

## Clinical Policy: Lenalidomide (Revlimid)

Reference Number: CP.PHAR.71

Effective Date: 07.01.11

Last Review Date: 05.20

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<sup>®</sup>) 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-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<sup>®</sup>)
- 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<sup>®</sup> that Revlimid is **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  $\geq$  18 years;
4. Will be used for one of the following indications (a, b, c, or d):
  - a. In combination with dexamethasone;
  - b. As a single agent in steroid-intolerant patients with previously treated myeloma with relapse or progressive disease;
  - c. As maintenance therapy as a single agent or in combination with bortezomib following autologous hematopoietic stem cell transplantation;

- d. As maintenance therapy as a single agent or in combination with bortezomib for active (symptomatic) myeloma after response to primary myeloma therapy;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 25 mg/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 - Length of Benefit**

**B. Myelodysplastic Syndrome (must meet all):**

1. Diagnosis of MDS;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age  $\geq$  18 years;
4. Member has one of the following (a or b):
  - a. Symptomatic or transfusion-dependent anemia due to MDS;
  - b. MDS and myeloproliferative overlap neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T);
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 10 mg/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 - Length of Benefit**

**C. Mantle Cell Lymphoma (must meet all):**

1. Diagnosis of MCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age  $\geq$  18 years;
4. Will be used for one of the following indications (a, b, or c):
  - a. Relapsed or progressive disease after two prior therapies, one of which included bortezomib (Velcade);
  - b. In combination with rituximab\*;
  - c. Second-line therapy as a single agent or in combination with rituximab\*;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 25 mg/day;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

*\*Prior authorization may be required for rituximab*  
*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**

**Medicaid/HIM - 6 months**

**Commercial - Length of Benefit**

**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  $\geq$  18 years;
4. Will be used for one of the following indications (a or b):
  - a. Second-line or subsequent therapy;
  - b. Histologic transformation of MZL to non-germinal center diffuse large B-cell lymphoma after multiple lines of chemoimmunotherapy for indolent or transformed disease;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 20 mg/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** – Length of Benefit

**E. Follicular Lymphoma** (must meet all):

1. Diagnosis of FL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age  $\geq$  18 years;
4. Will be used for one of the following indications (a, b, or c):
  - a. First-line therapy in combination with rituximab;\*
  - b. Second-line or subsequent therapy;
  - c. Treatment of histologic transformation to non-germinal center diffuse large B-cell lymphoma after multiple lines of chemoimmunotherapy for indolent or transformed disease;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 20 mg/day;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

*\*Prior authorization may be required for rituximab.*

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

**Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

**F. Other NCCN Compendium Supported Diagnoses/Indications (off-label)** (must meet all):

1. Prescribed for one of the following NCCN category 1 or 2a recommended indications:
  - a. Myelofibrosis-associated anemia;
  - b. Systemic light chain amyloidosis in combination with dexamethasone;
  - c. Primary central nervous system (CNS) lymphoma for relapsed or refractory disease;

- d. Classic Hodgkin lymphoma as subsequent therapy for relapsed or refractory disease, or as palliative therapy;
  - e. Any of the following non-Hodgkin lymphoma subtypes:
    - i. T-cell leukemia/lymphoma as second-line or subsequent therapy;
    - ii. AIDS-related B-cell lymphoma as second-line or subsequent therapy;
    - iii. AIDS-Related Kaposi Sarcoma as subsequent therapy for relapsed or refractory disease;
    - iv. Castleman's disease (CD) as subsequent therapy following treatment of relapsed, refractory, or progressive disease;
    - v. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) as first or second-line maintenance therapy, or for relapsed or refractory disease;
    - vi. Diffuse large B-cell lymphoma as second-line or subsequent therapy;
    - vii. Hepatosplenic gamma-delta T-cell lymphoma for refractory disease after two primary treatment regimens;
    - viii. High-grade B-cell lymphoma as second-line or subsequent therapy;
    - ix. Mycosis fungoides/Sezary syndrome;
    - x. Peripheral T-cell lymphoma as second-line and subsequent therapy;
    - xi. Primary CNS lymphoma as a single agent or in combination with rituximab\* for relapsed or refractory disease;
    - xii. Primary cutaneous CD30+ T-cell lymphoproliferative disorders as therapy for relapsed or refractory anaplastic large cell lymphoma with multifocal lesions or regional nodes;
    - xiii. Post-transplant lymphoproliferative disorders of B-cell lymphomas as second-line or subsequent therapy;
- \*Prior authorization is (or may be) required for rituximab
2. Prescribed by or in consultation with an oncologist or hematologist;
  3. Age  $\geq$  18 years;
  4. Request meets one of the following (a or b):\*
    - a. Dose does not exceed 25 mg/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 - Length of Benefit**

**G. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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 Revlimid for a covered indication and has received this medication for at least 30 days;

2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):\*
  - a. New dose does not exceed 10 mg/day for MDS, 20 mg/day for MZL and FL, and 25 mg/day for all other indications;
  - 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** – Length of Benefit

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

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less);** or

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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.PHAR.21 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

FDA: Food and Drug Administration

FL: follicular lymphoma

MALT: mucosa-associated lymphoid tissue

MCL: mantle cell lymphoma

MDS: myelodysplastic syndrome

MM: multiple myeloma

MZL: marginal zone lymphomas

NCCN: National Comprehensive Cancer Network

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)	<p><b>Multiple Myeloma</b> (Conventional primary therapy)</p> <p>melphalan 8 mg/m<sup>2</sup>/day PO days 1-4; prednisone 60 mg/m<sup>2</sup>/day PO days 1-4. Repeat cycle every 28 days</p>	As recommended in dosing regimen
vincristine*/ doxorubicin*/ dexamethasone (VAD)	<p><b>Multiple Myeloma</b> (Conventional primary therapy)</p> <p>vincristine 0.4 mg/day IV continuous infusion days 1- 4; doxorubicin 9 mg/m<sup>2</sup>/day IV continuous infusion days 1-4; dexamethasone 40 mg PO days 1-4, 9-12, 17-20. Repeat cycle every 28-35 days</p>	As recommended in dosing regimen
dexamethasone (pulse dose as single agent)	<p><b>Multiple Myeloma</b> (Conventional primary therapy)</p> <p>dexamethasone 40 mg PO days 1-4, 9-12, 17-20</p>	As recommended in dosing regimen
Thalomid <sup>®</sup> (thalidomide)/ dexamethasone	<p><b>Multiple Myeloma</b> (Conventional primary therapy)</p> <p>thalidomide 200 mg/day PO daily; dexamethasone 40 mg/day days 1-4, 9- 12,17-20 for odd cycles and days 1-4 for even cycles. Repeat cycle every 28 days</p>	As recommended in dosing regimen
Pomalyst <sup>®</sup> (pomalidomide)	<p><b>Multiple Myeloma</b></p> <p>4 mg PO QD on days 1-21 of repeated 28- day cycles until disease progression. Pomalyst may be given in combination with dexamethasone. Pomalyst may be given in combination with Kyprolis/dexamethasone Avoid Pomalyst in patients with a serum creatinine greater than 3.0 mg/dL</p>	4 mg/day
Bortezomib (Velcade)	<b>Mantle Cell Lymphoma</b>	1.3 mg/m <sup>2</sup> /dose

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	<p>1.3 mg/m<sup>2</sup>/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). At least 72 hours should elapse between consecutive doses of Velcade</p>	

*Therapeutic alternatives are listed as Brand name<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) when the drug is available by both brand and generic.*

*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 CHOP [Cytosin, Adriamycin, vincristine, and prednisone], hyperCVAD [Cytosin, vincristine, Adriamycin, and dexamethasone], RDHA [Rituxan, dexamethasone, cytarabine], NORDIC regimen, bendamustine + Rituxan, VR-CAP [bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone]), and b) second-line therapy (including Calquence<sup>®</sup>, Venclexta<sup>®</sup>, Imbruvica<sup>®</sup> ± 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.

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.  After 3 cycles of maintenance therapy, the dose can be increased to 15 mg once daily if tolerated.	15 mg/day
MM (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 (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 (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.  <u>Cycle 1:</u> 20 mg/m <sup>2</sup> IV over 10 minutes on days 1-2. If tolerated, increase to target dose of 27 mg/m <sup>2</sup> IV over 10 minutes on days 8, 9, 15, 16 <u>Cycles 2-12:</u> 27 mg/m <sup>2</sup> IV over 10 minutes on days 1, 2, 8, 9, 15, 16 <u>Cycles 3-18</u> 27 mg/m <sup>2</sup> IV over 10 minutes on days 1, 2, 15, 16  Kyprolis dosed at a maximum body surface area of 2.2 m <sup>2</sup>	25 mg/day
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**

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

**VII. References**

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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Added efficacy data for all 3 indications Reviewed and added references Added appendix A, B, C Changed authorization period to 3 months in algorithm for safety purposes	07.14	07.14
Added pregnancy testing and age requirements to narrative and algorithm Removed requirement to try other therapies before Revlimid for MM in algorithm as Figure 1: Added age requirement and REMS questions; removed requirement to try other therapies before Revlimid for MM in algorithm as Revlimid is for both newly diagnosed and relapsed/refractory MM – removed corresponding Appendix of possible previous therapies for MM; edited approval periods in algorithm per Centene policy. Updated safety information	05.15	06.15
Converted policy to new template. Documentation requests removed. Age requirement removed. NCCN recommended uses added. Added REMS program and safety information to background.	05.16	06.16
Converted policy to new template. Updated FDA indication for use as maintenance therapy as a single agent following autologous hematopoietic stem cell transplantation. Removed hypersensitivity criteria.	03.17	06.17
For MM, NCCN recommended uses updated to include 1) regimens for primary therapy or subsequent therapy for disease relapse after 6 months with same regimen, 2) subsequent therapies for relapsed, progressive or refractory disease in addition to single agent therapy. Under myelodysplastic syndrome, NCCN recommended use changed	05.17	06.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>from “serum erythropoietin levels <math>\leq</math> 500 mU/mL, no response to erythropoietins,” to “serum erythropoietin levels <math>\leq</math> 500 mU/mL, in combination with epoetin alpha or darbepoetin alpha if no response to erythropoietins alone”.</p> <p>Under MCL, NCCN recommended uses updated to include 1) induction therapy, 2) change from “use as second-line therapy for stage I-II disease or aggressive stage II bulky, III, or IV disease for relapsed, refractory, or progressive disease” to “second-line therapy as a single agent, with rituximab, or with ibrutinib and rituximab for stage I-IV disease”.</p> <p>Under “other indications,” added myelofibrosis-associated anemia and marginal zone lymphoma. Maximum dose added. Safety information removed. Global Biopharm language added under “Other Diagnoses/Indications”. Approval durations increased from 3/6 to 6/12 months.</p>		
<p>2Q 2018 annual review: added HIM line of business; policies combined for Commercial and Medicaid lines of business; MDS: removed criteria requirements for low-risk disease and deletion 5q cytogenetic abnormality; MCL: removed disease staging; removed off-label use for primary cutaneous B-cell lymphoma; references reviewed and updated.</p>	01.22.18	05.18
<p>2Q 2019 annual review: added hematologist prescriber option; updated NCCN compendium supported uses to include primary CNS lymphoma and hepatosplenic gamma-delta T-cell lymphoma; MM: added use as a single agent in steroid-intolerant patients with previously treated myeloma with relapse or progressive disease; MCL: added option for second-line therapy in combination with Rituxan; reference reviewed and updated.</p>	02.05.19	05.19
<p>RT4: FL, MZL FDA approved indications added, previously presented as NCCN recommended uses; references reviewed and updated.</p>	07.02.19	
<p>2Q 2020 annual review: per NCCN Compendium for MM maintenance therapy added option for use in combination with bortezomib; for MDS added MDS and myeloproliferative overlap neoplasms; added primary CNS lymphoma and AIDS-Related Kaposi Sarcoma to Section IF; references reviewed and updated.</p>	02.13.20	05.20

**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.

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**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.

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