Clinical Policy: Lenalidomide (Revlimid)

Reference Number: ERX.SPA.56
Effective Date: 06.01.17
Last Review Date: 08.21 Revision Log
Line of Business: Commercial, Medicaid

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(s)
Revlimid is indicated for the treatment of:

- 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(s) 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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 ≥ 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. Revlimid is not prescribed concurrently with Thalomid® or Pomalyst®;
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:
Commercial – Length of Benefit
Medicaid – 6 months

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 either (a or b):
         a) Serum erythropoietin > 500 mU/mL;
         b) Serum erythropoietin ≤ 500 mU/mL, and failure of an erythropoiesis-stimulating agent (ESA; *Retacrit® and Aranesp® are preferred*)*, unless contraindicated or clinically significant adverse effects are experienced;
            **Prior authorization may be required*
   b. MDS and myeloproliferative overlap neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T);
5. Revlimid is not prescribed concurrently with Thalomid or Pomalyst;
6. 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:
Commercial – Length of Benefit
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 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. Revlimid is not prescribed concurrently with Thalomid or Pomalyst;
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:
Commercial – Length of Benefit
Medicaid – 6 months

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. Second-line or subsequent therapy, and is prescribed in combination with rituximab* or Gayzva®*;
      **Prior authorization may be required*
   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. Revlimid is not prescribed concurrently with Thalomid or Pomalyst;
6. 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:
Commercial – Length of Benefit
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. Revlimid is not prescribed concurrently with Thalomid or Pomalyst;
6. 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:
Commercial – Length of Benefit
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, and one of the following (i or ii):
      i. Serum erythropoietin > 500 mU/mL;
      ii. Serum erythropoietin ≤ 500 mU/mL, and failure of an ESA (*Retacrit and Aranesp are preferred*)*, unless contraindicated or clinically significant adverse effects are experienced;
   a. Systemic light chain amyloidosis in combination with dexamethasone;
   b. 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;
   c. Classic Hodgkin lymphoma as third-line or subsequent therapy for relapsed or refractory disease;
   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. AIDS-related Kaposi sarcoma (KS), and both of the following (1 and 2):
         1) Revlimid is prescribed in combination with antiretroviral therapy;

2) Failure of liposomal doxorubicin and paclitaxel, unless clinically significant adverse effects are experienced or both are contraindicated;

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 cutaneous CD30+ T-cell lymphoproliferative disorders as therapy for relapsed or refractory anaplastic large cell lymphoma with multifocal lesions or regional nodes;
xii. Post-transplant lymphoproliferative disorders of B-cell lymphomas as second-line or subsequent therapy;

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

2. Prescribed by or in consultation with one of the following specialists (a or b):
   a. AIDS-related KS: an oncologist or immunologist;
   b. All other diagnoses: an oncologist or hematologist;
3. Age ≥ 18 years;
4. Revlimid is not prescribed concurrently with Thalomid or Pomalyst;
5. 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:
Commercial – Length of Benefit
Medicaid – 6 months

G. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, 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. Revlimid is not prescribed concurrently with Thalomid or Pomalyst;
4. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 10 mg per day for MDS, 20 mg per day for MZL and FL, and 25 mg per 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:
Commercial – Length of Benefit
Medicaid – 12 months

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

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

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

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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
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 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/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
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 or 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	1.3 mg/m^2/dose

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	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	
liposomal doxorubicin (Doxil®, Lipodox® 50)	**AIDS-related KS** 20 mg/m^2 IV every 2-3 weeks with a cumulative lifetime dose of 400-450 mg/m^2 due to cardiotoxicity	See regimen
paclitaxel	**AIDS-related KS** 135 mg/m^2 IV every 3 weeks **or** 100 mg/m^2 every 2 weeks	See regimen
ESAs		
Aranesp® (darbepoetin alfa)	**Anemia associated with MDS†** 150-300 mcg SC every other week	500 mcg every other week
epoetin alfa (Epogen®, Procrit®, Retacrit®)	**Anemia associated with MDS†** 40,000-60,000 units SC one to two times weekly **Anemia associated with myelofibrosis†** 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

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 red blood cells 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.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MDS	10 mg PO QD Dosing is modified based upon clinical and laboratory findings	10 mg/day
MM (maintenance therapy following autologous hematopoietic stem cell transplantation)	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 Cycle 1: 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 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	As recommended in dosing regimen Kyprolis is dosed at 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
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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Reviews, Revisions, and Approvals	Date	P&T Approval Date
Added new indication for multiple myeloma as maintenance following autologous hematopoietic stem cell transplantation. Modified initial/continued approval durations from 3/6 months to 6/12 months.	03.17	05.17
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; modified sections for classical Hodgkin lymphoma, non-Hodgkin lymphoma, and systemic light chain amyloidosis to reference NCCN compendium supported use; approval durations changed to length of benefit; references reviewed and updated.	01.22.18	05.18
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; references reviewed and updated.	02.05.19	05.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
RT4: FL, MZL FDA approved indications added, previously presented as NCCN recommended uses; added Medicaid line of business with 6/12 month approval durations; references reviewed and updated.	07.02.19	
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.	02.13.20	05.20
AIDS-related KS: updated criteria to require concurrent use with antiretroviral therapy and failure of first line agents per NCCN guidelines; added immunologist as a prescriber option per specialist feedback.	06.29.20	11.20
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; 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

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.