell lymphoma (EATL)
        - Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL)
        - Nodal peripheral T-cell lymphoma with TFH phenotype
        - Follicular T-cell lymphoma
    ii. Lenalidomide will be used as monotherapy
- Primary cutaneous B-cell lymphoma and **BOTH** of the following ("i" and "ii"):
    i. The member has **EITHER** of the following subtypes:
        - Primary cutaneous marginal zone lymphoma (PCMZL) with extracutaneous disease relapse or progression
        - Primary cutaneous follicle center lymphoma (PCFCL) with extracutaneous disease relapse or progression
    ii. Lenalidomide will be used as either monotherapy or in combination with rituximab
- Primary cutaneous diffuse large B-cell lymphoma, leg type (non-GCB), and **BOTH** of the following ("i" and "ii"):
    i. Member is **NOT** a candidate for stem cell transplant
    ii. Lenalidomide will be used as either monotherapy or in combination with rituximab
- Primary cutaneous CD30+ T-cell lymphoproliferative disorder, and **BOTH** of the following ("i" and "ii"):
    i. The member has **EITHER** of the following subtypes:
        - Primary cutaneous anaplastic large cell lymphoma (ALCL) with multifocal lesions
        - Cutaneous ALCL with regional nodes (excludes systemic ALCL)
    ii. Lenalidomide will be used as monotherapy
- Splenic marginal zone lymphoma **AND** lenalidomide will be used as either monotherapy or in combination with rituximab

c. Member's dosage does not exceed 25 mg daily on days 1 to 21 of a 28-day cycle, and will be obtained using the fewest number of capsules possible

7. POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) syndrome, and **ALL** of the following ("a", "b", and "c"):
    a. Treatment is used as second-line or later therapy for relapsed or refractory disease
    b. Lenalidomide will be used as either monotherapy or in combination with rituximab
    c. Member's dosage does not exceed 25 mg daily on days 1 to 21 of a 28-day cycle, and will be obtained using the fewest number of capsules possible
8. Post-Transplant Lymphoproliferative Disorder (PTLD), and **ALL** of the following ("a", "b", "c", and "d"):

a. Treatment is used as second-line or later therapy for relapsed or refractory disease

b. Member was previously treated for non-germinal center B-cell (non-GBC) type monomorphic PTLD

c. Lenalidomide will be used as either monotherapy or in combination with rituximab

d. Member's dosage does not exceed 25 mg daily, and will be obtained using the fewest number of capsules possible

9. Primary Central Nervous System (CNS) Lymphoma (including primary DLBCL of the CNS), and **ALL** of the following ("a", "b", and "c"):

   a. Treatment is used as second-line or later therapy for relapsed or refractory disease

   b. Lenalidomide will be used as either monotherapy or in combination with rituximab (with or without radiation therapy)

   c. Member's dosage does not exceed 25 mg daily, and will be obtained using the fewest number of capsules possible

10. Systemic Light Chain Amyloidosis (SLCA), and **ALL** of the following ("a", "b", "c", and "d"):

    a. The diagnosis has been validated by confirming the presence of amyloid deposits in tissue **AND** the deposits are composed of light chains

    b. The member's baseline (i.e., within 90 days prior to initiating treatment with lenalidomide) serum free light chains (SFLC) level, as detected by serum free light chain assay (SFLCA), is provided

    c. One of the following regimens will be used ("i", "ii", or "iii"):

       i. Lenalidomide + cyclophosphamide + dexamethasone

       ii. Lenalidomide + dexamethasone

       iii. Lenalidomide monotherapy (only if the member has a contraindication or intolerance to systemic corticosteroid treatment – the specific contraindication or intolerance must be provided)

    d. Member's dosage does not exceed 25 mg daily on days 1 to 21 of a 28-day cycle, and will be obtained using the fewest number of capsules possible

11. 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 lenalidomide 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 lenalidomide (Revlimid) **meets the definition of medical necessity** when **ALL** of the following are met "1", "2", "3", and "4"):

1. Authorization or reauthorization for lenalidomide has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of multiple myeloma, systemic light chain amyloidosis, MDS, myelofibrosis-associated anemia, NHL (including all subtypes), CLL/SLL, primary CNS lymphoma (including primary DLBCL of the CNS), POEMS, post-transplant lymphoproliferative disorder, classical Hodgkin lymphoma, 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 is undetectable, **AND** no increase in the size or number of lytic bone lesions after at least two cycles of treatment with lenalidomide[†,#]
        ii. 18 or more months of treatment - provider attestation that the member has not had disease progression during lenalidomide 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 submitted

        [#]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. Systemic light chain amyloidosis:
        i. If less than18 months of treatment - there has been a reduction (improvement) in the member's SFLC level as compared to baseline[#] after at least two cycles of treatment with lenalidomide
        ii. If 18 or more months of treatment - provider attestation that the member has not had disease progression during lenalidomide treatment

        [#]An exception is permitted if a baseline SFLC value is unavailable. A follow-up SFLC level still must be submitted. The physician must provide an attestation of a beneficial clinical response.

    c. Anemia due to MDS or myelofibrosis-associated anemia:
        i. If less than18 months of treatment - the member is RBC transfusion independent, **OR** there has been a reduction in the frequency of transfusion as compared to baseline (i.e., before treatment with lenalidomide) – medical record documentation (e.g., chart note) of transfusion reduction or transfusion independence must be submitted
        ii. If 18 or more months of treatment - provider attestation that the member has had a beneficial response to lenalidomide treatment

    d. Palliative treatment of CHL: member has had a beneficial response to treatment

    e. All other indications: the member's disease has **NOT** progressed while receiving treatment with lenalidomide
3. Lenalidomide is **NOT** used in combination with another immunomodulatory drug [i.e., pomalidomide (Pomalyst), or thalidomide (Thalomid)]

4. The members dosage does not exceed the following depending on the indication for use:
    - Myelodysplastic Syndromes (MDS) or myelofibrosis-associated anemia – 10 mg daily obtained using the fewest number of capsules possible
    - CLL/SLL (maintenance or non-maintenance therapy), Post-Transplant Lymphoproliferative Disorder, or Primary CNS Lymphoma (including primary DLBCL of the CNS) - 25 mg daily obtained using the fewest number of capsules possible
    - Multiple myeloma maintenance therapy following stem cell transplant or maintenance therapy after primary therapy for non-transplant candidates – 15 mg daily obtained using the fewest number of capsules possible
    - Other multiple myelemia therapies - 25 mg daily on days 1 to 21 of a 28-day cycle or days 1 to 14 of a 21-day cycle obtained using the fewest number of capsules possible
    - NHL (including all subtypes), classical Hodgkin lymphoma, POEMS, and SLCA - 25 mg daily on days 1 to 21 of a 28-day cycle obtained using the fewest number of capsules possible
    - Other FDA-approved or NCCN-supported diagnosis (not previously listed above) - the maximum recommended in the FDA-approved prescribing information or the maximum recommended by the applicable NCCN guidelines for the diagnosis

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

Lenalidomide is indicated for the treatment of patients with: (1) multiple myeloma (MM), in combination with dexamethasone; (2) MM, as maintenance following autologous hematopoietic stem cell transplant; (3) transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities; (4) mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib; (5) previously treated follicular lymphoma, in combination with a rituximab product; and (6) previously treated marginal zone lymphoma (MZL), in combination with a rituximab product.

- Multiple Myeloma (MM): 25 mg once daily orally on Days 1-21 of repeated 28-day cycles until disease progression or unacceptable toxicity. For patients who are ASCT-eligible, hematopoietic stem cell mobilization should occur within 4 cycles of a lenalidomide-containing therapy. For patients > 75 years old, the starting dose of dexamethasone may be reduced. See the product package insert for the recommended dexamethasone dosage.
- MM Maintenance Therapy: After adequate hematologic recovery (ANC ≥1,000/mcL and/or platelet counts ≥75,000/mcL), 10 mg once daily continuously on Days 1-28 of repeated 28-day cycles. After 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated.
- Myelodysplastic Syndromes (MDS): 10 mg once daily
- Mantle Cell Lymphoma (MCL): 25 mg once daily orally on Days 1-21 of repeated 28-day cycles until disease progression or unacceptable toxicity.
- Follicular Lymphoma: or Marginal Zone Lymphoma: 20 mg orally once daily on Days 1-21 of repeated 28-day cycles for up to 12 cycles of treatment in combination with a rituximab-product.

The capsules should be swallowed whole with water and should not be opened, broken, or chewed.

Limitations of Use (per the product package insert): lenalidomide is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

Dose Adjustments

Renal impairment:

- CrCl >60 mL/min: No adjustment needed.
- CrCl 30 to 60 mL/min: 5 mg once daily (MM maintenance, MDS) or 10 mg once daily (MM, MCL, FL, MZL). For MM, FL, and MZL, consider escalating the dose to 15 mg after 2 cycles if the patient tolerates the 10 mg dose of lenalidomide without dose-limiting toxicity.
- CrCl <30 mL/min (not requiring dialysis): 2.5 mg once daily (MM maintenance, MDS), 5 mg once daily (FL, MZL), or 15 mg every 48 hours (MM, MCL).
- CrCl <30 mL/min (requiring dialysis): 2.5 mg once daily (MM maintenance, MDS) or 5 mg once daily (MM, MCL), after dialysis on dialysis days.

Hematologic toxicities: See the product package insert for specific dosage adjustments for thrombocytopenia and/or neutropenia.

Drug Availability

Capsules: 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

PRECAUTIONS:

Boxed Warning

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS and ARTERIAL THROMBOEMBOLISM

- Embryo-Fetal Toxicity - Do not use Revlimid during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting Revlimid treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after Revlimid treatment. To avoid embryo-fetal exposure to lenalidomide, Revlimid is only available through a restricted distribution program, the REVLIMID REMS program. Information about the REVLIMID REMS program is available at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436.
- Hematologic Toxicity (Neutropenia and Thrombocytopenia) - Revlimid can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndromes had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q myelodysplastic syndromes should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.
- Venous and Arterial Thromboembolism - Revlimid has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma who were treated with Revlimid and dexamethasone therapy. Monitor for and advise patients about signs and symptoms of thromboembolism. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest

pain, or arm or leg swelling. Thromboprophylaxis is recommended and the choice of regimen should be based on an assessment of the patient's underlying risks.

Contraindications

- Pregnancy - can cause fetal harm when administered to a pregnant female
- Hypersensitivity to lenalidomide - contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

Precautions/Warnings

- **Digoxin**: Periodic monitoring of digoxin plasma levels is recommended due to increase exposure during concomitant lenalidomide therapy.
- **Increased mortality**: serious and fatal cardiac adverse reactions occurred in patients with CLL treated with lenalidomide.
- **Tumor lysis syndrome**: monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions
- **Tumor flare reaction**: serious tumor flare reactions have occurred during investigational use for chronic lymphocytic leukemia and lymphoma
- **Hepatotoxicity**: hepatic failure including fatalities; monitor liver function. Stop treatment and evaluate if hepatotoxicity is suspected.
- **Second Primary Malignancies (SPM)**: higher incidences of SPM were observed in controlled trials of patients with multiple myeloma receiving lenalidomide.
- **Impaired Stem Cell mobilization**: a decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with lenalidomide has been reported. Consider early referral to transplant center.

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, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity:

B20	Human immunodeficiency virus [HIV] disease (must be billed in combination with C83.30-C83.39, C83.80-C83.89, or C85.80-C85.89)
C81.00 – C81.99	Hodgkin lymphoma
C82.00 – C82.09	Follicular lymphoma grade I
C82.10 – C82.19	Follicular lymphoma grade II
C82.20 – C82.29	Follicular lymphoma grade III, unspecified
C82.30 – C82.39	Follicular lymphoma grade IIIa

C82.40 – C82.49	Follicular lymphoma grade IIIb
C82.50 – C82.59	Diffuse follicle center lymphoma
C82.60 – C82.69	Cutaneous follicle center lymphoma
C82.80 – C82.89	Other types of follicular lymphoma
C82.90 – C82.99	Follicular lymphoma, unspecified
C83.00 – C83.09	Small cell B-cell lymphoma
C83.10 – C83.19	Mantle cell lymphoma
C83.30 – C83.39	Diffuse large B-cell lymphoma
C83.80 – C83.89	Other non-follicular lymphoma
C84.00 – C84.09	Mycosis fungoides
C84.40 – C84.49	Peripheral T-cell lymphoma, not classified
C84.90 – C84.99	Mature T/NK-cell lymphomas, unspecified
C84.Z0 – C84.Z9	Other mature T/NK-cell lymphomas
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 – C85.89	Other specified types of non-Hodgkin lymphoma
C86.1	Hepatosplenic T-cell lymphoma
C86.2	Enteropathy-type (intestinal) T-cell lymphoma
C86.5	Angioimmunoblastic T-cell lymphoma
C86.6	Primary cutaneous CD30-positive T-cell proliferations
C88.4	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue [MALT-lymphoma]
C88.8	Other malignant immunoproliferative diseases
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	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.31	Solitary plasmacytoma in remission
C90.32	Solitary plasmacytoma in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type, not having achieved remission
C92.11	Chronic lymphocytic leukemia of B-cell type, in remission
C91.12	Chronic lymphocytic leukemia of B-cell type, in relapse
C91.50	Adult T-cell lymphoma/leukemia (HTLV-1-associated), not having achieved remission
C91.52	Adult T-cell lymphoma/leukemia (HTLV-1-associated), in relapse
C92.10	Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission
C93.10	Chronic myelomonocytic leukemia not having achieved remission
C94.40 – C94.42	Acute panmyelosis with myelofibrosis
C94.6	Myelodysplastic disease, not classified
D36.0	Benign neoplasm of lymph nodes
D46.0	Refractory anemia without ring sideroblasts, so stated
D46.1	Refractory anemia with ring sideroblasts
D46.20 – D46.21	Refractory anemia with excess of blasts
D46.4	Refractory anemia, unspecified
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

D47.1	Chronic myeloproliferative disease
D47.4	Osteomyelofibrosis
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
D47.Z2	Castleman disease
D47.Z9	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D75.81	Myelofibrosis
E85.81	Light chain (AL) amyloidosis
E85.89	Other amyloidosis
E85.9	Amyloidosis, unspecified
G62.9	Polyneuropathy, unspecified [for POEMS syndrome only]
R59.0 - R59.9	Enlarged lymph nodes

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.

Multiple Myeloma: a malignant neoplasm of plasma cells in which the plasma cells proliferate and invade the bone marrow, causing destruction of the bone and resulting in pathologic fracture and bone pain. It is the most common type of monoglonal gammopathy, characterized by presence of a monoclonal immunoglobulin (immunoglobulin recognized as a single protein), Bence Jones proteins in the urine, anemia, and lowered resistance to infection. Also called plasma cell myeloma.

Myelodysplastic Syndrome (MDS): any of a group of related bone marrow disorders of varying duration preceding the development of overt acute myelogenous leukemia; they are characterized by abnormal hematopoietic stem cells, aneuia, neutropenia, and thrombocytopenia. Splenomegaly, hepatomegaly and lymphadenopathy may not occur until the onset of leukemia, which may be explosive. Also called preleukemia.

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.

Non-Hodgkin's Lymphoma: a large group of lymphatic cancers that comprise approximately 90% of all diagnosed lymphomas. All lymphomas are defined as cancerous growth of lymphocytes, better known as white blood cells, which are the body's primary defense against infection and disease. In lymphoma, these lymphocytes mutate and reproduce uncontrollably, crowding out healthy cells and forming tumors.

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).

Refractory (cancer): cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment.

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:

Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01

Bortezomib (Velcade) 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) Injection, 09-J2000-50

Erythropoiesis Stimulating Agents, 09-J0000-31

Ixazomib (Ninlaro), 09-J2000-51

Panobinostat (Farydak), 09-J2000-37

Pomalidomide (Pomalyst) Capsule, 09-J1000-95

Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

International Prognostic Scoring System (IPSS)

	Score Value				
Prognostic variable	0	0.5	1	1.5	2
Marrow blasts (%)	<5	5 to 10	--	>10 to 20	>20 to 30
Karyotype	Good	Intermediate	Poor	--	--
Cytopenia*	0 or 1	2 or 3			

- Low: score of 0
- INT-1: score of 0.5 or 1
- INT-2: score of 1.5 or 2
- High: score of 2.5 or greater

*Neutrophil count <1,800/mcL, platelets <100,000/mcL, Hb <10 g/dL

Revised International Prognostic Scoring System (IPSS)

	Score Value						
Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetic	Very good	--	Good	--	Intermediate	Poor	Very poor
Marrow blasts (%)	<2	--	>2 to <5	--	5 to 10	>10	--
Hemoglobin (g/dL)	≥10	--	8 to <10	<8	--	--	--
Platelets (per mcL)	≥100,000	50,000 to <100,000	<50,000				
ANC (per mcL)	≥800	<800					

- Very low: score of ≤1.5
- Low: score of >1.5 to 3
- Intermediate: score of >3 to 4.5

- High: score of >4.5 to 6
- Very High: score of >6

Website to calculator tool: http://www.ipss-r.com/

WHO-based Prognostic Scoring System (WPSS)

Variable	Variable scores			
	0	1	2	3
WHO category	RCUS, RARS, MDS with isolated del(5q)	RCMD	RAEB-1	RAEB-2
Karyotype	Good	Intermediate	Poor	-
Severe anemia (Hg <9 g/dl in biological males or <8 mg/dL in biological females)	Absent	Present	-	-

- Very low: score of 0
- Low: score of 1
- Intermediate: score of 2
- High: score of 3 or 4
- Very High: score of 5 or 6

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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:

11/15/08	New Medical Coverage Guideline.
11/15/09	Review and Revision; consisting of updating references.
02/15/11	Review and Revision; consisting of updating position statement, boxed warnings, coding and references.
11/15/11	Review and revision to guideline; consisting of updating precautions, coding and references.
11/15/12	Review and Revision; consisting of updating position statement, coding and references.
03/15/13	Revision to guideline; consisting of adding quantity limit to position statement.
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 position statement, description, coding, 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.
11/18/16	Revision: updates to Position Statement.
02/15/17	Revision to guideline consisting of updating the description, position statement, and references based on an update to the NCCN guidelines for B-cell lymphomas and CLL/SLL.

02/16/17	Revision: Update to Position Statement.
06/15/17	Revision to guideline consisting of updating the description, position statement, billing/coding, and references based on an update to the NCCN guideline for CLL/SLL regarding lenalidomide maintenance treatment.
10/01/17	New ICD-10 code
12/15/17	Review and revision of guidelines consisting of updating the description, position statement, and references.
03/15/17	Revision of guidelines consisting of clarifying the position statement for MM dosage and use in non-GBD DLBCL.
05/15/18	Revision of guidelines consisting of adding a new indication of Primary CNS Lymphoma to the position statement based on NCCN Guideline update.
07/15/18	Review and revision to guidelines consisting of updating the description section, position statement, billing/coding information, and references.
03/15/19	Revision to guideline consisting of updating the description section, position statement, billing/coding, and references based on updated NCCN B-Cell, Primary Cutaneous, and T-Cell Lymphoma treatment guidelines.
07/15/19	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, related guidelines, and references.