Clinical Policy: Lenalidomide (Revlimid)

Reference Number: CP.PHAR.71
Effective Date: 07.01.11
Last Review Date: 05.18
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:

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

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 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;
3. Age ≥ 18 years;
4. Will be used for one of the following indications (a, b, or c):
   a. In combination with dexamethasone;
   b. As maintenance therapy as a single agent following autologous hematopoietic stem cell transplantation;
   c. As maintenance therapy as a single agent 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*).

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;
3. Age ≥ 18 years;
4. Member has symptomatic or transfusion-dependent anemia due to MDS;
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*).

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;
3. Age ≥ 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;
   b. In combination with rituximab;
   c. Second-line therapy as a single agent;
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*).

Approval duration:
Medicaid/HIM - 6 months
Commercial - Length of Benefit

D. 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 (Refer to :
   a. Myelofibrosis-associated anemia;
   b. Systemic light chain amyloidosis in combination with dexamethasone;
   c. Classic Hodgkin lymphoma as subsequent therapy for relapsed or refractory disease, or as palliative therapy;
   d. Any of the following non-Hodgkin lymphoma subtypes:
      i. T-cell leukemia/lymphoma as second-line therapy;

ii. AIDS-related B-cell lymphoma as second-line or subsequent therapy;
iii. Castleman's disease (CD) as subsequent therapy following treatment of relapsed, refractory, or progressive disease;
iv. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) as first or second-line maintenance therapy, or for relapsed or refractory disease;
v. Diffuse large B-cell lymphoma;
vi. Follicular lymphoma as first-line therapy in combination with rituximab or as second-line or subsequent therapy;
vii. Gastric MALT lymphoma as first-line therapy in combination with rituximab or as second-line or subsequent therapy;
viii. Mycosis fungoides /Sezary syndrome;
ix. Nodal marginal zone lymphoma as first-line therapy in combination with rituximab or as second-line or subsequent therapy;
x. Nongastric MALT lymphoma as first-line therapy in combination with rituximab or as second-line or subsequent therapy;
xi. Peripheral T-cell lymphoma as second-line and subsequent therapy;
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. Splenic marginal zone lymphoma as first-line therapy in combination with rituximab or as second-line or subsequent therapy;
xiv. Post-transplant lymphoproliferative disorders of B-cell lymphomas as second-line or subsequent therapy

2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 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*).

Approval duration:
Medicaid/HIM - 6 months
Commercial - Length of Benefit

E. 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 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 25 mg/day for MM and MCL and 10 mg/day for MDS;
b. Requested new dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

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
FDA: Food and Drug Administration
MALT: mucosa-associated lymphoid tissue
MCL: mantle cell lymphoma
MDS: myelodysplastic syndrome
MM: multiple myeloma
CD: Castleman's disease
CLL: chronic lymphocytic leukemia
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)	**Multiple Myeloma** (Conventional primary therapy) melphalan 8 mg/m^2/day PO days 1-4; prednisone 60 mg/m2/day PO days 1-4. Repeat cycle every 28 days	As recommended in dosing regimen
vincristine*/ doxorubicin*/ dexamethasone (VAD)	**Multiple Myeloma** (Conventional primary therapy) vincristine 0.4 mg/day IV continuous infusion days 1- 4; doxorubicin 9 mg/m2/day IV continuous infusion days 1-4; dexamethasone 40 mg PO days 1-4, 9-12, 17-20. Repeat cycle every 28-35 days	As recommended in dosing regimen
dexamethasone (pulse dose as single agent)	**Multiple Myeloma** (Conventional primary therapy) dexamethasone 40 mg PO days 1-4, 9-12, 17-20	As recommended in dosing regimen
Thalomid® (thalidomide)/ dexamethasone	**Multiple Myeloma** (Conventional primary therapy) 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	As recommended in dosing regimen
Pomalyst® (pomalidomide)	**Multiple Myeloma** 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	4 mg/day
Velcade® (bortezomib)*	**Mantle Cell Lymphoma**	1.3 mg/m^2/dose

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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). At least 72 hours should elapse between consecutive doses of Velcade	

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.

Appendix C: 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 National Comprehensive Cancer Network (NCCN) guideline, the following are 2A recommendations: a) MDS with no deletion of 5q with a poor probability of response to immunosuppressive therapy or following no response to hematopoietic cytokines, b) systemic light chain amyloidosis, and c) second line therapy for Non-Hodgkins Lymphoma (Adult T-cell leukemia/lymphoma, AIDS Related B-Cell Lymphoma, Castleman's disease, Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), Diffuse Large B-Cell Lymphoma, Follicular Lymphoma, Gastric and Nongastric MALT Lymphoma, Mycosis fungoides /Sezary syndrome, Nodal marginal zone lymphoma, Peripheral T-cell lymphoma, Primary cutaneous CD30+ T-cell lymphoproliferative disorders, and Splenic Marginal Zone Lymphoma).
- According to NCCN guideline, current drug therapies for MCL include: a) induction therapy (including CHOP [Cytoxan, Adriamycin, vincristine, and prednisone] and hyperCVAD [Cytoxan, vincristine, Adriamycin, and dexamethasone] - given in frequent smaller doses, and b) second-line therapy (including Velcade+Rituxan and Revlimid+Rituxan).
- In the pivotal trial, patients with MCL were required to have received prior treatment with an anthracycline or mitoxantrone, cyclophosphamide, Rituxan, and Velcade, alone or in combination. Among these agents, Velcade is the only FDA approved medication indicated for the treatment of MCL.
- Inclusion criteria for studies with Revlimid allowed for previous use of Thalomid in patients with refractory/relapsing MM. Eight percent of patients previously treated with Thalomid demonstrated a complete response with 53.3% showing an overall response to Revlimid + Dexamethasone and 45.2% demonstrating a partial response.

- 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
Myelodysplastic Syndrome	10 mg PO QD Dosing is modified based upon clinical and laboratory findings	10 mg/day
Multiple Myeloma (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. Dosing is modified based upon clinical and laboratory findings	15 mg/day
Multiple Myeloma (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 Dosing is modified based upon clinical and laboratory findings	25 mg/day
Multiple Myeloma (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	25 mg/day

Indication	Dosing Regimen	Maximum Dose
	day cycle for the first 4 cycles then 40 mg QD for days 1-4 every 28 days Dosing is modified based upon clinical and laboratory findings	
Relapsed Multiple Myeloma (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^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 <u>Cycles 2-12:</u> 27 mg/m^2 IV over 10 minutes on days 1, 2, 8, 9, 15, 16 <u>Cycles 3-18</u> 27 mg/m^2 IV over 10 minutes on days 1, 2, 15, 16 Kyprolis dosed at a maximum body surface area of 2.2 m^2	25 mg/day
Mantle Cell Lymphoma	25 mg PO QD on Days 1-21 of repeated 28-day cycles Dosing is modified based upon clinical and laboratory findings	25 mg/day
Amyloidosis	25 mg PO QD days 1-21 of repeated 28 days cycles with dexamethasone 40 mg once per week. Dosing of Revlimid can be reduced to 15 mg/day for tolerability and can be	25 mg/day

Indication	Dosing Regimen	Maximum Dose
	combined with dexamethasone and either melphalan or cyclophosphamide	

VI. Product Availability

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

VII. References

1. Revlimid Prescribing Information. Summit, NJ: Celgene Corporation; December 2017. Available at: http://media.celgene.com/content/uploads/revlimid-pi.pdf. Accessed January 18, 2017.
2. List A, Kurtin S, Roe D, et al. Efficacy of Lenalidomide in Myelodysplastic Syndromes. N Engl J Med. 2005; 352 (6): 549-557.
3. National Comprehensive Cancer Network. Myelodysplastic Syndromes Version 1.2018. Available at: http://www.nccn.org/professionals/physician_gls/pdf/mds.pdf. Accessed January 22, 2018.
4. National Comprehensive Cancer Network. Multiple Myeloma Version 3.2018. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed January 22, 2018.
5. National Comprehensive Cancer Network. B-cell Lymphomas Version 7.2017. Available at https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed January 22, 2018.
6. National Comprehensive Cancer Network. Systemic Light Chain Amyloidosis Version 1.2018. Available at http://www.nccn.org/professionals/physician_gls/PDF/amyloidosis.pdf. Accessed January 22, 2018.
7. Weber DM, Chen C, et.al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007 Nov 22; 357(21):2133-42.
8. Lacy MQ, Ertz MA, et.al. Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. Mayo Clinic Proceedings. 2007 Oct; 82 (10):1179-84.
9. FDA Drug Safety Communication: Safety review update of cancer drug Revlimid (lenalidomide) and risk of developing new types of malignancies. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm302939.htm. Accessed January 22, 2018.
10. Revlimid. American Hospital Formulary Service Drug Information. Available at: http://www.medicinescomplete.com/mc/ahfs/current/. Accessed June 22, 2018.
11. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed January 22, 2018.
12. Clinical Pharmacology Web site. Available at: http://clinicalpharmacologyip.com/default.aspx. Accessed: January 22, 2018.
13. National Comprehensive Cancer Network Drugs & Biologics Compendium: Lenalidomide. Available at: https://www.nccn.org/professionals/drug_compendium/content/. Updated periodically. Accessed January 22, 2018.

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 from "serum erythropoietin levels ≤ 500 mU/mL, no response to erythropoietins," to "serum erythropoietin levels ≤ 500 mU/mL, in combination with epoetin alpha or darbepoetin alpha if no response to erythropoietins alone". 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". 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.	05.17	06.17
2Q 2018 annual review: added HIM line of business; policies combined for Commercial and Medicaid lines of business; MDS:	01.22.18	05.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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.		

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.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.