# Clinical Policy: Lenalidomide (Revlimid)

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Line of Business: Commercial, HIM, Medicaid Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

## Description

Lenalidomide (Revlimid®) is an immunomodulatory agent with antiangiogenic and antineoplastic properties.

## FDA Approved Indication

Revlimid is indicated for the treatment of patients with:

- Multiple myeloma (MM), in combination with dexamethasone
- MM as maintenance following autologous hematopoietic stem cell transplantation
- Transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q abnormality with or without additional cytogenetic abnormalities
- Mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (Velcade®)
- Previously treated follicular lymphoma (FL), in combination with a rituximab product
- Previously treated marginal zone lymphoma (MZL), in combination with a rituximab product

Limitation of use: Revlimid is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

## Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation® that lenalidomide and Revlimid are **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Multiple Myeloma** (must meet all):

1. Diagnosis of MM;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Will be used for one of the following indications (a, b, c, or d):
   a. In combination with dexamethasone;
   b. For previously treated relapsed or progressive disease, and prescribed as one of the following (i or ii):
      i. As a single agent in steroid-intolerant patients;

ii. In combination with dexamethasone and one of the following: bortezomib, carfilzomib, daratumumab, ixazomib, cyclophosphamide, elotuzumab, or bendamustine;

c. As maintenance therapy following autologous hematopoietic stem cell transplantation or symptomatic MM after response to primary myeloma therapy and prescribed in one of the following ways (i or ii):
   i. As a single agent;
   ii. In combination with one of the following: carfilzomib, bortezomib, daratumumab;

d. As primary therapy for one of the following (i or ii):
   i. High risk smoldering MM (asymptomatic) as a single agent;
   ii. Symptomatic MM as combination therapy;

5. The requested agent is not prescribed concurrently with Thalomid® or Pomalyst®;
6. For Revlimid requests, member must use generic lenalidomide, unless contraindicated, clinically significant adverse effects are experienced, or generic is unavailable due to shortage*;
   **Generic lenalidomide is currently in short supply and may be unavailable until sometime in 2026*
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 25 mg per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM -** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**B. Myelodysplastic Syndrome** (must meet all):
1. Diagnosis of lower risk (i.e., IPSS-R [Very Low, Low, Intermediate], IPSS [Low/Intermediate-1], WPSS [Very Low, Low, Intermediate]) MDS;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member has one of the following (a or b):
   a. Symptomatic or transfusion-dependent anemia due to MDS, and one of the following (i or ii):
      i. Presence of deletion 5q abnormality;
      ii. No deletion 5q abnormality, and one of the following (1 or 2):
         1) For ring sideroblasts ≥ 15% (or ≥ 5% if SF3B1 mutation): Failure of Reblozyl® or Rytelo™, unless contraindicated or clinically significant adverse effects are experienced;*
         2) For ring sideroblasts < 15% (or < 5% if SF3B1 mutation): One of the following (a or b):
            a) For serum erythropoietin > 500 mU/mL: Member has poor probability to respond to immunosuppressive therapy (*see Appendix D*);
            b) For serum erythropoietin ≤ 500 mU/mL: Failure of an erythropoiesis-stimulating agent (ESA; *Retacrit® is preferred*) or Reblozyl, unless contraindicated or clinically significant adverse effects are experienced;*

**Prior authorization may be required*

b. MDS and myeloproliferative overlap neoplasms with both of the following (i and ii):
   i. Thrombocytosis;
   ii. Presence of SF3B1 mutation;

5. The requested agent is not prescribed concurrently with Thalomid or Pomalyst;
6. For Revlimid requests, member must use generic lenalidomide, unless contraindicated, clinically significant adverse effects are experienced, or generic is unavailable due to shortage*;
   **Generic lenalidomide is currently in short supply and may be unavailable until sometime in 2026*
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 10 mg per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM -** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**C. Mantle Cell Lymphoma** (must meet all):
1. Diagnosis of MCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Will be used for one of the following indications (a or b):
   a. Relapsed or progressive disease after two prior therapies, one of which included bortezomib (Velcade);
   b. In combination with rituximab*;
   **Prior authorization may be required for rituximab*
5. The requested agent is not prescribed concurrently with Thalomid or Pomalyst;
6. For Revlimid requests, member must use generic lenalidomide, unless contraindicated, clinically significant adverse effects are experienced, or generic is unavailable due to shortage*;
   **Generic lenalidomide is currently in short supply and may be unavailable until sometime in 2026*
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 25 mg per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM -** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**D. Marginal Zone Lymphoma** (must meet all):
1. Diagnosis of MZL (including gastric or nongastric mucosa-associated lymphoid tissue (MALT) lymphoma, nodal MZL, and splenic MZL);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;

4. Will be used for one of the following indications (a or b):
   a. First-line therapy, and is prescribed in combination with rituximab;*
   b. Second-line or subsequent therapy, and is prescribed in combination with rituximab* or Gazyva®*;
   **Prior authorization may be required*
5. The requested agent is not prescribed concurrently with Thalomid or Pomalyst;
6. For Revlimid requests, member must use generic lenalidomide, unless contraindicated, clinically significant adverse effects are experienced, or generic is unavailable due to shortage*;
   **Generic lenalidomide is currently in short supply and may be unavailable until sometime in 2026*
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 20 mg per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**E. Follicular Lymphoma** (must meet all):
1. Diagnosis of FL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Will be used for one of the following indications (a or b):
   a. First-line therapy, and prescribed in combination with rituximab or Gazyva;*
   b. Second-line or subsequent therapy, and prescribed in one of the following ways (i or ii):
      i. As a single agent;
      ii. In combination with either rituximab ± Monjuvi, or Gazyva;*
      **Prior authorization may be required for rituximab, Monjuvi, and Gazyva*
5. The requested agent is not prescribed concurrently with Thalomid or Pomalyst;
6. For Revlimid requests, member must use generic lenalidomide, unless contraindicated, clinically significant adverse effects are experienced, or generic is unavailable due to shortage*;
   **Generic lenalidomide is currently in short supply and may be unavailable until sometime in 2026*
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 20 mg per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**F. Other NCCN Compendium Supported Diagnoses/Indications (off-label)** (must meet all):
1. Diagnosis of one of the following (a, b, c, d, e, f, or g):

a. Myelofibrosis-associated anemia in combination with prednisone taper and presence of del(5q);
b. Systemic light chain amyloidosis in combination with dexamethasone (for relapsed/refractory disease, dexamethasone can be used with or without cyclophosphamide, ixazomib, or daratumumab);
c. Primary central nervous system (CNS) lymphoma as a single agent or in combination with rituximab* for relapsed or refractory disease, or if member is unsuitable or intolerant to high-dose methotrexate;
d. Classic Hodgkin lymphoma as single agent palliative subsequent therapy for relapsed or refractory disease;
e. Langerhans cell histiocytosis as a single agent therapy;
f. Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin change (POEMS) syndrome in combination with dexamethasone (with or without daratumumab), and one of the following (i and ii):
    i. As induction therapy for transplant eligible members;
    ii. For transplant ineligible members;
g. One of the following non-Hodgkin lymphoma subtypes (i-vii):
    i. Adult T-cell leukemia/lymphoma as a single agent for second-line or subsequent therapy;
    ii. Kaposi sarcoma (KS) as subsequent therapy following treatment of first-line systemic therapy for relapsed, refractory, or advanced disease, and one of the following (1 or 2):
        1) If HIV-related, prescribed in combination with antiretroviral therapy;
        2) Prescribed as a single agent;
    iii. Castleman's disease (CD) with or without rituximab as subsequent therapy following treatment of relapsed, refractory, or progressive disease;
    iv. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) as a single agent or in combination with rituximab as second-line and subsequent therapy following prior therapy with Bruton tyrosine kinase inhibitor- and venetoclax-based regimens;
    v. Diffuse large B-cell lymphoma, high-grade B-cell lymphoma, HIV-related B-cell lymphoma, or post-transplant lymphoproliferative disorders of B-cell lymphomas as second-line or subsequent therapy in one of the following ways (1, 2, or 3):
        1) In combination with Monjuvi in members who are not candidates for transplant or CAR T-cell therapy);
        2) As a single agent;
        3) In combination with rituximab with or without brentuximab vedotin;
    vi. Hepatosplenic gamma-delta T-cell lymphoma as a single agent for refractory disease after two primary treatment regimens;
    vii. Peripheral T-cell lymphoma as initial palliative intent therapy, second-line, or subsequent therapy;

**Prior authorization may be required for rituximab, ESAs, and Monjuvi*

2. Prescribed by or in consultation with one of the following specialists (a or b):
    a. HIV-related KS: an oncologist or immunologist;
    b. All other diagnoses: an oncologist or hematologist;

3. Age ≥ 18 years;
4. The requested agent is not prescribed concurrently with Thalomid or Pomalyst;
5. For Revlimid requests, member must use generic lenalidomide, unless contraindicated, clinically significant adverse effects are experienced, or generic is unavailable due to shortage*;
   **Generic lenalidomide is currently in short supply and may be unavailable until sometime in 2026*
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 25 mg per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).
   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM -** 6 months
**Commercial –** 12 months or duration of request, whichever is less

**G. Other diagnoses/indications** (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

## II. Continued Therapy

**A. All Indications in Section I** (must meet all)**:**
1. Currently receiving medication via Centene benefit or documentation supports that member is currently receiving the requested agent for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. The requested agent is not prescribed concurrently with Thalomid or Pomalyst;
4. For Revlimid requests, member must use generic lenalidomide, unless contraindicated, clinically significant adverse effects are experienced, or generic is unavailable due to shortage*;
   **Generic lenalidomide is currently in short supply and may be unavailable until sometime in 2026*
5. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed one of the following (i, ii, or iii):
      i. For MDS: 10 mg per day;

ii. For MZL and FL: 20 mg per day;
iii. All other indications: 25 mg per day;

b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**
**Medicaid/HIM –** 12 months
**Commercial –** 12 months or duration of request, whichever is less

**B. Other diagnoses/indications** (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

## III. Diagnoses/Indications for which coverage is NOT authorized:

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

## IV. Appendices/General Information

*Appendix A: Abbreviation/Acronym Key*

AIDS: acquired immune deficiency syndrome
CD: Castleman's disease
CLL: chronic lymphocytic leukemia
ESA: erythropoiesis-stimulating agent
FDA: Food and Drug Administration
FL: follicular lymphoma
KS: Kaposi sarcoma
MALT: mucosa-associated lymphoid tissue
MCL: mantle cell lymphoma
MDS: myelodysplastic syndrome
MM: multiple myeloma
MZL: marginal zone lymphomas
NCCN: National Comprehensive Cancer Network
POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin change
REMS: Risk Evaluation and Mitigation Strategy
SLL: small lymphocytic lymphoma

*Appendix B: Therapeutic Alternatives*
*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| melphalan/ prednisone (MP) | **Multiple Myeloma**<br>(Conventional primary therapy)<br><br>melphalan 8 mg/m$^2$/day<br>PO days 1-4; prednisone<br>60 mg/m2/day PO days 1-4.<br>Repeat cycle every 28 days | As recommended in dosing regimen |
| vincristine*/ doxorubicin*/ dexamethasone (VAD) | **Multiple Myeloma**<br>(Conventional primary therapy)<br><br>vincristine 0.4 mg/day IV<br>continuous infusion days 1- 4; doxorubicin 9<br>mg/m2/day IV continuous<br>infusion days 1-4;<br>dexamethasone 40 mg PO<br>days 1-4, 9-12, 17-20.<br>Repeat cycle every 28-35 days | As recommended in dosing regimen |
| dexamethasone (pulse dose as single agent) | **Multiple Myeloma**<br>(Conventional primary therapy)<br><br>dexamethasone 40 mg PO<br>days 1-4, 9-12, 17-20 | As recommended in dosing regimen |
| Thalomid® (thalidomide)/ dexamethasone | **Multiple Myeloma**<br>(Conventional primary therapy)<br><br>thalidomide 200 mg/day PO daily;<br>dexamethasone 40 mg/day days 1-4, 9-12,17-20 for odd cycles and<br>days 1-4 for even cycles.<br>Repeat cycle every 28 days | As recommended in dosing regimen |
| Pomalyst® (pomalidomide) | **Multiple Myeloma**<br>4 mg PO QD on days 1-21 of repeated 28-day cycles until disease progression.<br>Pomalyst may be given in combination with dexamethasone.<br>Pomalyst may be given in combination with Kyprolis/dexamethasone<br>Avoid Pomalyst in patients | 4 mg/day |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| | with a serum creatinine greater than 3.0 mg/dL | |
| Kyprolis® (carfilzomib) | **Multiple Myeloma**<br>Varies | Varies depending on combination regimen |
| Bortezomib (Velcade) | **Mantle Cell Lymphoma**<br>1.3 mg/m$^2$/dose SC or IV BIW for 2 weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21) for six 3-week cycles. For extended therapy of more than 8 cycles, Velcade may be administered on the standard schedule or on a maintenance schedule of once weekly for 4 weeks (Days 1, 8, 15, and 22) followed by a 13-day rest period (Days 23 to 35).<br>At least 72 hours should elapse between consecutive doses of Velcade | 1.3 mg/m$^2$/dose |
| **ESAs** | | |
| Aranesp® (darbepoetin alfa) | **Anemia associated with MDS**†<br>150-300 mcg SC every other week | 500 mcg every other week |
| epoetin alfa (Epogen®, Procrit®, Retacrit®) | **Anemia associated with MDS**†<br>40,000-60,000 units SC one to two times weekly<br><br>**Anemia associated with myelofibrosis**†<br>In a clinical trial, patients initially received erythropoietin 10,000 units SC 3 days per week. Erythropoietin was increased to 20,000 units 3 days per week if a response was not obtained after 2 months and erythropoietin was discontinued in patients who did not experience a response at 3 months | Varies depending on indication and frequency of administration |
| Reblozyl® (luspatercept-aamt) | **MDS**<br>Initial: 1 mg/kg SC once every 3 weeks<br><br>Dose increases for insufficient response after initiation of treatment:<br>If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the dose to 1.33 mg/kg SC every 3 weeks. | 1.75 mg/kg/3 weeks |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| | If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg /kg dose level, increase the dose to a maximum of 1.75 mg/kg SC every 3 weeks.<br><br>Discontinue if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at 1.75 mg/kg | |
| Rytelo™ (imetelstat) | **MDS**<br>7.1 mg/kg IV every 4 weeks | 7.1 mg/kg/4 weeks |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*
*†Off-label*

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s): pregnancy; hypersensitivity
- Boxed warning(s): embryo-fetal toxicity, hematologic toxicity, venous and arterial thromboembolism

*Appendix D: General Information*

- Anemia is defined as hemoglobin level less than 10 g/dL.
- Transfusion dependence was defined in two different studies as either greater than 2 units or greater than 4 units of RBCs within 8 weeks prior to enrollment into the studies.
- According to NCCN guideline, current drug therapies for MCL include: a) induction therapy (including RCHOP [rituximab, Cytoxan, Adriamycin, vincristine, and prednisone], hyperCVAD [Cytoxan, vincristine, Adriamycin, and dexamethasone], RBAC500 (rituximab, bendamustine, cytarabine), NORDIC regimen, bendamustine + Rituxan, VR-CAP [bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone]), lenalidomide + rituximab, acalabrutinib + rituximab and b) second-line therapy (including Calquence®, Brukinsa®, Venclexta®, Imbruvica® ± Rituxan, bortezomib ± Rituxan, bendamustine ± Rituxan and Revlimid ± Rituxan).
- The FDA notified the public of an increased risk of second primary malignancies in patients with newly-diagnosed MM who received Revlimid. Clinical trials conducted after Revlimid was approved showed that newly-diagnosed patients treated with Revlimid had an increased risk of developing acute myelogenous leukemia, myelodysplastic syndromes, and Hodgkin lymphoma.
- Revlimid is only available under a restricted distribution program called the Revlimid REMS program due to the black box warning for fetal risk, hematologic toxicity, and deep vein thrombosis/pulmonary embolism. Patient and physician enrollment in the manufacturer's REMS program is required.
- Per NCCN, patients with a good probability to respond to immunosuppressive therapy for MDS are generally ≤ 60 years of age and with ≤ 5% marrow blasts, or those with

hypocellular marrows, PNH clone positivity, or STAT3-mutant cytotoxic T-cell clones, whereas patients with a poor probability to respond to immunosuppressive therapy lack these features.

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| MDS | 10 mg PO QD | 10 mg/day |
| MM (maintenance therapy) | 10 mg PO QD continuously (Days 1-28 of repeated 28-day cycles) until disease progression or unacceptable toxicity.<br><br>After 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated. | 15 mg/day |
| MM<br>(primary therapy for newly diagnosed patients) | 25 mg PO QD days 1-21 of repeated 28 day cycles with dexamethasone 40 mg PO QD on days 1, 8, 15, 22 of each 28 day cycle. | 25 mg/day |
| MM<br>(previously treated patients) | 25 mg PO QD days 1-21 of repeated 28 days cycles with dexamethasone 40 mg QD days 1-4, 9-12 and 17- 20 of each 28 day cycle for the first 4 cycles then 40 mg QD for days 1-4 every 28 days. | 25 mg/day |
| Relapsed MM<br>(previously treated patients) | 25 mg PO QD days 1-21 of repeated 28 day cycles with dexamethasone 40 mg PO QD on days 1, 8, 15, 22 and Kyprolis. Maximum 18 cycles for Kyprolis.<br><br><u>Cycle 1:</u><br>20 mg/m$^2$ IV over 10 minutes on days 1-2. If tolerated, increase to target dose of 27 mg/m$^2$ IV over 10 minutes on days 8, 9, 15, 16<br><u>Cycles 2-12:</u><br>27 mg/m$^2$ IV over 10 minutes on days 1, 2, 8, 9, 15, 16<br><u>Cycles 3-18</u><br>27 mg/m$^2$ IV over 10 minutes on days 1, 2, 15, 16<br><br>Kyprolis dosed at a maximum body surface area of 2.2 m$^2$ | 25 mg/day |

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| MCL | 25 mg PO QD on Days 1- 21 of repeated 28-day cycles | 25 mg/day |
| MZL and FL | 20 mg PO QD on Days 1- 21 of repeated 28-day cycles | 20 mg/day |

## VI. Product Availability

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

## VII. References

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16. Revlimid. American Hospital Formulary Service Drug Information. Available at: http://www.medicinescomplete.com/mc/ahfs/current/. Accessed February 6, 2025.
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| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 2Q 2021 annual review: per NCCN Compendium modified the following - for MCL removed optional use as second-line therapy as a single agent; consolidated off-label use for primary CNS lymphoma and expanded use to members unsuitable or intolerant to high-dose methotrexate; for classic Hodgkin lymphoma clarified use is for third-line or subsequent therapy and removed optional use as palliative therapy. Oral oncology generic redirection language added; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated. | 01.21.21 | 05.21 |
| MDS and myelofibrosis-associated anemia: added specific NCCN recommended uses; MZL: added requirement for concurrent use with rituximab or Gazyva for non-transformative disease per FDA and NCCN; all indications: added requirement for no concurrent use with Thalomid or Pomalyst since all are thalidomide analogs. | 06.24.21 | 08.21 |
| Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less | 09.27.21 | 02.22 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| 2Q 2022 annual review: per NCCN added additional use in combination with Monjuvi for MZL and FL, for myelofibrosis-associated anemia corrected requirements for ≥ 500 vs < 500 (previously was > 500 vs ≤ 500), added off-label use for Langerhans cell histiocytosis as a single agent therapy, modified KS requirements to allow use in non-AIDs related KS, revised CLL/SLL to remove options for first-line therapy; removed mycosis fungoides/Sezary syndrome off-label use; removed primary cutaneous CD30+ T-cell lymphoproliferative disorders off-label use; modified peripheral T-cell lymphoma to allow use as initial palliative intent therapy; references reviewed and updated. | 02.16.22 | 05.22 |
| Revised generic redirection language to allow bypass due to drug shortage. Template changes applied to other diagnoses/indications. | 10.10.22 | |
| 2Q 2023 annual review: per NCCN Compendium updated MM criteria updated maintenance therapy following autologous hematopoietic stem cell transplantation to include option for carfilzomib or bortezomib with dexamethasone, for myelodysplastic syndrome added SF3B1 mutation status, for myelofibrosis-associated anemia, added "in combination with prednisone taper", updated off-label criteria for systemic light chain amyloidosis to include combination therapy, for classic Hodgkin lymphoma changed "as third-line" to "as fourth-line" to align with NCCN Hodgkin Lymphoma guideline, for HIV related B-cell lymphoma, post-transplant lymphoproliferative disorder of B-cell lymphomas and high grade B-cell diffuse lymphoma added "in combination with Monjuvi for non-transplant candidates", added off-label criteria for POEMS syndrome per NCCN 2A recommendation; references reviewed and updated. | 02.22.23 | 05.23 |
| 2Q 2024 annual review: for MM, updated relapse or progressive disease criteria to include " in combination with dexamethasone and one of the following: bortezomib, carfilzomib, daratumumab, ixazomib, cyclophosphamide, elotuzumab, or bendamustine" and maintenance therapy to include "combination with one of the following: carfilzomib, bortezomib, daratumumab" per NCCN compendium; for MDS, added Reblozyl option for serum erythropoietin ≤ 500 mU/mL per NCCN compendium; for MZL and FL, removed criteria "histologic transformation after multiple lines of chemoimmunotherapy for indolent or transformed disease" as not supported on NCCN compendium; for off-label indications, updated myelofibrosis-associated anemia to "in combination with prednisone taper and presence of del(5q) and removed serum erythropoietin requirement; for systemic light chain amyloidosis off-label indication, removed "bortezomib" requirement as not supported by NCCN compendium; for KS off-label indication, added "subsequent therapy | 01.12.24 | 05.24 |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| following treatment of first-line systemic therapy for relapsed, refractory, or advanced disease", removed failure of liposomal doxorubicin and paclitaxel, added prescribed as a single agent, and revised "AIDS-related KS" to "HIV-related KS"; updated Appendix B with relevant therapeutic alternatives; for Appendix D, revised current drug therapies for MCL per NCCN B-Cell Lymphomas guideline; updated generic lenalidomide shortage criteria to "unavailable until sometime in 2026"; references reviewed and updated. | | |
| 2Q 2025 annual review: revised policy/criteria section to also include generic lenalidomide; per NCCN – for MM, added use as primary therapy for high-risk smoldering MM and symptomatic MM; for MDS, clarified recommended uses for no deletion 5q abnormality depending on ring sideroblasts (including addition of trial of Reblozyl or Rytelo for ring sideroblasts ≥ 15% [or ≥ 5% if SF3B1 mutation]), added that member has poor probability to respond to immunosuppressive therapy for serum erythropoietin > 500 mU/mL, and removed allowance for MDS/myeloproliferative overlap neoplasms that are wild-type for SF3B1 mutation; for MZL, added use as first-line therapy in combination with rituximab and removed use in combination with Monjuvi; for FL, added use as first-line in combination with Gazyva, specified use as a single agent or combination therapy for second-line or subsequent therapy, and removed specific requirements surrounding combination use with Monjuvi in non-transplant candidates; for classic Hodgkin lymphoma, removed requirement for use as fourth-line or later therapy and added use as single agent palliative subsequent therapy; for adult T-cell leukemia/lymphoma and hepatosplenic gamma-delta T-cell lymphoma, specified use must be as a single agent; for CLL/SLL, specified use must be as a single agent or in combination with rituximab and specified prior therapies that must be tried; for B-cell lymphomas, clarified that Monjuvi can also be used in non-CAR T-cell therapy candidates and added additional pathways for use; references reviewed and updated. | 02.10.25 | 05.25 |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note:**
**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.