Lenalidomide Treatment of Cutaneous Lupus Erythematosus

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Disclosures

• I have no financial (or other relevant) conflicts of interest

• Lenalidomide is not FDA-approved for treatment of cutaneous lupus
Overview

• Briefly discuss studies describing lenalidomide as an effective treatment of cutaneous lupus (LE)
• Review the Mayo Clinic experience of lenalidomide treatment of cutaneous LE
• (Hopefully!) some take home “learning pearls” you can use in your clinical practice
Any new options for treating recalcitrant cutaneous lupus?

• *What options exist for patients who have failed to respond to (or were intolerant of):*
  
  • Antimalarials (singly or in combination), PLUS
  
  • At least one conventional immunosuppressive agent (e.g. mycophenolate mofetil, methotrexate, azathioprine)

• Thalidomide works extremely well, but its use is limited by peripheral neuropathy

• **Lenalidomide** – a thalidomide analogue with a markedly reduced risk of peripheral neuropathy
Antimalarial effectiveness:
- Discoid lupus (DLE): 57%
- Subacute cutaneous lupus (SCLE): 63%
- Acute cutaneous lupus (ACLE): 91%
Thalidomide much more effective than others – but high rate of adverse effects

Table 2. Treatment Outcomes in Patients With Antimalarial-Refractory CLE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse Effects, No. (%)</th>
<th>Clinical Response, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Substantial(^a)</td>
<td>Partial(^b)</td>
<td>None(^c)</td>
</tr>
<tr>
<td>Chloroquine phosphate</td>
<td>7/35 (20)</td>
<td>15/33 (45)</td>
<td>7/33 (21)</td>
</tr>
<tr>
<td>Quinacrine</td>
<td>4/19 (21)</td>
<td>10/19 (53)</td>
<td>2/19 (11)</td>
</tr>
<tr>
<td>Methotrexate sodium</td>
<td>6/23 (26)</td>
<td>10/19 (53)</td>
<td>3/19 (16)</td>
</tr>
<tr>
<td><strong>Thalidomide</strong></td>
<td>11/13 (85)</td>
<td>10/11 (91)</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>4/20 (20)</td>
<td>8/18 (44)</td>
<td>3/18 (17)</td>
</tr>
<tr>
<td>Belimumab</td>
<td>0/16</td>
<td>6/16 (38)</td>
<td>3/16 (19)</td>
</tr>
<tr>
<td>Azathioprine sodium</td>
<td>6/15 (40)</td>
<td>3/12 (25)</td>
<td>0/12</td>
</tr>
<tr>
<td>Mycophenolate mofetil hydrochloride</td>
<td>5/27 (19)</td>
<td>9/25 (36)</td>
<td>3/25 (12)</td>
</tr>
</tbody>
</table>

Abbreviation: CLE, cutaneous lupus erythematosus; NA, not applicable.

\(^a\) Defined as at least 50% improvement in erythema, scaling, hypertrophy, and alopecia.

\(^b\) Defined as less than 50% improvement in erythema, scaling, hypertrophy, and alopecia.

\(^c\) Defined as no improvement in erythema, scaling, hypertrophy, and alopecia.

\(^d\) The \(\chi^2\) analysis was performed for non-antimalarial regimens only (methotrexate, thalidomide, dapsone, belimumab, azathioprine, and mycophenolate mofetil).
### Table 1: Treatment recommendations for cutaneous lupus erythematosus

<table>
<thead>
<tr>
<th>Treatment stage</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention</td>
<td>Minimize sun exposure</td>
</tr>
<tr>
<td></td>
<td>Sunscreen adherence</td>
</tr>
<tr>
<td>First-line treatment</td>
<td>Topical steroids</td>
</tr>
<tr>
<td></td>
<td>Topical calcineurin inhibitors</td>
</tr>
<tr>
<td></td>
<td>Antimalarials</td>
</tr>
<tr>
<td>Second-line treatment</td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Mycophenolate mofetil/sodium</td>
</tr>
<tr>
<td></td>
<td>Azathiolprine</td>
</tr>
<tr>
<td></td>
<td><strong>Thalidomide</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Lenalidomide</strong></td>
</tr>
<tr>
<td>Third-line treatment</td>
<td>Retinoids</td>
</tr>
<tr>
<td></td>
<td>Dapsone</td>
</tr>
<tr>
<td></td>
<td>Biologics</td>
</tr>
<tr>
<td></td>
<td>IVIG</td>
</tr>
</tbody>
</table>

Localized disease may be treated with topical steroids or calcineurin inhibitors. Antimalarials may be added when disease is not controlled with topical treatment alone or with scarring disease. For widespread disease antimalarials should be started early along with topical treatment. If these fail, second-line treatments may be added. In cases of recalcitrant disease, third-line and experimental therapies should be considered.

*IVIG* intravenous immunoglobulin

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**General treatment approach to cutaneous LE**
Thalidomide very effective, BUT...

18% of patients developed paresthesias

- 12 of 29 (41.4%) patients treated with thalidomide developed peripheral neuropathy
  - Including 4 of 10 (40%) with cutaneous LE (newer study by Fruchter et al 2017 showed 6 of 13 [46%])
Lenalidomide for cutaneous LE

Lenalidomide for the Treatment of Resistant Discoid Lupus Erythematosus

Asha Shah, MD; Joerg Albrecht, MD; Zuleika Bonilla-Martinez, MD; Joyce Ohawa, RN; Mathew Rose, MD; Mirha Rosenbach, MD; Victoria P. Werth, MD

**Background:** Discoid lupus erythematosus (DLE) is a chronic, disfiguring disease that is characterized by scaly, erythematous, disk-shaped patches and plaques followed by atrophy, scarring, and dyspigmentation. It is refractory to standard therapies in a small population of patients. We investigated the use of lenalidomide, a thalidomide analogue, as a novel alternative therapy in 2 cases of refractory DLE and report our results.

**Observations:** Two patients with chronic, severe DLE were treated with low-dose lenalidomide. Improvement was noted within 1 month at a dosage of 5 mg/d in one case and was maintained for 10 months before the dosage was doubled to 10 mg/d for 12 months because of a slight worsening of symptoms. Clinical improvement was demonstrated by a sustained reduction in the Cutaneous Lupus Erythematosus Disease Area and Severity Index activity score, with no change in the Cutaneous Lupus Erythematosus Disease Area and Severity Index damage score. Within 5 months, oral prednisone therapy (60 mg/d) was tapered and discontinued; it was restarted at a low dosage (5 mg/d), however, to manage the symptoms of systemic LE. Of note, the patient experienced mild neutropenia after taking 10 mg/d of lenalidomide, which carries a black box warning regarding neutropenia; therefore, the complete blood cell count should be monitored weekly for the first 2 months and then monthly thereafter. The second case failed to show clinical improvement, and lenalidomide therapy was discontinued after 6 months.

**Conclusions:** Lenalidomide therapy is a potential alternative or adjunctive treatment for patients with severe, chronic DLE that is refractory to standard therapies. A larger study is needed to clarify its role in the treatment of DLE and other forms of cutaneous LE.

*Arch Dermatol. 2009;145(3):303-306*

(This study served as the impetus for our use of lenalidomide treatment of cutaneous LE at Mayo Clinic)
Additional studies of lenalidomide treatment of cutaneous LE

- 12 of 14 (86%) patients had complete response (CR) (1 additional patient withdrew from study)
- Frequent clinical relapse (75% of patients) – usually 2-8 weeks after stopping lenalidomide

- 14 of 16 (88%) patients had response (2 CR, 12 had >50% RCLASI improvement)
  - 4 patients had previously not responded to thalidomide
  - No peripheral neuropathy

**References**


*Lenalidomide for refractory chronic and subacute cutaneous lupus erythematosus: 16 patients.*

Fennira F¹, Chasset F¹, Soubrier M², Cordel N³, Petit A⁴, Francès C⁵.
50 reported cases of lenalidomide treatment of cutaneous LE in adults (as of January 2, 2018) (38 of 50 [76%] had DLE)

- [Includes Mayo (9 cases – see later); all cases above; 16 cases of Fennira et al (JAAD 2016 – previous slide); and 1 case of DLE with >75% response (Nahmias et al – previous slide)]

**Notice adverse effects:**

*Lack of neuropathy

*1 patient (with cutaneous LE only) later developed SLE (will discuss later)
Lenalidomide in the pediatric population

- 10 “adolescent” SLE patients with skin manifestations (age 13-22)
  - Discoid lesions (2 pts), malar rash, vasculitis, panniculitis, bullous lesions, alopecia, nasal/oral ulcers, Raynaud’s with ulcers
  - Complete or near resolution within 6 months in all patients
  - No hematologic or other side effects observed
  - One patient experienced “serologic” flare of SLE while on lenalidomide (elevated anti-dsDNA, hypocomplementemia)
What is the Mayo Clinic experience of treating cutaneous LE with lenalidomide?
• All patients had not responded to (or were intolerant to) at least one antimalarial agent and one immunosuppressive agent prior to initiating lenalidomide
5 of 6 discoid LE patients had a complete response (CR)

Median time to CR: 3 months

Typical effective dose: 5-10 mg/day
Figure 1  Clinical examination of Patient 4, who demonstrated a complete response to lenalidomide therapy, shows (a, b) generalized discoid lupus erythematosus on the chest, arms, and neck, and scalp, ear, face, neck, and upper back before treatment, and (c, d) a complete response to treatment 5 months later.
Figure 2 Clinical examination of Patient 1, who demonstrated a complete response to lenalidomide therapy, shows (a) generalized discoid lupus erythematosus on the back and proximal upper extremities prior to lenalidomide treatment, and (b, c) a complete response to treatment 10 months later.
• Typically a dose of 10 mg daily was needed to achieve CR
• Median time to initial response: 4 weeks
• Median time to complete response: 3 months
• Disease free maintenance dose (mg/d): Usually 5 mg, but as low as 5 mg every three days (patient 2, updated follow-up info)
• Median duration of treatment (as of Dec 2014): 12 months
  • Up to 67 months
• Median duration of total follow-up (as of Dec 2014): 48 months
  • Up to 103 months
Any side effects from lenalidomide observed in our Mayo cohort?
Side effects were generally mild

- 4 patients - *mild cytopenias*

- 1 patient (#7) stopped lenalidomide due to multiple symptoms
  - Had similar intolerance to other meds

- 1 patient (#3) had hypoxic encephalopathy of unknown cause requiring hospitalization and lenalidomide was stopped
  - *Deep venous thrombosis (DVT) occurred while in the hospital* – cannot exclude role of lenalidomide

<table>
<thead>
<tr>
<th>Patient</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Leg cramps (improved with magnesium supplementation), mild lymphopenia</td>
</tr>
<tr>
<td>2</td>
<td>Mild dyspepsia (improved with antacids)</td>
</tr>
<tr>
<td>3</td>
<td>Deep vein thrombosis of the arm that occurred during a hospitalization</td>
</tr>
<tr>
<td>4</td>
<td>Intermittent mild worsening of baseline leukopenia (improved when lenalidomide was discontinued for a few weeks; baseline, 2.7–5.9; during treatment, 2.0–3.9; reference, 4.5–11.0)</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Mild worsening of baseline leukopenia (baseline, 3.1–6.6; during treatment, 2.5–4.8; reference, 4.5–11.0)</td>
</tr>
<tr>
<td>7</td>
<td>Nausea, difficulty sleeping, poor appetite, weakness, fatigue, decreased taste at 12 months (reported similar symptoms with multiple other medications in the past; also receiving concomitant prednisone)</td>
</tr>
<tr>
<td>8</td>
<td>Mild pruritus and facial edema (resolved quickly), mild fatigue</td>
</tr>
<tr>
<td>9</td>
<td>Mild pruritus and peeling of skin on palms and soles (resolved quickly despite continuing therapy), mild intermittent neutropenia</td>
</tr>
</tbody>
</table>
Adverse effects – Mayo study compared to other studies

- **Mayo**: no cases of peripheral neuropathy
  - Similar to previous studies

- **Mayo**: mild cytopenias not requiring drug cessation
  - Similar to previous studies

- **Mayo**: 1 case of DVT of unclear cause
  - *Fennira et al (JAAD, 2016)*: 1 case of possible transient ischemic attack

- **Mayo**: no cases of new-onset or worsening SLE (2 of 9 patients had 4 of 11 ACR SLE criteria at baseline)
  - *Fennira et al*: 2 patients with baseline SLE had flare of SLE after 26 and 36 weeks of lenalidomide (no further details provided)
  - *Braunstein et al (JAAD, 2012)*: 1 patient progressed to SLE (proteinuria, arthralgias)
**Adverse effects of lenalidomide when treating hematologic conditions**

Comparison of serious adverse reactions between thalidomide and lenalidomide: analysis in the French Pharmacovigilance database.

Olivier-Abbai P', Teisseire AC, Montastruc JL; French Association of Regional Pharmacovigilance Centers.

**Abstract**
Thalidomide and lenalidomide are structural analogs and immunomodulatory drugs. Lenalidomide appears to have a different safety profile than thalidomide and could be less toxic, and as far as we know, we did not find any study comparing their safety profile. The objective of our study was to review and compare serious adverse drug reactions (SADRs) of thalidomide and lenalidomide spontaneously reported to the French Pharmacovigilance database. We extracted all medically confirmed spontaneous reports of SADR for lenalidomide-based regimens and thalidomide-based regimens from the French Pharmacovigilance database. A "serious" adverse drug reaction (ADR) was defined as an ADR that is fatal or life threatening, which causes hospitalization or prolongation of hospitalization, or permanent or significant disability. The study period was between marketing of 2 drugs and January 15, 2012. A total of 392 SADRs related to thalidomide-based regimens were identified in 244 patients and 377 SADRs related to lenalidomide-based regimens in 220 patients. In spite of their structural analogy, this study highlights interesting differences between lenalidomide and thalidomide's safety profile: nervous system and vascular disorders are more frequent with thalidomide-based regimens while hematologic, skin, infectious disorders and secondary primary cancers are more frequent with lenalidomide-based regimens.

Among the 220 patients exposed to lenalidomide, 173 (78.6%) suffered from multiple myeloma (label use). Off-label use of lenalidomide was found in 44 patients (20.0%), with 27 patients treated for a myelodysplasia, 7 for various lymphomas, 2 for amyloidosis, 2 for refractory anemia, 2 for acute myeloid leukemia and 4 for other diseases. Indication was unknown for 3 patients (1.4%).

- **Lenalidomide (compared to thalidomide) more commonly caused:** hematologic, skin, infectious, and secondary primary cancers
- **Indication for lenalidomide in all patients** was underlying hematologic disease (mostly multiple myeloma)
Risk factors included multiple myeloma (MM) and other MM treatments (including chemotherapy)

As lenalidomide and thalidomide have immunomodulatory properties, occurrence after a long-term exposure of second cancer must be discussed. In our study, lenalidomide-based regimens induced significantly more frequently SPC. Our results should be interpreted with caution because of the small number of patients and the different reporting period for each drug. In December 2010, results from 3 randomized phase 3 trials showed an excess of hematologic cancers among patients receiving lenalidomide maintenance therapy [41–43]. Even if MM is known to be associated with an increased risk of some types of SPCs, such as acute myeloid leukemia and non-Hodgkin lymphoma, a recent review explained that the development of SPCs after MM is most likely a multifactorial process. Contributing factors probably include various multiple myeloma drugs (alkylating agents, anthracycline), multiple myeloma-related factors, host-related factors, as well as environmental and behavioral factors [44]. Further studies are needed to better characterize underlying mechanisms of these observations, and the clinical benefit of lenalidomide should be clearly balanced with this risk.

### Table 2: Thalidomide- and lenalidomide-induced SADRs classified by System Organ Class (MedDRA classification)

<table>
<thead>
<tr>
<th>SADRs</th>
<th>Thalidomide n (%)</th>
<th>Lenalidomide n (%)</th>
<th>OR [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>392 (100)</td>
<td>377 (100)</td>
<td>2.61 [1.64–4.15]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Blood and lymphatic disorders</td>
<td>29 (7.4)</td>
<td>65 (17.2)</td>
<td>3.43 [1.44–9.46]</td>
<td>0.01*</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>5</td>
<td>13</td>
<td>1.13 [0.51–2.51]</td>
<td>NS</td>
</tr>
<tr>
<td>Neurotoxicity and myelodysplasia</td>
<td>12</td>
<td>13</td>
<td>5.27 [1.54–18.7]</td>
<td>0.003*</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>3</td>
<td>15</td>
<td>4.77 [1.02–22.22]</td>
<td>0.003*</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>44 (11.2)</td>
<td>69 (18.3)</td>
<td>1.77 [1.18–2.66]</td>
<td>0.005*</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>26 (6.6)</td>
<td>27 (7.2)</td>
<td>1.09 [0.62–1.90]</td>
<td>NS</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>16</td>
<td>11</td>
<td>0.71 [0.33–1.55]</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>40 (10.2)</td>
<td>24 (6.4)</td>
<td>0.60 [0.35–1.02]</td>
<td>0.053*</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>32</td>
<td>20</td>
<td>0.63 [0.35–1.12]</td>
<td>NS</td>
</tr>
<tr>
<td>General disorders and administration site disorders</td>
<td>32 (8.2)</td>
<td>33 (8.8)</td>
<td>1.08 [0.65–1.80]</td>
<td>NS</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>116 (29.6)</td>
<td>34 (9.0)</td>
<td>0.24 [0.16–0.36]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>49</td>
<td>11</td>
<td>0.21 [0.11–0.41]</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>19 (4.8)</td>
<td>17 (4.5)</td>
<td>0.93 [0.48–1.82]</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>18 (4.6)</td>
<td>18 (4.8)</td>
<td>1.04 [0.53–2.03]</td>
<td>NS</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>6 (1.5)</td>
<td>14 (3.7)</td>
<td>2.48 [0.94–6.52]</td>
<td>NS</td>
</tr>
<tr>
<td>Infectious and infestations</td>
<td>7 (1.8)</td>
<td>20 (5.3)</td>
<td>3.08 [1.29–7.37]</td>
<td>0.008*</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>7 (1.8)</td>
<td>11 (2.9)</td>
<td>1.65 [0.63–4.30]</td>
<td>NS</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified</td>
<td>6 (1.5)</td>
<td>22 (5.8)</td>
<td>3.99 [1.60–9.95]</td>
<td>0.001*</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>9 (2.3)</td>
<td>8 (2.1)</td>
<td>0.93 [0.36–2.44]</td>
<td>NS</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>10 (2.6)</td>
<td>4 (1.1)</td>
<td>0.41 [0.13–1.32]</td>
<td>NS</td>
</tr>
<tr>
<td>Endocrine disorders</td>
<td>1 (0.3)</td>
<td>3 (0.8)</td>
<td>3.14 [0.33–30.32]</td>
<td>NS</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>4 (1.0)</td>
<td>2 (0.5)</td>
<td>0.52 [0.09–2.86]</td>
<td>NS</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1.04 [0.06–16.69]</td>
<td>NS</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>9 (2.3)</td>
<td>4 (1.1)</td>
<td>0.46 [0.14–1.51]</td>
<td>NS</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>3 (0.8)</td>
<td>1 (0.3)</td>
<td>0.34 [0.04–3.28]</td>
<td>NS</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>3 (0.8)</td>
<td>0 (0.0)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Investigations</td>
<td>2 (0.5)</td>
<td>0 (0.0)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Significant
NS nonsignificant. SADR serious adverse drug reaction. OR odds ratio. CI confidence interval
How do we prescribe and monitor lenalidomide at Mayo Clinic?

- Baseline complete blood count (CBC) with differential
- Two initial negative pregnancy tests (women of childbearing potential)

- **CBC** – weekly X 4 weeks, then every 1-2 months thereafter
- Pregnancy test (women of childbearing potential) – weekly X 4 weeks, then monthly thereafter

- 5-10 mg once daily (*typically 10 mg in my experience*) (can decrease to days 1-21 of a 28-day cycle if cytopenias are problematic)

- **Typically on concomitant antimalarial and/or low-dose aspirin (to mitigate thromboembolic risk)**
  - *Also recommended by Shah et al (2009) and Fennira et al (2016)*

- Use cautiously: Women of childbearing potential; history of DVT/PE; current smoker; baseline cytopenias

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Lenalidomide prescribing at the study institution

The approach to patients with CLE and the therapeutic ladder vary among providers at the present institution. In general, antimalarials (either singly or in combination) are considered first-line systemic therapy for cutaneous lupus. If antimalarials fail, second-line therapy typically includes the addition of a conventional immunosuppressive agent (mycophenolate mofetil, methotrexate, or azathioprine). Lenalidomide is typically considered if antimalarials and at least one immunosuppressive agent fail. In general, there are no criteria that exclude the prescribing of lenalidomide at this institution. However, lenalidomide is prescribed very cautiously in patients with childbearing potential or with a history of venous thromboembolism, smoking, or cytopenias.

Laboratory monitoring for patients in the present series was not standardized. The drug manufacturer has established a safety program because of the potential for embryo-fetal toxicity and hematologic toxicity. Providers must be enrolled in the program to prescribe lenalidomide. Women of reproductive potential must have two negative pregnancy tests before treatment can be initiated and must then undergo weekly tests for 4 weeks and monthly tests thereafter. In addition, a baseline complete blood count (CBC) with differential is obtained and checked weekly for 4 weeks and then every 1-2 months thereafter.
Mandatory program – must be enrolled in order to prescribe lenalidomide

Welcome to the REVLIMID REMS® program

REVLIMID® (lenalidomide) in combination with dexamethasone is indicated for the treatment of patients with multiple myeloma (MM).

REVLIMID is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

REVLIMID is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

Important information about REVLIMID and the REVLIMID Risk Evaluation and Mitigation Strategy (REMS) program

- REVLIMID is contraindicated in pregnant females and females capable of becoming pregnant. Females of reproductive potential may be treated with REVLIMID provided adequate precautions are taken to avoid pregnancy.
- To avoid embryo-fetal exposure, REVLIMID is only available under a restricted distribution program called "REVLIMID REMS®" (formerly known as the RevAssist® program).
- Only prescribers and pharmacies certified by the REVLIMID REMS® program can prescribe and dispense REVLIMID to patients who are enrolled and meet all the conditions of the REVLIMID REMS® program.

The goals of the REVLIMID risk evaluation and mitigation strategy are as follows:
1. To prevent the risk of embryo-fetal exposure to REVLIMID
2. To inform prescribers, patients, and pharmacists on the serious risks and safe-use conditions for REVLIMID

http://www.revlimidrems.com
FEMLIMID REMS® Prescriber Enrollment Form

When prescribing FEMLIMID® (lenalidomide), I agree to:

- Provide patient counseling on the benefits and risks of FEMLIMID therapy, including Boxed Warnings
- Submit a completed FEMLIMID® (lenalidomide) Patient-Physician Agreement Form for each new patient
- Provide contraception and emergency contraception counseling with each new prescription prior to and during FEMLIMID treatment
- Provide scheduled pregnancy testing for females of reproductive potential and verify negative pregnancy test results prior to writing a new prescription or subsequent prescriptions
- Report any pregnancies in female patients or female partners of male patients prescribed FEMLIMID immediately to Celgene Drug Safety (or Celgene Customer Care Center)
- Complete a mandatory and confidential prescriber survey online or by telephone for all patients and obtain a new authorization number for each prescription written. The authorization number and patient risk category must then be written on each prescription
- Facilitate female patient compliance with an initial mandatory confidential patient survey online or by telephone
- Prescribe no more than a 4-week (28-day) supply, with no automatic refills or telephone prescriptions
- Contact a FEMLIMID REMS® certified pharmacy to fill the prescription
- Remind patients to return all FEMLIMID capsules to Celgene Corporation or their FEMLIMID prescriber, or to the pharmacy that dispensed the FEMLIMID to them
- Return to Celgene all FEMLIMID capsules that are returned by patients. Shipping fees will be paid by Celgene Corporation. To arrange returns, call the Celgene Customer Care Center
- Re-enroll patients in the FEMLIMID REMS® program if FEMLIMID is required and previous therapy with FEMLIMID has been discontinued for 12 consecutive months

Please fill out the spaces below completely.

Prescriber Name

Degree: MD/DO/PA/NP/Fellow/Medical Resident
Specialty

Prescriber Identification Number (e.g., DEA Number, Social Security Number, NPI Number, etc.)

Females of Reproductive Potential
Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning FEMLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing FEMLIMID therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles [see Use in Specific Populations (8.6)].
Take home messages

• **Lenalidomide 5-10 mg/d is generally very effective** for the treatment of refractory cutaneous LE (particularly discoid LE)
  - Initial response in 1 month; complete response in 3 months
  - Taper to lowest effective dose (e.g. 5 mg every third day)

• No apparent risk of peripheral neuropathy

• **Minimal risk of development or progression of SLE** while on lenalidomide (4 of 50 [8%] previously published adult patients)
  - 1 patient with new-onset SLE (Braunstein et al, 2012)
  - 3 patients with flare of SLE (2 pts – Fennira et al; 1 pt – Cortes-Hernandez et al, 2012 [“arthralgias and mild arthritis”])

• **Thromboembolic risk appears to be low**, but low-dose aspirin (81 mg/d) generally recommended to decrease risk

• Must be enrolled in Revlimid REMS to prescribe lenalidomide