lenalidomide (Revlimid®), pomalidomide (Pomalyst®), thalidomide (Thalomid®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO111

Description

Thalidomide (Thalomid) is an oral immunomodulatory medication that inhibits FGF-dependent angiogenesis in vivo and exhibits antineoplastic activity. Lenalidomide (Revlimid) and pomalidomide (Pomalyst) are orally administered thalidomide analogues. These agents are thought to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and cytokine circuits, among others.

Length of Authorization

- Initial:
  - i. Lenalidomide (Revlimid)
    1. Follicular lymphoma/Marginal zone lymphoma: 12 months
    2. All other indications: Six months
  - ii. Pomalidomide (Pomalyst) and thalidomide (Thalomid)
    1. All indications: Three months
- Renewal:
  - i. Lenalidomide (Revlimid)
    1. Follicular lymphoma/Marginal zone lymphoma: Cannot be renewed
    2. All other indications: 12 months
  - ii. Pomalidomide (Pomalyst)
    1. All indications: 12 months
  - iii. Thalidomide (Thalomid)
    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	60 capsules/30 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		

Initial Evaluation

I. **Lenalidomide (Revlimid)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. A diagnosis of **multiple myeloma (MM)** when the following is met:
      1. Medication will be used with dexamethasone as part of a doublet or triplet regimen; **OR**
      2. Medication will be used as monotherapy; **OR**
   C. A diagnosis of **myelodysplastic syndrome (MDS)** when the following are met:
      1. Member has lower risk disease (e.g. IPSS Low or Intermediate-1; IPSS-R Very Low, Low, Intermediate; WPSS Very Low, Low, Intermediate); **AND**
      2. Member has transfusion-dependent anemia (i.e. 2 or more units of red blood cells in the previous 8 weeks); **AND**
         i. MDS with del(5q) abnormality; **OR**
         ii. MDS without del(5q) abnormality; **AND**

a. Serum erythropoietin levels are less than 500 mU/mL; **AND**
    i. Medication will be used in combination with an erythropoiesis-stimulating agent (ESA) (e.g. Procrit, Retacrit, or Aranesp) with or without granulocyte-colony stimulating factor (GCSF) (e.g., filgrastim, pegfilgrastim); **AND**
        1. History of inadequate response to ESA with or without GCSF; **OR**

b. Serum erythropoietin levels are greater than 500 mU/mL; **AND**
    i. History of failure, contraindication, or intolerance to immunosuppressive therapy (IST) (e.g. anti-thymocyte globulin ± cyclosporine A); **OR**

D. A diagnosis of **mantle cell lymphoma (MCL)** when the following is met:
    1. Member has relapsed or progressed after two prior regimens, one of which included bortezomib; **OR**

E. A diagnosis of **follicular lymphoma (FL)** when the following are met:
    1. Member was previously treated with at least one prior regimen for FL (e.g. bendamustine + rituximab/obinutuzumab, cyclophosphamide/doxorubicin/vincristine/prednisone); **AND**
    2. The medication will be used in combination with rituximab; **OR**

F. A diagnosis of **marginal zone lymphoma (MZL)** when the following are met:
    1. Member was previously treated with at least one prior regimen for MZL (e.g. bendamustine + rituximab, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, rituximab/cyclophosphamide/vincristine/prednisone); **AND**
    2. The medication will be used in combination with rituximab

II. **Pomalidomide (Pomalyst)** may be considered medically necessary when the following criteria are met:
A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
B. A diagnosis of **multiple myeloma (MM)** when the following are met:
    1. Member has relapsed and/or refractory MM; **AND**
    2. Member has received at least two prior therapies for MM, including lenalidomide (Revlimid) and a proteasome inhibitor (e.g. bortezomib); **AND**
    3. Medication will be initiated within 60 days of completion of the last therapy; **AND**
    4. Medication will be used with dexamethasone as part of a doublet or triplet regimen

III. **Thalidomide (Thalomid)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
      1. A diagnosis of **multiple myeloma (MM)** when the following are met:
         i. Medication will be used with dexamethasone as part of a doublet or triplet regimen; **OR**
   B. Medication is prescribed by, or in consultation with, an infectious disease specialist
      1. A diagnosis of **erythema nodosum leprosum (ENL)** when the following are met:
         i. Medication will be used for the acute treatment of the cutaneous manifestations of moderate to severe ENL; **AND**
            a. If moderate to severe neuritis is present, the medication will be used in combination with corticosteroids; **OR**
         ii. Medication will be used as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence

IV. Lenalidomide (Revlimid) is considered not medically necessary when used for all other conditions, including but not limited to:
   A. Chronic lymphocytic leukemia (CLL), relapsed or refractory

V. Lenalidomide (Revlimid), pomalidomide (Pomalyst), and thalidomide (Thalomid) is/are considered investigational when used for all other conditions, including but not limited to:
   A. Kaposi sarcoma)
   B. Behçet syndrome
   C. Diffuse large B-cell lymphoma (DLBCL)
   D. Multiple myeloma (MM) when given as part of a quadruplet (“quad”) regimen
   E. Myelofibrosis
   F. Non-Hodgkin's lymphoma (NHL)
   G. POEMS syndrome
   H. Systemic light chain amyloidosis (AL)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy 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. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms; **AND**

Supporting Evidence

I. **Multiple myeloma (MM)**:

Lenalidomide (Revlimid)

- Efficacy of lenalidomide (Revlimid) was established in an open-label trial comparing lenalidomide (Revlimid) with low dose dexamethasone (Rd) to melphalan, prednisone, and thalidomide (Thalomid) (MPT) in newly diagnosed MM patients who were not candidates 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.
- 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.
- Numerous regimens have been used for the treatment of MM, both in patients who are transplant eligible and those who are not transplant eligible.
- Three-drug regimens are the mainstay of initial therapy for most patients with newly diagnosed MM. For all patients with MM, regardless of transplant status, triplet regimens have shown to induce higher response rates and depth of response in clinical trials.
    i. Lenalidomide (Revlimid)/bortezomib/dexamethasone
        1. Phase 2 and Phase 3 trials have demonstrated that initial treatment with the combination is active and well tolerated in newly diagnosed patients with MM, regardless of transplant eligibility.
        2. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for both MM patients, regardless of transplant status.
    ii. Lenalidomide (Revlimid)/low-dose dexamethasone
        1. Two-drug regimens are typically reserved for elderly and/or frail patients.
        2. Lenalidomide (Revlimid) in combination with low-dose dexamethasone is a well-tolerated and effective regimen for transplant-ineligible and elderly patients.
        3. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for non-transplant candidates.
    iii. Lenalidomide (Revlimid)/daratumumab (Darzalex)/dexamethasone

1. An open-label, randomized, active control Phase 3 study compared treatment with the addition of daratumumab (Darzalex) to lenalidomide (Revlimid)/dexamethasone compared to lenalidomide (Revlimid)/dexamethasone alone in 737 patients with newly diagnosed MM ineligible for transplant.
2. Median PFS has not been reached in the triplet combination arm compared to 31.9 months in the control arm.
3. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for non-transplant candidates.

- Lenalidomide (Revlimid) is also used in previously treated MM, typically as part of similar triplet regimens.
    i. Lenalidomide (Revlimid)/bortezomib/dexamethasone
        1. The results of Phase 1 and Phase 2 studies show that the triplet combination is well tolerated and active, with durable responses in heavily pretreated patients with relapsed and/or refractory MM, including patients who have had prior lenalidomide (Revlimid), bortezomib, thalidomide, and transplant.
        2. After a median follow-up of 44 months, the median PFS was 9.5 months and median overall survival (OS) was 30 months.
        3. This combination is included as a preferred NCCN category 2A recommendation for previously treated MM
    ii. Lenalidomide (Revlimid)/elotuzumab (Empliciti)/dexamethasone
        1. This combination is FDA approved for the treatment of patients with MM who have received one to three prior therapies.
        2. Efficacy and safety were demonstrated in a Phase 3 trial which randomized 646 patients to receive either elotuzumab (Empliciti) in combination with lenalidomide (Revlimid) and dexamethasone or lenalidomide (Revlimid)/dexamethasone alone.
        3. Median PFS in the elotuzumab (Empliciti)-containing regimen was 19.4 months vs 14.9 months in those receiving lenalidomide (Revlimid)/dexamethasone alone.
        4. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.
    iii. Lenalidomide (Revlimid)/carfilzomib (Kyprolis)/dexamethasone
        1. The combination was evaluated in a randomized, open-label trial compared to lenalidomide (Revlimid)/dexamethasone alone in patients with relapsed and/or refractory MM.

2. Median PFS was 26.3 months for the triple combination therapy vs 17.6 months for lenalidomide (Revlimid)/dexamethasone.
3. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.

iv. Lenalidomide (Revlimid)/daratumumab (Darzalex)/dexamethasone
1. A Phase 3 trial in 569 patients evaluated the addition of daratumumab (Darzalex) to lenalidomide (Revlimid)/dexamethasone vs lenalidomide (Revlimid)/dexamethasone alone.
2. The overall response rate (ORR) was higher in the daratumumab group, and the estimated rate of PFS at 12 months was 83.2% compared with 60% in the control group.
3. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.

v. Lenalidomide (Revlimid)/ixazomib (Ninlaro)/dexamethasone
1. The combination is FDA approved for the treatment of patients with MM who have received at least one prior therapy.
2. The safety and efficacy were evaluated in a randomized, controlled trial in patients who had received at least one prior MM therapy (e.g. bortezomib-containing regimen). Patients were randomized to lenalidomide (Revlimid)/ixazomib (Ninlaro)/dexamethasone vs lenalidomide (Revlimid)/dexamethasone alone.
3. The triple combination resulted in a PFS of 20.6 months compared to 14.7 months for the control arm.
4. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.

Pomalidomide (Pomalyst)

- Pomalidomide (Pomalyst) is indicated for patients with multiple myeloma, in combination with dexamethasone, who have received at least two prior therapies including lenalidomide (Revlimid) and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of last therapy.
- A Phase 3 randomized, open-label study compared the efficacy and safety of pomalidomide (Pomalyst) and low-dose dexamethasone vs high-dose dexamethasone in patients with relapsed MM who were refractory to both lenalidomide (Revlimid) and bortezomib. The primary endpoint, PFS, was significantly longer in patients who received pomalidomide (Pomalyst) and low-dose dexamethasone compared to those who received high-dose dexamethasone (4.0 vs 1.9 months; $P < 0.0001$). Overall survival was significantly longer in the pomalidomide (Pomalyst) group also (12. 7 vs 8.1 months; $P = 0.0285$).

- A Phase 2, randomized open-label trial evaluated the safety and efficacy of pomalidomide (Pomalyst) alone or pomalidomide (Pomalyst) with low-dose dexamethasone in patients with relapsed or refractory MM. The ORR was 29.2% in patients who received combination therapy versus 7.4% in the monotherapy arm.
- Additional data regarding single agent pomalidomide (Pomalyst) therapy is available but is considered low quality. Pomalidomide (Pomalyst) monotherapy was evaluated in a Phase 1 trial of 24 patients and demonstrated an ORR of 50%. In a subsequent Phase 1 study, the ORR was much lower at 15%.
- Immunomodulatory agents are usually given in combination with dexamethasone and/or other agents, but the NCCN Multiple Myeloma Panel suggests considering pomalidomide (Pomalyst) monotherapy in patients who are steroid-intolerant.

Thalidomide (Thalomid)

- Although thalidomide (Thalomid) was the first immunomodulatory agent to show efficacy in MM, other agents such as lenalidomide (Revlimid) and pomalidomide (Pomalyst) have since been developed and offer a more favorable safety profile.
- The efficacy and safety of thalidomide (Thalomid) plus dexamethasone vs dexamethasone alone in multiple myeloma was evaluated in two open-label studies in symptomatic patients with newly diagnosed multiple myeloma. In one study, response rates (based on serum or urine paraprotein measurements) were significantly higher in the combination arm (52% vs 36%). In another study, the time to progression (TTP) was statistically significantly longer in the combination arm.
- The NCCN Guideline for Multiple Myeloma does not include thalidomide (Thalomid)-based regimens as preferred or recommended for any setting. Regimens containing thalidomide (Thalomid) may be useful in certain circumstances when used in combination with other active multiple myeloma agents (e.g. bortezomib). The combination of bortezomib, thalidomide (Thalomid), and dexamethasone is a Category 1 recommendation as primary therapy for transplant candidates in certain circumstances.
- There is no evidence to support the use of thalidomide (Thalomid) as monotherapy for the treatment of multiple myeloma.

II. **Myelodysplastic syndromes (MDS):**

- Lower-risk MDS with del(5q) generally has a relatively good prognosis and is highly responsive to lenalidomide (Revlimid) therapy.
    i. A Phase 3 trial in 205 patients demonstrated superiority of lenalidomide (Revlimid) compared to placebo for achieving RBC transfusion-independence.
        1. Patients with transfusion-dependent, lower risk MDS with del(5q) were treated with low dose lenalidomide (Revlimid) (10 mg), lower dose lenalidomide (Revlimid) (5 mg), and placebo.

2. The rates of transfusion-independence for greater than 26 weeks were 57%, 37%, and 2% respectively for low dose lenalidomide (Revlimid), lower dose lenalidomide (Revlimid), and placebo.
3. The risk of transformation to acute myeloid leukemia (AML) was not significantly different between lenalidomide (Revlimid) and placebo.

ii. Additionally, a Phase 2 trial in anemic transfusion-dependent patients with del(5q) also reported similar hematologic responses in two-thirds of the 148 patients with del(5q).

- The safety and efficacy of lenalidomide (Revlimid) for lower-risk MDS without del(5q) was evaluated in a Phase 3 trial in 239 patients with transfusion-dependent MDS.
  i. Patients receiving lenalidomide (Revlimid) compared to placebo had a higher rate of transfusion-independence (26.9% vs 2.5%; p< 0.001). Transfusion reduction of four or more units of packed RBCs was seen in 22% of lenalidomide (Revlimid)-treated patients while no reduction was seen in the placebo group.
  ii. Incidence of treatment-related mortality was 2.5% in both groups, but the incidence of myelosuppression was higher in the lenalidomide-treated group. Furthermore, when comparing lenalidomide (Revlimid) to placebo, the incidence of grade 3 or 4 neutropenia was 61.9% vs 12.7%, respectively, and the rate of thrombocytopenia was 35.6% vs 3.8%, respectively.

III. **Mantle cell lymphoma (MCL):**

- Lenalidomide (Revlimid) is approved for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
- The safety and efficacy of single-agent lenalidomide (Revlimid) for relapsed or refractory MCL was evaluated in a Phase 2, open-label trial in 134 patients with prior bortezomib therapy. The ORR was 28% and a median duration of response (DoR) was 16.6 months.
- An additional Phase 2 trial included 254 patients with relapsed MCL who were not candidates for intensive therapy were randomized to receive single-agent lenalidomide (Revlimid) or single-agent of the investigator's choice (e.g. rituximab, gemcitabine, fludarabine, chlorambucil, cytarabine) and were allowed to receive lenalidomide (Revlimid) at the time of progression. After a median follow-up of 15.9 months, PFS was 8.7 months for lenalidomide (Revlimid) verses 5.2 months for the control arm.
- The NCCN B-Cell Lymphomas guideline suggests the use of lenalidomide (Revlimid) outside of the relapsed/refractory setting, including as initial treatment or in the second-line setting. However, there is limited evidence to support use outside of the

relapsed/refractory setting. A small Phase 2 study evaluated the use of lenalidomide (Revlimid) plus rituximab as initial therapy for patients with MCL. The ORR in the intention-to-treat population (n = 38) was 87% and 92% in the population that could be evaluated (n = 36).

IV. **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.
- 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.
    i. 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.
- 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.
    i. Overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median DoR 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 DoR not reached within a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

V. **Erythema nodosum leprosum (ENL)**

- Erythema nodosum leprosum (ENL) is a serious immunological complication of leprosy, causing inflammation of skin, nerves, other organs, and general malaise. There is limited high-quality, prospective data supporting the use of thalidomide (Thalomid) for ENL. Data are mainly derived from small randomized trials or retrospective studies conducted by the U.S. Public Health Service. These data consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL.
- Thalidomide (Thalomid) 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 (Thalomid) 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.
- In patients with moderate to severe neuritis associated with a severe erythema nodosum leprosum reaction, corticosteroids may be started concomitantly with thalidomide (Thalomid). Steroid usage can be tapered and discontinued when the neuritis has improved.

Investigational or Not Medically Necessary Uses

I. Kaposi sarcoma
   A. A preliminary study of thalidomide (Thalomid) has shown some activity in patients with AIDS-related KS; however, further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
   B. Pomalidomide (Pomalyst) was studied in one ongoing, open-label, single center, single arm, Phase 1/2 trial with 28 patients with KS. There were 18 HIV-positive patients and 10 HIV-negative patients included in the trial. The HIV-positive patients continued on HAART. The primary efficacy outcome was ORR. The ORR was 71% (95% CI 51, 87) for all patients with 12 HIV-positive patients and 8 HIV-negative patients having a response. The duration of response was 12.5 months (95% CI 6.5, 24.9) for HIV-positive patients and 10.5 months (95% CI 3.9, 24.2) for HIV-negative patients. NCCN guidelines recommend pomalidomide (Pomalyst) as the preferred subsequent systemic therapy for relapsed/refractory therapy after first-line systemic options liposomal doxorubicin or paclitaxel; however, this is based on preliminary evidence from an early-phase, single center, open-label trial. Further evaluation in larger, well-controlled studies are needed to support the use of pomalidomide (Pomalyst) in the setting of KS.

II. Behçet syndrome
   A. The efficacy of thalidomide monotherapy for mucocutaneous manifestations of Behçet syndrome was evaluated in 96 patients compared to placebo. Only a minority of thalidomide (Thalomid)-treated patients responded to treatment, and some symptoms worsened. Furthermore, 7% of thalidomide-treated patients developed peripheral neuropathy.
   B. The use of thalidomide (Thalomid) for Behçet syndrome has fallen out of favor due to lack of proven efficacy and significant risk of neuropathy and teratogenicity.

III. Chronic lymphocytic leukemia (CLL)
   A. 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 PFS and OS; the primary endpoint was later changed to OS after the data cutoff for analysis. With a median follow-up of 31.5 months, there was no significant difference in OS between the lenalidomide (Revlimid) 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).

IV. Diffuse large B-cell lymphoma (DLBCL)
    A. NCCN guidelines list 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 2 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 2, open-label trials consisting of low-quality evidence. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
V. Multiple myeloma, as part of quadruple ("quad") regimen
    A. Although triplet regimens remain the standard of care for MM, there is growing interest in quad regimens which may include the addition of monoclonal antibodies [e.g. daratumumab (Darzalex), elotuzumab (Empliciti)] to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.
VI. Non-Hodgkin's lymphoma (NHL)
    A. Lenalidomide (Revlimid) was evaluated in patients with relapsed or refractory aggressive NHL, in an open-label, Phase 2 trial (n=49). Treatment with lenalidomide (Revlimid) led to an ORR of 35% and a median PFS of 4 months. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
VII. Myelofibrosis
    A. Lenalidomide (Revlimid) was evaluated in a small, open-label, Phase 2 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 2 trials of patients with myelofibrosis (n=125), single agent lenalidomide (Revlimid) and lenalidomide (Revlimid) plus prednisone produced higher response rates than thalidomide (Thalomid), though not statistically significant (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.
    B. Pomalidomide (Pomalyst) has been evaluated as a treatment option for MF-associated anemia. Results from two small randomized studies produced conflicting results.

C. Enrollment in a clinical trial should be considered for all patients with myelofibrosis-associated anemia.

VIII. POEMS syndrome

A. Regimens used as systemic therapy for POEMS syndrome with widespread osteosclerotic lesions or bone marrow involvement are modelled after those used in other conditions, such as MM. There are limited data to guide choice in therapy.

B. Case reports have demonstrated clinical improvement after treatment with lenalidomide (Revlimid) with or without dexamethasone. Two small, uncontrolled studies reported responses in over 70% with 60 to 75% progression free at three years.

C. Thalidomide (Thalomid) has also shown activity but is associated with a less favorable side effect profile.

D. Larger, well-controlled trials are needed to confirm the safety and efficacy of these agents for POEMS syndrome.

IX. Systemic light chain amyloidosis (AL)

A. There is insufficient evidence to support the use of lenalidomide (Revlimid) or pomalidomide (Pomalyst) for the management of AL. Both medications are listed in NCCN guidelines among several other treatment options; however, the optimal treatment of the underlying plasma cell disorder has not been identified. Treatment of AL should be in the context of a clinical trial when possible.

References

1. Revlimid [Prescribing Information]. Summit, NJ: Celgene; October 2019.
2. Thalomid [Prescribing Information]. Summit, NJ: Celgene; October 2019.
3. Pomalyst [Prescribing Information]. Summit, NJ: Celgene; October 2019.
4. National Comprehensive Cancer Network. NCCN Guidelines: Multiple Myeloma v3.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf (Accessed on April 06, 2020).
5. National Comprehensive Cancer Network. NCCN Guidelines: Myelodysplastic Syndrome v2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf (Accessed on April 06, 2020).
6. National Comprehensive Cancer Network. NCCN Guidelines: B-Cell Lymphomas v1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf (Accessed on April 06, 2020).
7. National Comprehensive Cancer Network. NCCN Guidelines: Myeloproliferative Neoplasms v3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf (accessed on April 06, 2020).
8. National Comprehensive Cancer Network. NCCN Guidelines: Systemic Light Chain Amyloidosis v1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf (accessed on April 6, 2020).
9. National Comprehensive Cancer Network. NCCN Guidelines: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf (Accessed on April 06, 2020).
10. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019;37(14):1188-1199.

11. Chanan-Khan A, Miller KC, Musial L, Lawrence D, Padmanabhan S, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol. 2006 Dec 1;24(34):5343-9.
12. Ferrajoli A, Lee BN, Schlette EJ, O'Brien SM, Gao H, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood. 2008;111(11):5291-7.
13. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. J Clin Oncol 2013;31:584-591.
14. Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular, and transformed lymphoma: a phase II clinical trial. Leukemia 2013;27:1902-1909.
15. Czuczman MS, Trneny M, Davies A, et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. Clin Cancer Res 2017;23:4127-4137.
16. Ferreri AJ, Sassone M, Zaja F, et al. Lenalidomide maintenance in patients with relapsed diffuse large B-cell lymphoma who are not eligible for autologous stem cell transplantation: an open label, single-arm, multicentre phase 2 trial. Lancet Haematol. 2017;4(3):e137-e146.
17. Wiernik PH, Lossos IS, Tuscano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2008;26(30):4952-7.
18. Jabbour E, Thomas D, Kantarjian H, et al. Comparison of thalidomide and lenalidomide as therapy for myelofibrosis. Blood. 2011;118(4):899-902.
19. Mesa RA, Yao X, Cripe LD, Li CY, Litzow M, et al. Lenalidomide and prednisone for myelofibrosis: Eastern Cooperative Oncology Group (ECOG) phase 2 trial E4903. Blood. 2010;116(22):4436-8. 24.
20. Daver N, Cortes J, Newberry K, et al. Ruxolitinib in combination with lenalidomide as therapy for patients with myelofibrosis. Haematologica. 2015;100(8):1058-63.
21. Santini V, Almeida A, Giagounidis A, et al. Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents. J Clin Oncol. 2016;34(25):2988-96.
22. Drug Facts and Comparisons. Facts & Comparisons® eAnswers [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed April 5, 2012.
23. Ruan J, Martin P, Shah B, et al. Lenalidomide plus rituximab as initial treatment of mantle-cell lymphoma. N Engl J Med. 2015;373:1835-1844.
24. Pomalidomide. In: DRUGDEX Evaluations. Grenwood Village (CO): Thomson Healthcare; 1974- 2013 [cited February25, 2013]. Available from http://thomsonhc.comwith subscription.
25. Freedman AS. Treatment of relapsed or refractory mantle cell lymphoma. In: UpToDate, Lister A (Ed), UpToDate, Waltham, MA. (Accessed on February 05, 2020).
26. Rajkumar SV. Multiple myeloma: Regimens used for relapsed or refractory disease. In: UpToDate, Kyle RA (Ed), UpToDate, Waltham, MA. (Accessed on February 03, 2020).
27. Scollard DS. Leprosy: Treatment and prevention. In: UpToDate, von Reyn CF (Ed), UpToDate, Waltham, MA. (Accessed on February 07, 2020).
28. Schlenk RF, Stegelmann F, Reiter A, et al. Pomalidomide in myeloproliferative neoplasm-associated myelofibrosis. Leukemia 2017;31:889-895.
29. Tefferi A, Al-Ali HK, Barosi G, et al. A randomized study of pomalidomide vs placebo in person with myeloproliferative neoplasm-associated myelofibrosis and RBC-transfusion dependence. Leukemia 2017;31:896-902
30. Nozza A, Terenghi F, Gallia F, et al. Lenalidomide and dexamethasone in patients with POEMS syndrome: results of a prospective, open-label trial. Br J Haematol. 2017;179(5):748-755.
31. Li J, Huang XF, Cai QQ, et al. A prospective phase II study of low dose lenalidomide plus dexamethasone in patients with newly diagnosed polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. Am J Hematol. 2018;93(6):803-809.

32. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone verses lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29-37
33. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355:1456-1465
34. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndtomes with karyotypes other than deletion 5q. Blood 2008;111:86-93
35. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transition-dependent patients with lower risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol 2016;34:2988-2996
36. Hamuryudan V, Mat C, Saip S, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1998;128(6):443-50.
37. Little RF, Wyvill KM, Pluda JM, et al. Activity of thalidomide in AIDS-related Kaposi's sarcoma. J Clin Oncol. 2000;18(13):2593-602.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication for Kaposi Sarcoma for Pomalyst as experimental and investigational	06/2020
• For multiple myeloma indications, updated language to clarify use as either monotherapy, or with dexamethasone as part of a double-drug or triple-drug regimen • Added CLL to the not medically necessary section • Added the following experimental/investigational indications: - As part of a quadruple regimen for MM - Systemic light chain amyloidosis - POEMS - Behçet syndrome	04/2020
Added pomalidomide (Pomalyst) and thalidomide (Thalomid) agents to policy; removed black box warnings and precautions readily available in compendia; removed laboratory 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
Previous reviews	09/2012, 10/2012, 10/2014, 09/2015, 01/2016
Policy created	08/2012