Angiogenesis Inhibitors

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO111

Description

Thalidomide is an immunomodulatory drug (IMiDs) that inhibits FGF-dependent angiogenesis in vivo and exhibits antineoplastic activity. Lenalidomide (Revlimid) and pomalidomide (Pomalyst) are orally administered thalidomide analogues.

Length of Authorization

- Initial:
  - i. Lenalidomide
    1. Follicular lymphoma/Marginal zone lymphoma: 12 months
    2. All other indications: Six months
  - ii. Pomalidomide and Thalidomide
    1. All indications: Three months
- Renewal:
  - i. Lenalidomide
    1. Follicular lymphoma/Marginal zone lymphoma: Cannot be renewed
    2. All other indications: 12 months
  - ii. Pomalidomide
    1. All indications: 12 months
  - iii. Thalidomide
    1. Cutaneous manifestations of moderate to severe Erythema Nodosum Leprosum (ENL): three months
    2. Multiple myeloma: six months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
lenalidomide (Revlimid)	2.5 mg capsules	Follicular lymphoma; Marginal zone lymphoma; Multiple myeloma; Myelodysplastic syndromes	28 capsules/28 days
	5 mg capsules	Follicular lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Multiple myeloma; Multiple myeloma maintenance therapy following auto-HSCT; Myelodysplastic syndromes;	28 capsules/28 days
	10 mg capsules		28 capsules/28 days
	15 mg capsules		28 capsules/28 days
	20 mg capsules		21 capsules/28 days
	25 mg capsules	Mantle cell lymphoma; Multiple myeloma	21 capsules/28 days

pomalidomide (Pomalyst)	1 mg capsules	Multiple Myeloma	21 capsules/28 days
	2 mg capsules		
	3 mg capsules		
	4 mg capsules		
Thalidomide (Thalomid)	50 mg capsules	Multiple Myeloma	28 capsules/28 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		
	50 mg capsules	Erythema Nodosum Leprosum	28 capsules/28 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		

Initial Evaluation

I. Lenalidomide (Revlimid), pomalidomide (Pomalyst), or thalidomide (Thalomid) may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. A diagnosis of one of the following:
      1. **Multiple myeloma (MM); AND**
         i. Lenalidomide (Revlimid) will be taken with dexamethasone; **OR**
            a. Monotherapy in the maintenance setting following autologous hematopoietic stem cell transplant (auto-HSCT); **OR**
         ii. Pomalidamide (Pomalyst) will be used for the treatment of recurrent multiple myeloma; **AND**
            a. Will be taken in combination with dexamethasone; **OR**
            b. Documentation of treatment with dexamethasone resulting in a contraindication or was not tolerated; **AND**
            c. Documentation of trial and failure of least two prior treatments, including lenalidomide (Revlimid) and bortezomib (Velcade); **OR**

iii. Thalidomide (Thalomid) is being used in newly diagnosed multiple myeloma; **AND**
   a. Will be taken in combination with dexamethasone; **OR**
   b. Documentation of treatment with dexamethasone resulting in a contraindication or was not tolerated; **OR**

2. **Myelodysplastic syndromes (MDS); AND**
   i. Member has transfusion-dependent anemia due to MDS; **AND**
   ii. MDS is a low- or intermediate-1-risk; **AND**
      a. MDS is associated with a deletion 5q abnormality; **OR**
      b. Serum erythropoietin levels are greater than 500 mU/mL; **OR**
      c. Serum erythropoietin levels are less than 500 mU/mL; **AND**
         i. History of failure, contraindication, or intolerance to erythropoietins [e.g.,Retacrit (epoetin alfa)]; **AND**
   iii. Request is for lenalidomide (Revlimid); **OR**
3. **Mantle cell lymphoma (MCL); AND**
   i. Member has relapsed or progressed after two prior regimens, one of which included bortezomib; **AND**
   ii. Request is for lenalidomide (Revlimid); **OR**
4. **Follicular lymphoma (FL); AND**
   i. Member was previously treated; **AND**
   ii. Lenalidomide (Revlimid) will be used in combination with rituximab (Rituxan); **OR**
5. **Marginal zone lymphoma (MZL); AND**
   i. Member was previously treated; **AND**
   ii. Lenalidomide (Revlimid) will be used in combination with rituximab (Rituxan); **OR**
6. **Cutaneous manifestations of moderate to severe erythema nodosum leprosm (ENL); AND**
   i. Use is intended to prevent and suppress recurrence; **AND**
   ii. Documentation of moderate to severe neuritis; **AND**
   iii. Request is for thalidomide (Thalomid); **AND**
   iv. Will be taken in combination with dexamethasone.

II. Lenalidomide (Revlimid), pomalidomide (Pomalyst), and/or thalidomide (Thalomid) is/are considered investigational when used for all other conditions, including but not limited to:
   A. Chronic lymphocytic leukemia (CLL)
   B. Diffuse large B-cell lymphoma (DLBCL)
   C. Non-Hodgkin's lymphoma (NHL)
   D. Myelofibrosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Request is to continue a regimen that was not initially established through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. **Lenalidomide**
- **Multiple myeloma (MM)**: Efficacy of lenalidomide (Revlimid) was established in an open-label trial comparing lenalidomide (Revlimid) with low dose dexamethasone (Rd) to melphalan, prednisone, and thalidomide (MPT) in newly diagnosed MM patients who were not a candidate for stem cell transplant. The primary outcome of progression free survival (PFS) was significantly longer with Rd continuous than MPT: HR 0.72 (95% CI: 0.61-0.85 p <0.0001). The improvement in median PFS time in the Rd continuous arm compared with the MPT arm was 4.3 months.
    i. In MM patients following auto-HSCT, efficacy was established in two multicenter, randomized, double-blind, parallel group, placebo-controlled studies. In both studies, the primary analysis of PFS was significantly longer with lenalidomide (Revlimid) compared to placebo.
- **Myelodysplastic syndromes (MDS):** Lenalidomide (Revlimid) treatment significantly increased transfusion-independence when compared with placebo in a phase 3, multicenter, randomized, double-blind, placebo-controlled study (MDS-004; n=205). Lenalidomide (Revlimid) was also effective in producing RBC transfusion-independence in an open-label, single-arm clinical trial (n=148) in patients with transfusion-dependent anemia, chromosome 5q deletion (isolated or with other cytogenetic abnormalities), and low- or intermediate-1 risk MDS.
    i. The risk group was calculated based on the International Prognostic Scoring System (IPSS), a tool typically used in practice. Lenalidomide was further studied in a phase III trial, in 239 RBC transfusion dependent patients with lower risk non-del (5q) MDS who are ineligible or refractory to erythropoiesis-stimulating agents (ESAs).

ii. Lenalidomide was studied versus placebo and reported a higher rate of transfusion independence for at least eight weeks (26.9% of patients vs 2.5%). Within those who responded, 90% responded within 16 weeks of treatment. Transfusion reduction of ≥ 4 units packed RBCs within a 112-day assessment, was 21.8% in the lenalidomide group and 0% in the placebo group.

- **Mantle cell lymphoma (MCL):** Lenalidomide (Revlimid) produced an overall response rate of 28% and a median duration of response of 16.6 months in heavily pretreated patients with mantle cell lymphoma who had relapsed, refractory, or progressive disease following bortezomib in the single-armed EMERGE study (N=134).
- Lenalidomide provided a complete response unconfirmed rate of 7.5%, median time to response of 2.2 months, median progression-free survival of 4 months, median overall survival of 19 months, median time to progression of 5.4 months, and time to treatment failure of 3.8 months.
- **Previously treated follicular lymphoma (FL)/marginal zone lymphoma (MZL):** The efficacy of lenalidomide (Revlimid) with rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma was evaluated in the AUGMENT (NCT01938001) and MAGNIFY (NCT01996865) trials.
  i. AUGMENT was a randomized, double-blind, multicenter trial (n=358) in patients with relapsed or refractory follicular or marginal zone lymphoma who received lenalidomide (Revlimid) and rituximab or rituximab and placebo for a maximum of 12 cycles or until unacceptable toxicity.
  ii. Efficacy results in the follicular and marginal zone lymphoma population reported a PFS of 39.4 months in the lenalidomide (Revlimid) and rituximab arm versus 14.1 months in the rituximab plus placebo arm.
  iii. MAGNIFY is an open-label, multicenter trial (n=232) in which patients with relapsed or refractory follicular, marginal zone, or mantle cell lymphoma received 12 induction cycles of lenalidomide (Revlimid) and rituximab.
  iv. Overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median duration of response was not reached within a median follow-up time of 7.9 months [95% CI: 4.6, 9.2]. With an overall response of 51% (23/45) [95% CI: 36, 66] for patients with marginal zone lymphoma and median duration of response not reached within a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

II. **Thalidomide**

- The mechanism of action of thalidomide is not completely understood. It is thought that it has immunomodulatory, anti-inflammatory, and antiangiogenic properties. The immunologic activity may be due to an ability to suppress tumor necrosis

factor–alpha (TNF-α) and to reduce adhesion molecules involved in cell trafficking. It is also proposed thalidomide may suppress macrophage involvement in prostaglandin synthesis, modulate interleukin (IL)-10 and IL-12, and the proliferation of endothelial cells thereby inhibiting angiogenesis.

- Thalidomide is NOT indicated as monotherapy for ENL treatment in the presence of moderate to severe neuritis. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering should be maintained on the minimum dose necessary to control the reaction. Tapering off the medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.
- Dosing with thalidomide in ENL should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering should be maintained on the minimum dose necessary to control the reaction. Tapering off the medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.
- Concomitant therapy: In patients with moderate to severe neuritis associated with a severe erythema nodosum leprosum reaction, corticosteroids may be started concomitantly with thalidomide. Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

III. **Pomalidomide**

- Pomalidomide inhibits proliferation, induces apoptosis of hematopoietic tumor cells, enhances T-cell and natural killer cell-mediated immunity, and inhibits pro-inflammatory cytokine production. When given in combination with dexamethasone, pomalidomide induces tumor cell apoptosis in lenalidomide-sensitive and lenalidomide-resistant cell lines.
- Pomalidomide (Pomalyst) is Indicated for patients with multiple myeloma, in combination with dexamethasone, who have received at least two prior treatment regimens including lenalidomide and bortezomib (either in one regimen or in total) and have demonstrated disease progression on or within 60 days of last therapy. Lenalidomide and bortezomib are agents contained in first-line regimens per NCCN guidelines (may be together or in separate regimens).
- During clinical trials, the overall response rate was greater among patients who were treated with pomalidomide and low-dose dexamethasone compared to pomalidomide alone; however, NCCN guidelines state that in steroid-intolerant individuals the NCCN MM Panel suggests pomalidomide monotherapy should be a consideration.

Investigational or Not Medically Necessary Uses

I. Chronic lymphocytic leukemia (CLL)
   A. Lenalidomide (Revlimid) was studied in a small phase II, single arm trials consisting of low-quality evidence. Further evaluation of lenalidomide (Revlimid) is needed to support its use in this setting. Lenalidomide (Revlimid) was studied in patients with previously treated CLL in a randomized, double-blind, placebo-controlled, phase 3 trial (CONTINUUM). Patients included in the trial had been treated with two lines of therapy with at least a partial response after second-line therapy, had received a purine analogue, bendamustine, anti-CD20 antibody, chlorambucil, or alemtuzumab as first-line or second-line treatment; and had an Eastern Cooperative Oncology Group performance score of 0–2. Co-primary endpoints were progression-free survival and overall survival; the primary endpoint was later changed to overall survival after the data cutoff for analysis. With a median follow-up of 31.5 months, there was no significant difference in overall survival between the lenalidomide and the placebo groups (median 70·4 months, 95% CI 57·5–not estimable [NE] vs NE, 95% CI 62·8–NE; hazard ratio [HR] 0·96, 95% CI 0·63–1·48; p=0·86).

II. Diffuse large B-cell lymphoma (DLBCL)
   A. NCCN guidelines lists lenalidomide (Revlimid) maintenance for patients 60-80 years of age as a Category 2B recommendation. This is based off the results of an open label, single arm, phase II trial in 48 adults with de novo DLBCL. Further evaluation in higher quality trials is needed to support its use.
   B. In the relapsed setting, lenalidomide (Revlimid) was studied in small, phase II, open label trials consisting of low-quality evidence. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.

III. Non-Hodgkin's lymphoma (NHL)
   A. Lenalidomide (Revlimid) was evaluated in patients with relapsed or refractory aggressive NHL, in an open-label, phase II trial (N=49). Treatment with lenalidomide led to an objective response rate (ORR) of 35% and a median PFS of 4 months. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.

IV. Myelofibrosis
   A. Lenalidomide (Revlimid) was evaluated in a small, open label, phase II trial in combination with prednisone that reported a treatment response in 10 of 42 subjects, with 37 patients reporting a grade 3 or 4 toxicity. In an analysis of three consecutive phase II trials of patients with myelofibrosis (n=125), single agent lenalidomide and lenalidomide plus prednisone produced higher response rates than thalidomide, though not statistically significantly higher (p=0.06). Further studies are warranted. An additional trial by Daver et al. that evaluated lenalidomide (Revlimid) in combination with ruxolitinib (Jakafi) was terminated early due to failure to meet the predetermined efficacy rules for treatment success.

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Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	December 2019
Last Reviewed	09/2012, 10/2012, 10/2014, 09/2015, 01/2016, 01/2018, 08/2019, 12/2019

Action and Summary of Changes	Date
Added pomalidomide and thalidomide agents to policy; removed black box warnings and precautions readily available in compendia; removed laboratory and other micromanagement criteria.	12/2019
Converted lenalidomide (Revlimid) to policy format. Added new indication of follicular lymphoma and marginal zone lymphoma. Allowed coverage as monotherapy in multiple myeloma maintenance following autologous hematopoietic stem cell transplant. Allowed a route to coverage in myelodysplastic syndromes without a deletion 5q abnormality following phase III trial data.	08/2019
Excluded package insert/monitoring question and removed renewal question regarding regular hematological laboratory tests, extended initial approval from 3 months to 6 months.	01/2018