Clinical Policy: Lenalidomide (Revlimid)
Reference Number: ERX.SPA.56
Effective Date: 06.01.17
Last Review Date: 05.18

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:

- 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(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.

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;
      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 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: 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: 6 months

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: 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:
      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*).
E. 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. 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. New dose is supported by practice guidelines or peer-reviewed literature for the relevant
            off-label use (prescriber must submit supporting evidence).

   Approval duration: Length of Benefit

   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);
      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
   FDA: Food and Drug Administration
   MALT: mucosa-associated lymphoid tissue
   MCL: mantle cell lymphoma
   MM: multiple myeloma
   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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>melphalan/prednisone (MP)</td>
<td><strong>Multiple Myeloma</strong> (Conventional primary therapy) melphalan 8 mg/m²/day PO days 1-4; prednisone 60 mg/m²/day PO days 1-4. Repeat cycle every 28 days</td>
<td>As recommended in dosing regimen</td>
</tr>
<tr>
<td>vincristine*/doxorubicin*/dexamethasone (VAD)</td>
<td><strong>Multiple Myeloma</strong> (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</td>
<td>As recommended in dosing regimen</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Regimen</td>
<td>Dose Limit/ Maximum Dose</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>dexamethasone (pulse dose as</td>
<td><strong>Multiple Myeloma</strong> (Conventional primary therapy) dexamethasone 40 mg PO</td>
<td>As recommended in dosing regimen</td>
</tr>
<tr>
<td>single agent)</td>
<td>days 1-4, 9-12, 17-20</td>
<td></td>
</tr>
<tr>
<td>Thalomid® (thalidomide)/</td>
<td><strong>Multiple Myeloma</strong> (Conventional primary therapy) thalidomide 200 mg/day</td>
<td>As recommended in dosing regimen</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>PO daily; dexamethasone 40 mg/day days 1-4, 9-12, 17-20 for odd cycles and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>days 1-4 for even cycles. Repeat cycle every 28 days</td>
<td></td>
</tr>
<tr>
<td>Pomalyst® (pomalidomide)</td>
<td><strong>Multiple Myeloma</strong></td>
<td>4 mg/day</td>
</tr>
<tr>
<td></td>
<td>4 mg PO QD on days 1-21 of repeated 28-day cycles until disease progression.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pomalyst may be given in combination with dexamethasone or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kyprolis/dexamethasone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Avoid Pomalyst in patients with a serum creatinine greater than 3.0 mg/dL.</td>
<td></td>
</tr>
<tr>
<td>Velcade® (bortezomib)*</td>
<td><strong>Mantle Cell Lymphoma</strong></td>
<td>1.3 mg/m²/dose</td>
</tr>
<tr>
<td></td>
<td>1.3 mg/m²/dose SC or IV BIW for 2 weeks (Days 1, 4, 8, and 11) followed by</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a 10-day rest period (Days 12-21) for six 3-week cycles. For extended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>therapy of more than 8 cycles, Velcade may be administered on the standard</td>
<td></td>
</tr>
<tr>
<td></td>
<td>schedule or on a maintenance schedule of once weekly for 4 weeks (Days 1, 8,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15, and 22) followed by a 13-day rest period (Days 23 to 35). At least 72</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hours should elapse between consecutive doses of Velcade.</td>
<td></td>
</tr>
</tbody>
</table>

**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 red blood cells within 8 weeks prior to enrollment into the studies.
- According to National Comprehensive Cancer Network (NCCN) guidelines, 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 guidelines, 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>10 mg PO QD</td>
<td>10 mg/day</td>
</tr>
<tr>
<td></td>
<td>Dosing is modified based upon clinical and laboratory findings</td>
<td></td>
</tr>
<tr>
<td>MM (maintenance therapy following autologous hematopoietic stem cell transplantation)</td>
<td>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</td>
<td>15 mg/day</td>
</tr>
<tr>
<td>MM (primary therapy for newly diagnosed patients)</td>
<td>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</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>MM (previously treated patients)</td>
<td>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 Dosing is modified based upon clinical and laboratory findings</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Relapsed MM (previously treated patients)</td>
<td>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/m² IV over 10 minutes on days 1-2. If tolerated, increase to target dose of 27 mg/m² IV over 10 minutes on days 8, 9, 15, 16. Cycles 2-12: 27 mg/m² IV over 10 minutes on days 1, 2, 8, 9, 15, 16 Cycles 3-18 27 mg/m² IV over 10 minutes on days 1, 2, 15, 16.</td>
<td>As recommended in dosing regimen Kyprolis is dosed at maximum body surface area of 2.2 m²</td>
</tr>
<tr>
<td>MCL</td>
<td>25 mg PO QD on Days 1-21 of repeated 28-day cycles Dosing is modified based upon clinical and laboratory findings</td>
<td>25 mg/day</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>25 mg PO QD days 1-21 of repeated 28 days cycles with dexamethasone 40 mg once per week</td>
<td>25 mg/day</td>
</tr>
</tbody>
</table>
Indication | Dosing Regimen | Maximum Dose
--- | --- | ---
 | Dosing of Revlimid can be reduced to 15 mg/day for tolerability and can be combined with dexamethasone and either melphalan or cyclophosphamide | |

VI. Product Availability
Capsules: 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg

VII. References

Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>02.14</td>
<td>03.14</td>
</tr>
<tr>
<td>02.15</td>
<td>03.15</td>
</tr>
<tr>
<td>08.16</td>
<td>09.16</td>
</tr>
</tbody>
</table>
### Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>diagnosed and relapsed/refractory MM. Modified approval periods to 3 months for initial and 6 months for re-auth.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>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.</td>
<td>03.17</td>
<td>05.17</td>
</tr>
<tr>
<td>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.</td>
<td>01.22.18</td>
<td>05.18</td>
</tr>
</tbody>
</table>

**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.

This policy is the property of Envolve Pharmacy Solutions. Unauthorized copying, use, and distribution of this Policy or any information contained herein is strictly prohibited. By accessing this policy, you agree to be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.

©2017 Envolve Pharmacy Solutions. All rights reserved. All materials are exclusively owned by Envolve Pharmacy Solutions and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Envolve Pharmacy Solutions. You may not alter or remove any trademark, copyright or other notice contained herein.