PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Oral – Immunomodulator) – Lenalidomide Prior Authorization Policy
- Revlimid® (lenalidomide capsules – Celgene/Bristol Myers Squibb, generic)

REVIEW DATE: 05/14/2025

INSTRUCTIONS FOR USE

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CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Lenalidomide, a thalidomide analog, is indicated for the following uses in adults:[1]
- **Follicular lymphoma**, previously treated, in combination with a rituximab product.
- **Mantle cell lymphoma**, in patients whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
- **Marginal zone lymphoma**, previously treated, in combination with a rituximab product.
- **Multiple myeloma**, as maintenance following autologous hematopoietic stem cell transplantation.
- **Multiple myeloma**, treatment, in combination with dexamethasone.

- **Myelodysplastic syndrome**, for transfusion-dependent anemia due to low- or intermediate-1-risk disease, associated with a deletion 5q abnormality with or without cytogenetic abnormalities.

Guidelines

Lenalidomide is incorporated into various guidelines by the National Comprehensive Cancer Network (NCCN).[2-13]

- **B-Cell Lymphomas:** NCCN guidelines (version 2.2025 – February 10, 2025) discuss therapeutic options for diffuse large B-cell lymphoma (DLBCL), the most common type of other B-cell lymphoma.[2] Lenalidomide ± rituximab is mentioned as a second-line therapy as "useful in certain circumstances" (category 2A). Monjuvi® (tafasitamab-cxix intravenous infusion) + lenalidomide is recommended as a "preferred" regimen as second-line therapy (category 2A). Lenalidomide is also recommended in combination with other medications for third-line and subsequent therapy settings (category 2A). Other types of B-cell lymphomas (high grade B-cell lymphomas [not otherwise specified], post-transplant lymphoproliferative disorders, human immunodeficiency virus (HIV) related B-cell lymphomas, are also cited in the guidelines and note a place in therapy of lenalidomide. Regimens recommended in these clinical scenarios are similar to those used in DLBCL.
    - **Follicular Lymphomas:** Lenalidomide + rituximab is recommended as a "preferred regimen " for first-line therapy for high tumor burden and second-line therapy (both category 2A). Lenalidomide + Gazyva® (obinutuzumab intravenous infusion) is listed as "other recommended regimen" for first-line therapy (category 2B) and second-line therapy (category 2A). Other regimens including lenalidomide are also listed as second-line therapy.
    - **Mantle Cell Lymphoma:** Lenalidomide + rituximab is recommended as a "preferred regimen" as a less aggressive induction therapy (category 2A) and as a "preferred regimen" for second-line and subsequent therapy (category 2A).
    - **Marginal Zone Lymphoma:** Lenalidomide + rituximab is listed for first-line therapy as an "other recommended regimen" (category 2B) and as a "preferred regimen" for second-line and subsequent therapy (category 2A). Lenalidomide + Gazyva is also listed as "other recommended regimens" for second-line and subsequent therapy (category 2A).
- **Castleman Disease:** NCCN guidelines (version 2.2025 – January 28, 2025) recommend lenalidomide as an option as second-line and subsequent therapy, with or without rituximab, for multi-centric Castleman's disease that is relapsed/refractory or progressive disease (category 2A).[2]
- **Central Nervous System (CNS) Cancers:** NCCN guidelines (version 5.2024 – March 18, 2025) recommend lenalidomide ± rituximab as induction therapy if the patient is unsuitable for or intolerant to high-dose methotrexate or for relapsed or refractory disease (both category 2A) for primary CNS lymphoma.[3]
- **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**: NCCN guidelines (version 3.2025 – April 2, 2025) recommend lenalidomide ± rituximab as therapy for relapsed or refractory disease after prior Bruton

tyrosine-kinase based and B-cell lymphoma 2 inhibitor containing regimens as "other recommended regimens" (category 2A).[14] Although the guidelines recommend off-label use in chronic lymphocytic leukemia, the prescribing information does note that a limitation of use with lenalidomide is that it is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia outside of controlled clinical trials.[1]

- **Histiocytic Neoplasms:** NCCN guidelines (version 3.2024 – January 7, 2025) recommend lenalidomide for Langerhans cell histiocytosis as first-line or as subsequent therapy for single system multifocal skin disease (including mucosa) or relapsed or refractory disease and for Rosai-Dorfman disease (both category 2A).[4,13]
- **Hodgkin Lymphoma:** NCCN guidelines (version 2.2025 – January 30, 2025) recommend lenalidomide as a subsequent therapy (if not previously given) for primary refractory disease or suspected relapse and for patients who are not a candidate for high-dose therapy and autologous stem cell rescue as a single agent palliative treatment option (category 2A).[5]
- **Kaposi Sarcoma:** NCCN guidelines (version 2.2025 – January 14, 2025) recommend lenalidomide as "other recommended regimens" as subsequent therapy for relapsed/refractory advanced cutaneous, oral, visceral or nodal disease that has progressed on or not responded to first-line systemic therapy and progressed on alternative first-line systemic therapy (category 2A).[9] This includes use when given alone (in patients without human immunodeficiency virus [HIV]) or with antiretroviral therapy for patients with HIV. First-line systemic therapy options include liposomal doxorubicin (preferred) and paclitaxel.
- **Multiple Myeloma:** NCCN guidelines (version 2.2025 – April 11, 2025) feature lenalidomide prominently in a variety of scenarios with several category 1 recommendations.[6] The agent is also cited in other regimens with category 2A and 2B recommendations. Lenalidomide is also indicated for treatment in combination with dexamethasone for the management of POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome as induction therapy for transplant eligible patients and for transplant ineligible patients (category 2A).
- **Myelodysplastic Syndrome:** NCCN guidelines (version 2.2025 – January 17, 2025) recommend lenalidomide in a variety of clinical scenarios among patients with symptomatic anemia both with and without 5q deletion (del-[5q]) abnormalities (category 2A).[7] Lenalidomide is also recommended for myelodysplastic syndrome/myeloproliferative overlap neoplasm with *SF3B1* mutation and thrombocytosis as a single agent or in combination with a hypomethylating agent (category 2A).
- **Myeloproliferative Neoplasms:** NCCN guidelines (version 1.2025 – February 21, 2025) discuss myelofibrosis with related anemia.[8] Lenalidomide is recommended as "useful in certain circumstances" (category 2B) in combination with prednisone taper for del(5q), if there are no symptomatic splenomegaly and/or constitutional symptoms.
- **Systemic Light Chain Amyloidosis:** NCCN guidelines (version 2.2025 – March 12, 2025) cite lenalidomide as a therapeutic option used in combination

with dexamethasone, and in some circumstances with additional medications as primary therapy or for relapsed/refractory disease (category 2A).

- **T-Cell Lymphomas:** NCCN guidelines for T-cell lymphomas (version 1.2025 – November 11, 2024) make several recommendations that include lenalidomide.[11] For peripheral T-cell lymphomas, lenalidomide is recommended as initial palliative-intent therapy as "other recommended regimen" (category 2A) and for second-line and subsequent therapy as "other recommended regimens" as a monotherapy (category 2A). For adult T-cell leukemia/lymphoma, lenalidomide is recommended as a second-line and subsequent therapy (category 2A). For hepatosplenic T-cell lymphoma, lenalidomide is recommended for refractory disease after two first-line therapy regimens (category 2A).

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of lenalidomide. All approvals are provided for the duration noted below.

- **Revlimid® (lenalidomide capsules - Celgene/Bristol Myers Squibb, generic)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Follicular Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i, ii, or iii):
      i. The medication is used in combination with rituximab; OR
      ii. The medication is used in combination with Gazyva (obinutuzumab intravenous infusion); OR
      iii. Patient has tried at least one other regimen.
      Note: Examples of regimens include bendamustine plus Gazyva (obinutuzumab intravenous infusion) or rituximab; bendamustine plus Gazyva; CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) plus Gazyva or rituximab; CVP (cyclophosphamide, vincristine, prednisone) plus Gazyva or rituximab; chlorambucil with or without rituximab; or cyclophosphamide with or without rituximab; rituximab; Gazyva.

2. **Mantle Cell Lymphoma**. Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. The medication is used in combination with rituximab; OR
      ii. Patient has tried at least one other regimen.

Note: Examples include HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) + rituximab; the NORDIC regimen (dose-intensified induction immunochemotherapy with rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone alternating with rituximab and high-dose cytarabine); RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); bendamustine injection plus rituximab; RDHA (rituximab, dexamethasone, cytarabine) + platinum therapy (carboplatin, cisplatin, or oxaliplatin); Imbruvica (ibrutinib capsules, tablets, and oral suspension) with or without rituximab; Calquence (acalabrutinib tablets); or Brukinsa (zanubrutinib capsules).

3. **Marginal Zone Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. The medication is used in combination with rituximab; OR
      ii. Patient has tried least one other regimen.
      Note: Examples of a regimen include CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab; bendamustine + rituximab; CVP (cyclophosphamide, vincristine, prednisone) + rituximab; rituximab; chlorambucil with or without rituximab; or cyclophosphamide with or without rituximab.

4. **Multiple Myeloma.** Approve for 1 year if the patient is ≥ 18 years of age.

5. **Myelodysplastic Syndrome.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i, ii, iii, or iv):
      i. Patient has symptomatic anemia; OR
      ii. Patient has transfusion-dependent anemia; OR
      iii. Patient has anemia that is not controlled with an erythropoiesis-stimulating agent; OR
      Note: Examples include Epogen/Procrit (epoetin alfa injection), Aranesp (darbepoetin alfa injection).
      iv. Patient meets ALL of the following (a, b, and c):
         a) Patient has myelodysplastic syndrome/myeloproliferative neoplasm overlap neoplasm; AND
         b) The cancer has a *SF3B1* mutation; AND
         c) Patient has thrombocytosis.

Other Uses with Supportive Evidence

6. **B-Cell-Lymphomas (Other):** Approve for 1 year if the patient meets BOTH of the following (A and B):

Note: Examples include diffuse large B-cell lymphoma (DLBCL); high grade B-cell lymphomas; post-transplant lymphoproliferative disorders; Human Immunodeficiency Virus (HIV)-related B-cell lymphomas.

A) Patient is ≥ 18 years of age; AND

B) Patient has tried at least one other regimen.
Note: Examples include RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone); dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab; RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine); DHA (dexamethasone, cytarabine) plus platinum (carboplatin, cisplatin, oxaliplatin) ± rituximab; ICE (Ifex, carboplatin, etoposide) ± rituximab; RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone); GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or gemcitabine, dexamethasone, carboplatin) ± rituximab; R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine); or bendamustine ± rituximab.

7. **Castleman Disease.** Approve for 1 year if the patient has relapsed/refractory or progressive disease.

8. **Chronic Lymphocytic Leukemia**. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has relapsed or refractory disease; AND
   C) Patient has tried at least one Bruton-tyrosine kinase inhibitor; AND
   Note: Examples of Bruton-tyrosine kinase inhibitor include Imbruvica (ibrutinib capsules, tablets, and oral suspension); Calquence (acalabrutinib tablets), Brukinsa (zanubrutinib capsules); or Jaypirca (pirtobrutinib tablets).
   D) Patient has tried at least one B-cell lymphoma (BCL)2 inhibitor.
   Note: Example of a B-cell lymphoma (BCL)2 inhibitor includes Venclexta (venetoclax tablet).

9. **Histiocytic Neoplasms.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   A) Patient is ≥ 18 years of age; AND
   B) Patient meets ONE of the following (i or ii):
      i. Patient has Langerhans cell histiocytosis and meets ONE of the following (a or b):
         a) Patient has single-system multifocal skin disease; OR
         b) Patient has relapsed or refractory disease; OR
      ii. Patient has Rosai-Dorfman disease.

10. **Hodgkin Lymphoma, Classic.** Approve for 1 year if the patient meets ALL of the following (A, B and C):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has relapsed or refractory disease; AND
    C) According to the prescriber, the patient is not a candidate for high-dose therapy and autologous stem cell rescue.

11. **Kaposi Sarcoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
    A) Patient has relapsed or refractory disease; AND
    B) Patient has tried at least one other medication.
    Note: Examples include liposomal doxorubicin, paclitaxel, Pomalyst (pomalidomide capsules), Thalomid (thalidomide capsules), and imatinib.

12. **Myelofibrosis.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
    A) Patient is ≥ 18 years of age; AND
    B) According to the prescriber, the patient has anemia with presence of del(5q); AND
    C) The medication is used in combination with prednisone.

13. **Primary Central Nervous System Lymphoma.** Approve for 1 year if patient meets ONE of the following (A or B):
    A) Patient has relapsed or refractory disease; OR
    B) Patient meets ONE of the following (i or ii):
        i. According to the prescriber, the patient is not a candidate for high-dose methotrexate; OR
        ii. Patient has had intolerance to high-dose methotrexate.

14. **POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) Syndrome.** Approve for 1 year if the patient meets BOTH of the following (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) The medication is used in combination with dexamethasone.

15. **Small Lymphocytic Leukemia.** Approve for 1 year if patient meets ALL of the following (A, B, C, and D):
    A) Patient is ≥ 18 years of age; AND
    B) Patient has relapsed or refractory disease; AND
    C) Patient has tried at least one Bruton-tyrosine kinase inhibitor; AND
    Note: Examples of Bruton-tyrosine kinase inhibitor include Imbruvica (ibrutinib capsules, tablets, and oral suspension); Calquence (acalabrutinib tablets), Brukinsa (zanubrutinib capsules); or Jaypirca (pirtobrutinib tablets).
    D) Patient has tried at least one B-cell lymphoma (BCL)2 inhibitor.
    Note: Example of a B-cell lymphoma (BCL)2 inhibitor includes Venclexta (venetoclax tablet).

16. **Systemic Light Chain Amyloidosis.** Approve for 1 year if the patient meets BOTH of the following (A and B):
    A) Patient is ≥ 18 years of age; AND
    B) The medication is used in combination with dexamethasone.

17. **T-Cell Lymphoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):

A) Patient is ≥ 18 years of age; AND
B) Patient meets ONE of the following (i, ii, or iii):
- **i.** Patient has peripheral T-cell lymphoma; OR
- **ii.** Patient meets BOTH of the following (a and b):
  - **a)** Patient has T-cell leukemia/lymphoma; AND
  - **b)** Patient has tried at least one other regimen; OR
    Note: Examples of a regimen include Adcetris (brentuximab vedotin intravenous infusion) plus CHP (cyclophosphamide, doxorubicin, and prednisone); CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone); dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin); HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine.
- **iii.** Patient meets BOTH of the following (a and b):
  - **a)** Patient has hepatosplenic T-cell lymphoma; AND
  - **b)** Patient has tried at least two other regimens.
    Note: Examples of a regimen include ICE (ifosfamide, carboplatin, and etoposide), DHA (dexamethasone and cytarabine) + platinum therapy (carboplatin, cisplatin, or oxaliplatin), dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin); HyperCVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone) alternating with high-dose methotrexate and cytarabine, or IVAC (ifosfamide, etoposide, and cytarabine).

CONDITIONS NOT COVERED

- **Revlimid® (lenalidomide capsules - Celgene/Bristol Myers Squibb, generic)**

is(are) considered not medically necessary for ANY other use(s); criteria will be updated as new published data are available.

REFERENCES

1. Revlimid® capsules [prescribing information]. Summit, NJ: Celgene; March 2023.
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3. The NCCN Castleman Disease Clinical Practice Guidelines in Oncology (version 2.2025 – January 28, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 30, 2025.
4. The NCCN Central Nervous System Cancers Guidelines in Oncology (version 5.2024 – March 18, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 30, 2025.
5. The NCCN Histiocytic Neoplasms (version 3.2024 – January 7, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 30, 2025.
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13. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed May 5, 2025. Search term: lenalidomide.
14. The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Clinical Practice Guidelines in Oncology (version 3.2025 – April 2, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on April 30, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Myelodysplastic Syndrome:** Examples of regimens are provided in a Note. **Hodgkin Lymphoma, Classical:** Criterion has been updated to state patient has tried at least "three" other regimens, as per guidelines. Previously it said one other regimen. ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin) was removed from the list of examples in Note.	05/10/2023
Annual Revision	**Histiocytic Neoplasms:** Added new condition of approval and criteria. **Langerhans Cell Histiocytosis:** Deleted approval condition and criteria since it is now addressed under "Histiocytic Neoplasm." **Myelofibrosis:** Deleted criteria referring to serum erythropoietin levels and response to erythropoiesis-stimulating agents. New criteria were added requiring combination use with prednisone. In criteria verifying presence of anemia, added qualifier that is for del(5q) mutation. **Peripheral T-Cell Lymphoma:** Deleted criterion "patient has tried at least one other regimen," since lenalidomide can be used for initial palliative intent therapy or subsequent therapy.	05/29/2024
Update	04/08/2025: The policy name was changed from "Oncology – Lenalidomide PA Policy" to "Oncology (Oral – Immunomodulator) – Lenalidomide PA Policy".	N/A
Annual Revision	**Follicular Lymphoma:** The following option of approval was added, "The medication is used in combination with Gazyva (obinutuzumab intravenous infusion)." Aliqopa (copanlisib intravenous infusion) was removed from the Note with examples of other regimens. **Mantle Cell Lymphoma:** The requirement that the patient has tried "at least two" other regimens was changed to "at least one" other regimen.	05/14/2025

	Marginal Zone Lymphoma: The following regimens were removed from the Note of examples of a regimen, "bendamustine + Gazyva (obinutuzumab intravenous infusion); Copiktra (duvelisib capsules); Aliqopa (copanlisib intravenous infusion); or Zydelig (idelalisib capsules)." **Myelodysplastic Syndrome:** An option for approval was added for a patient with myelodysplastic syndrome/myeloproliferative neoplasm overlap neoplasm, a *SF3B1* mutation, and thrombocytosis. **B-Cell Lymphomas (Other):** The following revisions were made to the Note with examples of B-cell Lymphomas: the wording "not otherwise specified" was removed from high grade B-cell lymphomas; AIDS-related B-cell lymphoma was reworded to Human Immunodeficiency Virus (HIV)-related B-cell lymphoma; and high-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) was removed. **Castleman Disease:** Previously, this condition of approval was called Castleman's Disease. **Chronic Lymphocytic Leukemia:** This condition and criteria for approval to Other Uses With Supportive Evidence. **Histiocytic Neoplasms:** For a patient with Langerhans cell histiocytosis, an option of approval was added for relapsed or refractory disease. **Hodgkin Lymphoma, Classic:** Previously, the condition of approval was worded as Hodgkin Lymphoma, Classical. The following requirement was added, "patient has relapsed or refractory disease and according to the prescriber, the patient is not a candidate for high-dose therapy and autologous stem cell rescue." The requirement that the patient has tried at least three other regimens with the Note of examples of regimens was removed. **Peripheral T-Cell Lymphomas**: This condition of approval was moved under the new condition of approval called T-Cell Lymphoma. The Note of types of peripheral T-cell lymphoma was removed. **Primary Central Nervous System Lymphoma:** Previously this condition of approval was called "central nervous system lymphoma." The wording "according to the prescriber" was removed from the requirement "patient has relapsed or refractory disease." The following option for approval were added, "according to the prescriber, the patient is not a candidate for high-dose methotrexate" or "patient has had intolerance to high-dose methotrexate." **Small Lymphocytic Lymphoma:** This condition and criteria for approval were added to Other Uses With Supportive Evidence. **T-Cell Lymphomas**. This condition and criteria for approval were added. Previously, conditions of approval of Peripheral T-Cell Lymphomas and T-Cell Leukemia/Lymphoma were rolled into this one. The option for approval for a patient with hepatosplenic T-cell lymphoma who has tried at least two other regimens was added with a Note of examples of regimens. **T-Cell Leukemia/Lymphoma**: This condition and criteria for approval were moved under the new condition of approval called T-Cell Lymphomas.	