Evolent Clinical Guideline 3045 for Revlimid™ (lenalidomide)

Guideline Number:	Applicable Codes	
Evolent_CG_3045		
"Evolent" refers to Evolent Health LLC and Evolent Specialty Services, Inc. 		
Original Date:	**Last Revised Date:**	**Implementation Date:**
January 2012	March 2025	March 2025

TABLE OF CONTENTS

STATEMENT

Purpose

To define and describe the accepted indications for Revlimid (lenalidomide) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)

- NOTE: Lenalidomide +/- rituximab/rituximab biosimilar is not supported by Evolent Policy for Revlimid (lenalidomide) for the treatment of CLL/SLL. This policy position is based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes with the above regimen compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at **Evolent Pathways**.

Multiple Myeloma (MM)

- The member has multiple myeloma and Revlimid (lenalidomide) may be used in the following clinical settings:
    - Initial/First Line Therapy
        - In combination with bortezomib +/- steroid
        - In combination with daratumumab + bortezomib +/- steroid (for transplant eligible members only)
        - In combination with daratumumab +/- steroid for transplant-ineligible members
        - In combination with isatuximab-irfc + bortezomib +/- steroid for transplant-

ineligible members

- In combination with cyclophosphamide +/- steroid
- NOTE: [Daratumumab + carfilzomib + lenalidomide +/- dexamethasone] is not supported by Evolent Policy for Revlimid (lenalidomide) for initial therapy of newly diagnosed multiple myeloma. This policy position is based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes compared to Evolent recommended alternative agents/regimens, including but not limited to regimens at **Evolent Pathways**.

- Subsequent Line therapy and Maintenance Therapy:
  - Maintenance therapy as a single agent:
    - After completion of therapy for newly diagnosed or relapsed/refractory disease OR
    - After completion of autologous stem cell transplant.
  - For relapsed or refractory disease as ONE of the following:
    - As a single agent or with dexamethasone
    - With Darzalex/Darzalex Faspro (daratumumab) +/- dexamethasone
    - With bortezomib +/- dexamethasone
    - With Ninlaro (ixazomib) +/- dexamethasone
    - With Kyprolis (carfilzomib) +/- dexamethasone
    - With Empliciti (elotuzumab) +/- dexamethasone
    - With bendamustine +/- dexamethasone
    - With Cytoxan (cyclophosphamide) +/- dexamethasone.

Myelodysplastic Syndrome (MDS)

- The member has very low, low, or intermediate risk MDS associated with symptomatic anemia and Revlimid (lenalidomide) is being used as ONE of the following:
  - In members with del(5q) chromosomal abnormality with or without an ESA.
  - In members without del(5q) chromosomal abnormality with or without an ESA.

Non-Hodgkin's Lymphoma (NHL)

- The member has Non-Hodgkin's Lymphoma including Follicular Lymphoma, Nodal Marginal Zone Lymphoma, Mantle Cell Lymphoma, and Splenic Marginal Zone Lymphoma AND Revlimid (lenalidomide) may be used for relapsed/refractory disease as second-line or subsequent therapy for recurrent or progressive disease, with or without rituximab/rituximab biosimilar.
- Revlimid (lenalidomide) may be used in combination with Adcetris (brentuximab vedotin) and rituximab/rituximab biosimilar in adult members with relapsed or refractory large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS), DLBCL arising from indolent lymphoma, or high-grade B-cell lymphoma (HGBL), after two or more lines of systemic therapy who are ineligible for autologous hematopoietic stem cell transplantation (auto-HSCT) or CAR T-cell therapy.

- NOTE: The following regimens are not supported by Evolent Policy for Revlimid (lenalidomide) for the following treatment settings:
    - Diffuse Large B Cell Lymphoma (DLBCL) maintenance: single agent Revlimid (lenalidomide).
    - Marginal Zone Lymphomas (MZL), initial therapy: Lenalidomide + rituximab (any rituximab product).
    - Mantle Cell Lymphoma (MCL), second line and subsequent therapy: ibrutinib + lenalidomide + rituximab (any rituximab product).
    - The above policy positions are based on the lack of Level 1 Evidence (randomized clinical trial and/or meta-analyses) to show superior outcomes compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at **Evolent Pathways**.

CONTRAINDICATIONS/WARNINGS

- Contraindications
    - Pregnancy
    - Severe hypersensitivity to lenalidomide
- Warnings
    - Lenalidomide can cause significant neutropenia and thrombocytopenia. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.
    - Lenalidomide has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma who were treated with lenalidomide and dexamethasone therapy. Monitor for and advise patients about the signs and symptoms of thromboembolism.

EXCLUSION CRITERIA

- Member has disease progression while taking Revlimid (lenalidomide).
- Dosing exceeds single dose limit of Revlimid (lenalidomide) 20 mg (for FL/MZL), 10 mg (for MDS), or 25 mg (for MM/DLBCL/MCL).
- Treatment exceeds the maximum limit of 21 (2.5 mg), 21 (5 mg), 21 (10 mg), 21 (15 mg), 21 (20 mg), or 21 (25 mg) capsules/month.
- Investigational use of Revlimid (lenalidomide) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
    - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
    - Whether the administered chemotherapy/biologic therapy/immune

therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.

- Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
- Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J8999 - lenalidomide

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
March 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1193 Revlimid

	(lenalidomide) ● Added new indication ● Updated references
December 2024	● Added Evolent disclaimer language ● Added Coding Information section with HCPCS code ● Added new MM indication for initial therapy for transplant-ineligible members in combination with isatuximab-irfc + bortezomib +/- steroid ● Updated single dose limits in exclusion criteria ● Added new reference ● Updated NCH verbiage to Evolent

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Kim JA, et al. Brentuximab vedotin in combination with lenalidomide and rituximab in patients with relapsed/refractory diffuse large B-cell lymphoma: Results from the phase 3 ECHELON-3 study. *Journal of Clinical Oncology*. 2024 June 5; 42(17). https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA7005.
2. Voorhees PM, et al. Daratumumab plus RVd for newly diagnosed multiple myeloma: final analysis of the safety run-in cohort of GRIFFIN. *Blood Adv*. 2021 Feb 23;5(4):1092-1096. doi: 10.1182/bloodadvances.2020003642.
3. Facon T, et al; IMROZ Study Group. Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2024 Oct 31;391(17):1597-1609. doi: 10.1056/NEJMoa2400712.
4. Sonneveld P, et al; PERSEUS Trial Investigators. Daratumumab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2024 Jan 25;390(4):301-313. doi: 10.1056/NEJMoa2312054.
5. Costa LJ, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. *J Clin Oncol*. 2022 Sep 1;40(25):2901-2912. doi: 10.1200/JCO.21.01935.
6. Voorhees PM, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. *Blood*. 2020 Aug 20;136(8):936-945. doi: 10.1182/blood.2020005288.
7. Dimopoulos MA, et al; POLLUX Investigators. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016 Oct 6;375(14):1319-1331. doi: 10.1056/NEJMoa1607751.
8. Palumbo A, et al; CASTOR Investigators. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med*. 2016 Aug 25;375(8):754-66. doi: 10.1056/NEJMoa1606038.
9. Joseph NS, et al. Long-Term Follow-Up Results of Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy and Risk-Adapted Maintenance Approach in Newly Diagnosed Multiple Myeloma. *J Clin Oncol*. 2020 Jun 10;38(17):1928-1937. doi: 10.1200/JCO.19.02515.
10. Revlimid prescribing information. Celgene Corporation. Princeton, NJ 2023.
11. Clinical Pharmacology Elsevier Gold Standard 2025.
12. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2025.
13. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2025.
14. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2025.
15. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
16. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.
17. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.