Immune Modulators – Thalidomide Analogs

WA.PHAR.140 Effective Date: 10/1/2024

Related medical policies:

Policy Name	Indications
N/A	N/A

Note: *New-to-market drugs included in this class based on the Apple Health Preferred Drug List are non-preferred and subject to this prior authorization (PA) criteria. Non-preferred agents in this class require an inadequate response or documented intolerance due to severe adverse reaction or contraindication to at least TWO preferred agents. If there is only one preferred agent in the class documentation of inadequate response to ONE preferred agent is needed. If a drug within this policy receives a new indication approved by the Food and Drug Administration (FDA), medical necessity for the new indication will be determined on a case-by-case basis following FDA labeling.*

To see the list of the current publication of the Coordinated Care of Washington, Inc. Preferred Drug List (PDL), please visit:
https://www.coordinatedcarehealth.com/content/dam/centene/centene-pharmacy/pdl/FORMULARY-CoordinatedCare_Washington.pdf

Medical necessity

Drug	Medical Necessity
lenalidomide (Revlimid) pomalidomide (Pomalyst) thalidomide (Thalomid)	**Thalidomide Analogs** may be considered medically necessary in patients who meet the criteria described in the clinical policy below. If all criteria are not met, the clinical reviewer may determine there is a medically necessary need and approve on a case-by-case basis. The clinical reviewer may choose to use the reauthorization criteria when a patient has been previously established on therapy and is new to Apple Health.

Clinical policy:

Clinical Criteria	
Erythema Nodosum Leprosum (ENL) thalidomide (Thalomid)	Thalidomide (Thalomid) may be approved when all the following documented criteria are met: 1. Prescribed by, or in consultation with an infectious disease specialist; **AND** 2. Diagnosis of erythema nodosum leprosum (ENL); **AND** a. Medication will be used for the acute treatment of the cutaneous manifestations of moderate to severe ENL; **AND** i. If moderate to severe neuritis is present, the medication will be used in combination with

	corticosteroids unless not tolerated or contraindicated; **OR** b. Medication will be used as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. If ALL criteria are met, the request will be authorized for **6 months.**
	Criteria (Reauthorization) Thalidomide (Thalomid) may be approved when all the following documented criteria are met: 1. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms. If ALL criteria are met, the request will be authorized for **6 months.**
Follicular Lymphoma (FL) lenalidomide (Revlimid)	Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND** 2. Diagnosis of follicular lymphoma (FL); **AND** 3. If used as first-line treatment, lenalidomide will be used in combination with another medication (e.g. rituximab or obinutuzumab); **OR** 4. Patient was previously treated with at least one prior regimen for FL (e.g., bendamustine + rituximab/obinutuzumab, cyclophosphamide/doxorubicin/vincristine/prednisone) If ALL criteria are met, the request will be authorized for **6 months.**
	Criteria (Reauthorization) Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms. If ALL criteria are met, the request will be authorized for **6 months.**
Kaposi Sarcoma pomalidomide (Pomalyst)	Pomalidomide (Pomalyst) may be approved when all the following documented criteria are met: 1. Medication is prescribed by, or in consultation with an oncologist, dermatologist, or infectious disease specialist; **AND** 2. Diagnosis of Kaposi's sarcoma; **AND** 3. Patient has progressed on at least one prior systemic treatment (e.g. liposomal doxorubicin or paclitaxel) unless contraindicated; **AND** 4. If HIV-positive, patient remains on highly active antiretroviral therapy.

	If ALL criteria are met, the request will be authorized for **6 months.**
	Criteria (Reauthorization) Pomalidomide (Pomalyst) may be approved when all the following documented criteria are met: 1. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms If ALL criteria are met, the request will be authorized for **6 months.**
Mantle Cell Lymphoma (MCL) lenalidomide (Revlimid)	Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND** 2. Diagnosis of mantle cell lymphoma (MCL); **AND** 3. Lenalidomide is used in combination with rituximab. If ALL criteria are met, the request will be authorized for **6 months.**
	Criteria (Reauthorization) Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms. If ALL criteria are met, the request will be authorized for **6 months.**
Marginal Zone Lymphoma (MZL) lenalidomide (Revlimid)	Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND** 2. Diagnosis of marginal zone lymphoma (MZL); **AND** 3. If used as first-line treatment, lenalidomide will be used in combination with another medication (e.g. rituximab or obinutuzumab); **OR** 4. Patient was previously treated with at least one prior regimen for MZL (e.g., bendamustine + rituximab, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, rituximab/cyclophosphamide/vincristine/prednisone) If ALL criteria are met, the request will be authorized for **6 months.**
	Criteria (Reauthorization) Lenalidomide (Revlimid) may be approved when all the following documented criteria are met:

	1. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms. If ALL criteria are met, the request will be authorized for **6 months.**
Multiple Myeloma lenalidomide (Revlimid) pomalidomide (Pomalyst) thalidomide (Thalomid)	Lenalidomide (Revlimid), pomalidomide (Pomalyst), or thalidomide (Thalomid) may be approved when all the following documented criteria are met: 1. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND** 2. Diagnosis of multiple myeloma (MM); **AND** 3. Request is for lenalidomide (Revlimid); **AND** a. The medication will be used with dexamethasone as part of a doublet or triplet regimen; **OR** b. If used as maintenance therapy, the medication may be used as monotherapy; **OR** 4. The request is for pomalidomide (Pomalyst); **AND** a. Patient has received at least two prior treatments for MM, including one with lenalidomide (Revlimid) and a proteosome inhibitor (e.g., bortezomib); **AND** b. Patient has demonstrated disease progression on or within 60 days of completion of the last therapy; **AND** c. The medication will be used with dexamethasone as part of a doublet or triplet regimen; **OR** 5. The request is for thalidomide (Thalomid); **AND** a. The medication will be used with dexamethasone or prednisone. If ALL criteria are met, the request will be authorized for **6 months.**
	Criteria (Reauthorization) Lenalidomide (Revlimid), pomalidomide (Pomalyst), or thalidomide (Thalomid) may be approved when all the following documented criteria are met: 1. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms. If ALL criteria are met, the request will be authorized for **6 months.**
Myelodysplastic Syndrome (MDS) lenalidomide (Revlimid)	Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND** 2. Diagnosis of myelodysplastic syndrome (MDS); **AND** 3. Patient has lower risk disease (e.g. IPSS Low or Intermediate-1; IPSS-R Very Low, Low, Intermediate; WPSS Very Low, Low, Intermediate); **AND** 4. Patient has transfusion-dependent anemia defined as 2 or more units of red blood cells in the previous 8 weeks; **AND** a. MDS with del(5q) abnormality; **OR**

	b. MDS <u>without</u> del(5q) abnormality; **AND** i. Serum erythropoietin levels are less than 500 mIU/mL; **AND** 1. History of inadequate response to erythropoiesis stimulating agents (ESA) with or without granulocyte colony stimulating factor (G-CSF); **OR** ii. Serum erythropoietin levels are greater than 500 mIU/mL; **AND** 1. History of failure, contraindication, or intolerance to immunosuppressive therapy (e.g. anti-thymocyte globulin ± cyclosporine A) or demethylating agents (e.g. azacitidine or decitabine); **OR** 2. Verified SF3B1 mutation. If ALL criteria are met, the request will be authorized for **6 months.** **Criteria (Reauthorization)** Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms. If ALL criteria are met, the request will be authorized for **6 months.**
POEMS Syndrome Lenalidomide (Revlimid)	Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND** 2. Diagnosis of POEMS syndrome; **AND** 3. Patient has disseminated disease (e.g. more than 3 bone lesions) and is not a candidate for radiation-only therapy; **AND** 4. Provider attests that the patient is not a candidate for autologous hematopoietic cell transplantation (HCT); **AND** 5. The medication will be used in combination with dexamethasone. If ALL criteria are met, the request will be authorized for **6 months.** **Criteria (Reauthorization)** Lenalidomide (Revlimid) may be approved when all the following documented criteria are met: 1. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms. If ALL criteria are met, the request will be authorized for **6 months.**

Dosage and quantity limits

Drug	Indication	Approved Dose	Dosage Form and Quantity Limit
lenalidomide (Revlimid)	Follicular lymphoma (FL); Mantle cell lymphoma (MCL); Marginal zone lymphoma (MZL); Multiple myeloma (MM); Myelodysplastic syndromes (MDS) POEMS Syndrome (POEMS)	MM combination therapy: 25 mg once daily orally on days 1-21 of repeated 28-day cycles MM maintenance therapy following auto-HSCT: 10 mg once daily continuously on days 1-28 of repeated 28-day cycles FL or MZL: 20 mg once daily orally on days 1-21 of repeated 28-day cycles for up to 12 cycles MDS: 10 mg once daily MCL: 25 mg once daily orally on days 1-21 of repeated 28-day cycles POEMS: 25 mg once daily on days 1-21 of repeated 28-day cycles	• 2.5 mg capsules: 28 capsules/28 days • 5 mg, 10 mg, 15 mg capsules: 28 capsules/28 days • 20 mg, 25 mg capsules: 21 capsules/28 days
pomalidomide (Pomalyst)	Multiple Myeloma (MM); Kaposi's sarcoma	MM Kaposi's sarcoma: 4 mg once daily on days 1 to 21 of 28-day cycle	• 1 mg, 2 mg, 3 mg, 4 mg capsules: 21 capsules/28 days
thalidomide (Thalomid)	Erythema nodosum leprosum (ENL); Multiple myeloma (MM)	500 mg once daily	• 50 mg, 100 mg, 150 mg, 200 mg: 28 capsules/day days (MM) and 60 capsules/30 days (ENL)

Coding:

HCPCS Code	Description
N/A	N/A

Background:

Immunomodulatory drugs (IMiDs) are indicated for several different oncology and non-oncology indications. Lenalidomide (Revlimid) is commonly used in the first-line setting,[1] while pomalidomide (Pomalyst) is indicated in the relapsed/refractory setting.[2] Thalidomide (Thalomid)[3] has generally fallen out of favor given newer, second-generation immunomodulatory agents. When used for the treatment of MM, thalidomide analogs are part of the standard three-drug backbone based on superiority over two-drug regimens. The place in therapy for four-drug regimens is still evolving and should be limited to clinical trials. Lenalidomide (Revlimid) is considered a first-line therapy for MDS but is generally used in the relapsed/refractory setting for other indications such as FL, MZL, and MCL.

Erythema Nodosum Leprosum (ENL)

ENL is an immunologic reaction to leprosy, a mycobacterium infection, and may result in fever, neuritis, skin ulceration, pain, and redness. It is commonly treated with corticosteroids; however, thalidomide is also effective for treatment if available. In one retrospective study 102 thalidomide-treated patients with ENL were analyzed for recovery.[4] All patients who complied with treatment (67%) achieved full recovery. The most common side effect was pedal edema (73.5%). Additionally, due to teratogenicity, thalidomide must be dispensed in accordance with its REMs program.

Follicular Lymphoma (FL) and Marginal Zone Lymphoma (MZL)

Lenalidomide demonstrated effectiveness in follicular and marginal zone lymphoma in a randomized, double-blind clinical trial.[5] 358 participants with relapsed or refractory follicular or marginal zone lymphoma received either lenalidomide plus rituximab or rituximab plus placebo for a maximum of 12 cycles or until unacceptable toxicity. Progression free survival in the lenalidomide group and placebo group was 39.4 months and 14.1, respectively. Infections, neutropenia, leukopenia, and skin reactions were more common in the lenalidomide group.

Kaposi Sarcoma (KS)

Kaposi Sarcoma is an angioproliferative disorder that occurs in the presence of a herpes simplex virus-8, and often occurs with Autoimmune Immunodeficiency Disorder (AIDs) in HIV infected individuals. Pomalidomide was studied in one open-label, single arm, Phase 1/2 trial with 22 patients with KS.[6] There were 15 HIV-positive patients and 7 HIV-negative patients included in the trial. The HIV-positive patients continued antiretroviral therapy (ART), had a controlled HIV viral load for ≥ 2 months, and had progressive KS. The primary efficacy outcome was overall response rate (ORR) after at least two 28-day cycles of pomalidomide. ORR was 73% for all participants, defined as either partial response (at least a 50% reduction in lesions) or a complete response (full reduction in lesions). Grade ≥3 toxicities included neutropenia, decreased phosphate, elevated glucose, elevated creatinine, rash, diarrhea, and peripheral edema.

Mantle Cell Lymphoma (MCL) (7)

MCL is a subtype of non-Hodgkin lymphoma and accounts for 3% to 6% of cases. First line treatment involves chemotherapy in combination with immunotherapy, followed by autologous stem-cell transplantation. Lenalidomide is indicated in relapsed or refractory MCL after at least 2 prior therapies. The safety and efficacy of single-agent lenalidomide for relapsed or refractory MCL was evaluated in a Phase 2, open-label trial in 134 patients with prior bortezomib therapy.[7] The overall response rate was 28% and the median duration of response was 16.6 months. The most common serious adverse events were neutropenia, thrombocytopenia, anemia, pneumonia, and fatigue.

Multiple Myeloma (MM)

Lenalidomide, pomalidomide, and thalidomide are all approved for the treatment of multiple myeloma.[8] In one randomized clinical trial with 1623 patients lenalidomide plus dexamethasone was superior to standard of care (melphalan, prednisone, and thalidomide) for progression-free survival (25.5 months vs 21.2 months, P<0.001). Additionally, 59% of the lenalidomide group had survived at 4 years compared to 51% of the standard of care.

Pomalidomide demonstrated effectiveness for relapsed or refractory MM in an open-label, randomized phase 3 trial comparing pomalidomide plus low-dose dexamethasone to high-dose dexamethasone alone.[9] All 302 study participants had previously failed at least two treatments with bortezomib and lenalidomide. At 10 months, progression free survival in the pomalidomide group was 4 months compared to 1.9 months in the high-dose dexamethasone group ($p<0.0001$). Serious adverse effects in the pomalidomide group include neutropenia, thrombocytopenia, pneumonia, bone pain, and fatigue.

Myelodysplastic Syndrome (MDS)

Lenalidomide demonstrated effectiveness for myelodysplastic syndromes with del5q mutation in a phase 3, randomized, double-blind clinical trial.[10] All 205 participants were either low or intermediate-1 risk, according to the International Prognostic Scoring System, and were red blood cell (RBC) transfusion-dependent. Significantly more participants taking 5 mg/day and 10 mg/day of lenalidomide achieved RBC transfusion independence for 26 weeks or greater compared to placebo (42.6%, 56.1%, and 5.9%, respectively). Achievement of RBC transfusion independence for at least 8 weeks was associated with a significant reduction in progression to acute myeloid leukemia (AML) and death.

Although not FDA approved, lenalidomide has also demonstrated effectiveness in RBC transfusion-dependent MDS without del5q mutation.[11] In a randomized, placebo-controlled, double-bland study with 239 participants, RBC transfusion-independence for at least 8 weeks was achieved in 26.9% of those taking lenalidomide compared to 2.5% of patients taking a placebo. Lenalidomide was more effective in patients with a baseline erythropoietin level of 500 mU/mL or less. Adverse effects in both MDS trials were consistent with other lenalidomide trials.

References

1. Revlimid [Prescribing Information]. Princeton, NJ: Bristol-Myers Squibb; March 2023.
2. Pomalyst [Prescribing Information]. Princeton, NJ: Bristol-Myers Squibb; March 2023.
3. Thalomid [Prescribing Information]. Princeton, NJ: Bristol-Myers Squibb; March 2023.
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5. Leonard JP, Trneny M, Izutsu K, et al. Augment: a phase iii study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019;37(14):1188-1199.
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7. Goy A, Sinha R, Williams ME, et al. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (Emerge) study. J Clin Oncol. 2013;31(29):3688-3695.
8. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906-917.
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multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1055-1066. doi: 10.1016/S1470-2045(13)70380-2. Epub 2013 Sep 3. PMID: 24007748.
10. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with Low-/Intermediate-1-risk myelodysplastic syndromes with del5q. Blood. 2011;118(14):3765-3776.
11. Santini V, Almeida A, Giagounidis A, et al. Randomized phase iii study of lenalidomide versus placebo in rbc transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol. 2016;34(25):2988-2996.

History

Approved Date	Effective Date	Version	Action and Summary of Changes
04/17/2024	10/01/2024	99.39.20-1	New policy created that combines the three currently available thalidomide analogs into one policy Approved by DUR board