



PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Revlimid® (lenalidomide capsules – Celgene)

TAC APPROVAL DATE: 03/20/2019; selected revision 06/05/2019

OVERVIEW

Revlimid, a thalidomide analogue, is indicated in combination with dexamethasone for the treatment of patients with multiple myeloma.¹ It is also indicated as maintenance therapy in patients with multiple myeloma following autologous hematopoietic stem cell transplantation (auto-HSCT). Revlimid is also indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid is also indicated for the treatment of patients with mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included Velcade® (bortezomib injection). Revlimid is indicated in combination with a rituximab product for the treatment of adults with previously-treated follicular lymphoma. Revlimid is indicated in combination with a rituximab product for the treatment of adults with previously-treated marginal zone lymphoma. A limitation of use with Revlimid is that it is not indicated and is not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for B-Cell Lymphomas (version 3.2019 – May 6, 2019) discuss therapeutic options for mantle cell lymphoma.² Revlimid, in combination with rituximab, is recommended as a preferred less-aggressive induction therapy (category 2A). Revlimid with or without rituximab is recommended as a preferred second-line therapy (Category 2A). Other recommended second line therapy regimens include Imbruvica, Revlimid, plus rituximab. The NCCN guidelines cited many treatments and medications regimens for mantle cell lymphoma in various clinical scenarios.

The NCCN guidelines for multiple myeloma (version 2.2019 – November 16, 2018) recommend Revlimid in a variety of scenarios.³ Revlimid is use in various regimens and Revlimid combined with low-dose dexamethasone is cited as a Category 1 agent for primary therapy for non-transplant candidates. As a maintenance therapy, Revlimid also has a Category 1 recommendation. Revlimid, combined with other agents, is also part of a category 1 recommended therapy (preferred) for previously treated multiple myeloma.

The NCCN guidelines for MDS (version 2.2019 – October 18, 2018) recommend Revlimid in a variety of clinical scenarios among patients with symptomatic anemia both with and without 5q deletion abnormalities.⁴

The NCCN guidelines for B-Cell Lymphomas (version 2.2019 – March 6, 2019) recommend Revlimid as an option as subsequent therapy, with or without rituximab, for multi-centric Castleman's disease that has progressed after treatment of relapsed/refractory or progressive disease.²

NCCN guidelines for B-Cell Lymphomas (version 2.2019 – March 6, 2019) discuss therapeutic options for diffuse large B-cell lymphoma.² Revlimid, with or without rituximab, is mentioned as a second-line therapy. Many examples of first-line therapies are recommended (e.g., RCHOP [Rituximab cyclophosphamide, doxorubicin, vincristine, prednisone] {Category 1}, dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab {Category 2A}). One examples of a first-line therapy for patients with poor left ventricular function or in those who are frail include RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine). NCCN also recommends optional first-line consolidation therapy of Revlimid maintenance (Category 2B) for patients aged 60 to 80 years.

NCCN guidelines for B-Cell Lymphomas (version 3.2019 – May 6, 2019) discuss therapeutic options for follicular lymphoma.² Revlimid plus rituximab is a first-line recommended therapy (Category 2A). Many second-line and subsequent therapies are listed, which include Revlimid, with or without rituximab.

The NCCN Hodgkin Lymphoma clinical practice guidelines (version 3.2018 – April 16, 2018) recommend Revlimid as an additional therapy option for treatment of classical Hodgkin lymphoma as a single agent for refractory or relapsed disease.⁵

The NCCN guidelines for B-Cell Lymphomas (version 2.2019 – March 6, 2019) discuss marginal zone lymphomas.² Revlimid plus rituximab has a Category 2B recommendation for first-line therapy. Revlimid with or without rituximab is also recommended as a second-line and subsequent therapy.

The NCCN has guidelines regarding myeloproliferative neoplasms (version 2.2019 – October 29, 2018) that discuss myelofibrosis with related anemia.⁶ Revlimid is recommended, with or without prednisone, for patients with serum epoetin alfa levels > 500 mU/mL.

The NCCN guidelines for T-Cell Lymphomas (version 2.2019 – December 17, 2018) makes several recommendations that include Revlimid.⁷ For peripheral T-cell lymphomas, Revlimid is recommended as second-line and subsequent therapy as a monotherapy. Similarly, Revlimid is recommended as a second-line and subsequent therapy for adult T-cell leukemia/lymphoma.

NCCN guidelines for systemic light chain amyloidosis (version 1.2019 – October 26, 2018) cite Revlimid as a therapeutic option used in combination with other agents in several clinical scenarios, including newly-diagnosed disease.⁸ The NCCN guidelines state that Phase II studies have noted that Revlimid in combination with dexamethasone is active in the treatment of patients with systemic light chain amyloidosis, including patients with relapsed/refractory disease.

Other Uses with Supportive Evidence

Revlimid has been studied in myelofibrosis. An open-label, single-center, Phase II trial assessed the combination of Revlimid and prednisone in patients (aged ≥ 18 years) with primary myelofibrosis (n = 40).⁹ After a median follow-up of 22 months, overall responses were noted in 12 of 40 patients (30%) and are currently ongoing for 25% of patients (n = 10/40). Other Phase II data with Revlimid also show similar response rates.¹⁰ Jakafi is the only agent indicated for the treatment of patients with myelofibrosis.¹¹ Other treatment options for myelofibrosis include androgens, Epogen, Procrit, Aranesp, prednisone, danazol, Thalomid, melphalan, Myleran, alfa interferons, and hydroxyurea.¹²⁻¹³

Safety

In a prospective randomized clinical study in the first-line treatment of patients with CLL, use of Revlimid as a single agent increased the risk of death compared with chlorambucil given as a single agent.¹ The trial was stopped for safety in July 2013. In an interim analysis, 34 deaths occurred in 210 patients in the Revlimid treatment arm compared with 18 deaths among the 211 patients in the chlorambucil treatment arm (hazard ratio for overall survival was 1.92 [95% confidence interval {CI}: 1.08, 3.41]), which was consistent with a 92% increase in the risk of death. Also, serious adverse cardiovascular (CV) events, including atrial fibrillation, myocardial infarction, and cardiac failure, occurred more frequently in patients receiving Revlimid. Revlimid has a Boxed Warning regarding embryofetal toxicity, hematologic toxicity, and venous thromboembolism. Revlimid is only available through a restricted distribution program called the Revlimid Risk Evaluation Mitigation Strategy (REMS®). Males and females must follow the required reproductive precautions.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Revlimid. All approvals are provided for 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Revlimid is recommended in those who meet the following criteria:

FDA-Approved Indications

- 1. Follicular Lymphoma.** Approve for 3 years if the patient meets one of the following (A or B):
 - A) The patient is using Revlimid in combination with rituximab; OR
 - B) The patient has tried one prior therapy (e.g., Treanda® [bendamustine injection] plus rituximab; Treanda plus Gazyva® [obinutuzumab injection for intravenous use]; CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone] plus Gazyva or rituximab; CVP [cyclophosphamide, vincristine, prednisone] plus Gazyva or rituximab; chlorambucil with or without rituximab; cyclophosphamide with or without rituximab; Gazyva; Copiktra™ [duvelisib capsules]; Aliqopa® [copanlisib injection for intravenous use]; or Zydelig® [idelalisib capsules]).
- 2. Mantle Cell Lymphoma.** Approve for 3 years.
- 3. Marginal Zone Lymphoma.** Approve for 3 years.
- 4. Multiple Myeloma.** Approve for 3 years.
- 5. Myelodysplastic Syndrome (MDS).** Approve for 3 years if the patient meets ONE of the following (A, B, or C):
 - A) The patient has symptomatic anemia; OR
 - B) The patient has transfusion-dependent anemia; OR
 - C) The patient has anemia that is not controlled with an erythroid stimulating agent (ESA) [e.g., Eprex®/Procrit® {epoetin alfa injection}, Aranesp® {darbepoetin alfa injection}].

Other Uses with Supportive Evidence

6. **Castleman's Disease.** Approve for 3 years in patients with relapsed/refractory or progressive disease.
7. **Diffuse, Large B Cell Lymphoma (DLBCL) [Non-Hodgkin's Lymphoma].** Approve for 3 years if the patient has tried one other medication treatment regimen (e.g., RCHOP, dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin] + rituximab, RCEPP [rituximab, cyclophosphamide, etoposide, prednisone, procarbazine], DHAP [dexamethasone, cisplatin, cytarabine] ± rituximab, ICE [Ifex, carboplatin, etoposide] ± rituximab; or Treanda ± rituximab).
8. **Hodgkin Lymphoma, Classical (nodular sclerosis, mixed cellularity, lymphocyte depleted, and lymphocyte-rich subtypes of Hodgkin lymphoma).** Approve for 3 years in patients with relapsed or refractory disease.
9. **Myelofibrosis.** Approve for 3 years if the patient has tried one other therapy (e.g., Jakafi® [ruxolitinib tablets], androgens [e.g., nandrolone, oxymetholone], Epogen, Procrit, Aranesp, prednisone, danazol, Thalomid® [thalidomide capsules], melphalan, Myleran® [busulfan tablets], alpha interferons, or hydroxyurea).
10. **Peripheral T-Cell Lymphomas.** Approve for 3 years if the patient has tried one other chemotherapy regimen (e.g., Adcentris® [brentuximab vedotin injection for intravenous use] plus CHP [cyclophosphamide, doxorubicin, and prednisone]; CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]; dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin]; Beleodaq® [belinostat injection for intravenous infusion]; or Istodax® [romidepsin injection for intravenous infusion]).
11. **Systemic Light Chain Amyloidosis.** Approve for 3 years.
12. **T-Cell Leukemia/Lymphoma.** Approve for 3 years if the patient has tried one other chemotherapy regimen (e.g., Adcentris® [brentuximab vedotin injection for intravenous use] plus CHP [cyclophosphamide, doxorubicin, and prednisone]; CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone]; CHOEP [cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone], dose-adjusted EPOCH [etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin]; HyperCVAD [cyclophosphamide, vincristine, doxorubicin, and dexamethasone] alternating with high-dose methotrexate and cytarabine; or Beleodaq® [belinostat injection for intravenous infusion]).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Revlimid has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Metastatic Melanoma.** One Phase I¹⁴ and two Phase II/III studies¹⁵⁻¹⁶ have been done investigating the use of Revlimid in patients with metastatic melanoma. The two Phase II/III studies did not suggest benefit in parameters such as tumor response, time to progression or

overall survival in patients.¹⁵⁻¹⁶ NCCN guidelines for cutaneous melanoma (version 2.2019 – March 12, 2019) do not mention Revlimid as a treatment option for patients with metastatic melanoma.¹⁷

2. **Metastatic Renal Cell Carcinoma.** Some data, including Phase II investigations, are available regarding Revlimid in patients with metastatic renal cell carcinoma. Some data suggest benefits, but further investigation is needed.¹⁸⁻²⁰ NCCN guidelines for kidney cancer (version 3.2019 – February 6, 2019) do not mention Revlimid as a treatment option.²¹
3. **Ovarian Carcinoma.** Limited data are available regarding use of Revlimid in ovarian carcinoma.^{22,23} A Phase I trial (n = 20) investigated Revlimid in patients who had received at least one prior platinum-based chemotherapy regimen and noted that Revlimid had some activity as a single agent.²² NCCN guidelines for ovarian cancer including fallopian tube cancer and primary peritoneal cancer (version 1.2019 – March 8, 2019) do not mention Revlimid as a treatment option.²⁴ Further investigation is needed.
4. **Waldenström Macroglobulinemia.** A Phase II study assessed Revlimid and rituximab in patients with symptomatic Waldenström macroglobulinemia (n = 16).^{25,26} Efficacy was noted in some patients as the overall response and major response (< 50% decrease in serum IgM) rates were 50% and 25%, respectively.²⁵ However, clinically significant acute anemia was reported in many patients. Although data are available with Revlimid in Waldenström Macroglobulinemia, more data are needed before this therapy can be recommended. The NCCN guidelines for Waldenström macroglobulinemia and lymphoplasmacytic lymphoma (version 2.2019 – September 14, 2018) do not include Revlimid.²⁷
5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No criteria changes.	03/01/2017
Annual revision.	For mantle cell lymphoma, revised the alternative agents listed that would be examples of agents used for the management of the condition (added RDHAP and Calquence) and removed RICE, FC, and PCR.	03/07/2018
Annual revision	Added Venclexta as an option of agents that count as a trial for meeting the criteria for mantle cell lymphoma. Approval for marginal zone lymphoma was added. Added to approve for peripheral T-Cell Lymphomas and T-Cell leukemia/lymphoma if the patient has tried one other regimen.	03/20/2019
Selected revision	<ol style="list-style-type: none"> 1. Follicular Lymphoma: This condition was moved from Other Uses with Supportive Evidence to the Food and Drug Administration Approved Indications Section. In-line with the new labeling, the requirement was added that the patient is using Revlimid in combination with rituximab OR has tried one prior therapy with several examples provided in the policy. 2. Marginal Zone Lymphoma: This condition was moved from Other Uses with Supportive Evidence to the Food and Drug Administration Approved Indications Section. Criteria remain the same. 3. Mantle Cell Lymphoma: The requirement was removed that the patient had tried two prior regimens OR that the patient had tried one prior therapy or therapeutic regimen and cannot take Velcade according to the prescribing physician. 	06/05/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee; FDA – Food and Drug Administration.