Clinical Policy: Lenalidomide (Revlimid)

Reference Number: PA.CP.PHAR.71
Effective Date: 01/18
Last Review Date: 04/19

Revision Log

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-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®)

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
It is the policy of health plans affiliated with Pennsylvania Health and Wellness® that Revlimid is **medically necessary** when one of the following criteria is met:

I. Initial Approval Criteria

A. Multiple Myeloma (must meet all):

1. Diagnosis of multiple myeloma (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, or c):
   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 following autologous hematopoietic stem cell transplantation;
   d. 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: 6 months

B. Myelodysplastic Syndrome (must meet all):

1. Diagnosis of myelodysplastic syndrome (MDS);
2. Prescribed by or in consultation with an oncologist or hematologist;
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: 6 months

C. Mantle Cell Lymphoma (must meet all):
1. Diagnosis of mantle cell lymphoma (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, 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. Requested dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval duration: 6 months

D. Other NCCN Compendium Supported Diagnoses/Indications (off-label) (must meet all):
1. The following NCCN recommended use(s) meeting NCCN categories 1 or 2a may be covered provided that member meets the off-label criteria defined in PA.CP.PMN.53:
   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 or subsequent 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 as second-line or subsequent therapy;
      vi. Hepatosplenic gamma-delta T-cell lymphoma for refractory disease after two primary treatment regimens;
      vii. High-grade B-cell lymphoma as second-line or subsequent therapy;
      viii. Histologic transformation of MZL to diffuse large B-cell lymphoma after multiple lines of chemoimmunotherapy for indolent or transformed disease;

ix. Follicular lymphoma as first-line therapy in combination with rituximab or as second-line or subsequent therapy;
x. Marginal zone lymphomas (MZL) [including gastric or nongastric mucosa-associated lymphoid tissue (MALT) lymphoma, nodal MZL, and splenic MZL] as first-line therapy in combination with rituximab or as second-line or subsequent therapy;
xi. Mycosis fungoides /Sezary syndrome;
xii. Peripheral T-cell lymphoma as second-line and subsequent therapy;
xiii. Primary CNS lymphoma as a single agent or in combination with rituximab for relapsed or refractory disease;
xiv. Primary cutaneous CD30+ T-cell lymphoproliferative disorders as therapy for relapsed or refractory anaplastic large cell lymphoma with multifocal lesions or regional nodes;
xv. Post-transplant lymphoproliferative disorders of B-cell lymphomas as second-line or subsequent therapy;

2. Prescribed by or in consultation with an oncologist or hematologist;
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: 6 months

E. Other diagnoses/indications:
1. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed.

II. Continued Approval

A. All Indications in Section I (must meet all):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
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 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*).

Approval duration: 12 months

B. Other diagnoses/indications (1or 2):
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.

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

2. Refer to PA.CP.PMN.53

III. 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
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)	**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)	As recommended in dosing regimen

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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	
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
Bortezomib (Velcade)	**Mantle Cell Lymphoma** 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	1.3 mg/m^2/dose

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: 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 [Cytoxan, Adriamycin, vincristine, and prednisone],

hyperCVAD [Cytoxan, 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®, 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.

IV. 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^2 IV over 10 minutes on days 1-2. If tolerated, increase to target dose	25 mg/day

Indication	Dosing Regimen	Maximum Dose
	of 27 mg/m^2 IV over 10 minutes on days 8, 9, 15, 16 Cycles 2-12: 27 mg/m^2 IV over 10 minutes on days 1, 2, 8, 9, 15, 16 Cycles 3-18 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	
MCL	25 mg PO QD on Days 1- 21 of repeated 28-day cycles	25 mg/day

V. Product Availability

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

VI. References

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Reviews, Revisions, and Approvals	Date	Approval Date
2Q 2018 annual review: 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.	1.22.18	4.18
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.	04-2019	