RXADVANCE
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Clinical Policy Title:	lenalidomide
Policy Number:	RxA.461
Drug(s) Applied:	Revlimid®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

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

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®).
- 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
lenalidomide (Revlimid®)	MDS	10 mg PO OD	10 mg/day
	MM (maintenance therapy)	10 mg PO OD 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 OD days 1-21 of repeated 28 day cycles with dexamethasone 40 mg PO OD on days 1, 8, 15, 22 of each 28 day cycle.	25 mg/day

Drug Name	Indication	Dosing Regimen	Maximum Dose
lenalidomide (Revlimid®)	MM (previously treated patients)	25 mg PO OD days 1-21 of repeated 28 days cycles with dexamethasone 40 mg OD days 1-4, 9-12 and 17- 20 of each 28 day cycle for the first 4 cycles then 40 mg OD for days 1-4 every 28 days.	25 mg/day
	Relapsed MM (previously treated patients)	25 mg PO OD days 1-21 of repeated 28 day cycles with dexamethasone 40 mg PO OD 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/m2 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
	MCL	25 mg PO OD on Days 1- 21 of repeated 28-day cycles	25 mg/day
	MZL and FL	20 mg PO OD on Days 1- 21 of repeated 28-day cycles	20 mg/day

Dosage Forms

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

Clinical Policy

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

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. 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 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
Commercial: 6 months
Medicaid: 6 months

B. Myelodysplastic Syndrome (must meet all):
1. Diagnosis of 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;
   b. MDS and myeloproliferative overlap neoplasms with ring sideroblasts and thrombocytosis (MPN-RS-T);
5. Request meets one of the following (a or b):
   c. Dose does not exceed 10 mg/day;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

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, 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*;
   *Prior authorization may be required for 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).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

D. Marginal Zone Lymphoma (must meet all):
1. Diagnosis of MZL (including gastric or non-gastric 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. 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).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

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, 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;
   *Prior authorization may be required for rituximab.
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).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

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 ≥ 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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has met initial approval criteria 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).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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
MPN-RS-T: myeloproliferative overlap neoplasms with ring sideroblasts and thrombocytosis
NCCN: National Comprehensive Cancer Network

REMS: Risk Evaluation and Mitigation Strategy
SLL: small lymphocytic lymphoma

APPENDIX B: Therapeutic Alternatives

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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/m^2/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/m^2/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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Pomalyst® (pomalidomide)	**Multiple Myeloma** 4 mg PO OD 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 guidelines, 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) secondline 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.

References

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Line of business Policy Applies to was updated to "All lines of business". 3. Initial and Continued approval criteria's approval duration for Commercial was updated from "Length of benefit" to 6 months and 12 months respectively. 4. Continued therapy approval criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. References were reviewed and updated.	09/04/2020	12/07/2020