Ninlaro® (ixazomib)
(Oral)

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I. Length of Authorization

Coverage will be provided for 6 months and may be renewed, unless otherwise specified.

- Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma:
  - Primary therapy or repeat of primary therapy regimen following relapse after prolonged response: Coverage is limited to six (6) 28-day induction treatment cycles and six (6) 56-day maintenance treatment cycles
  - Alternative therapy for previously treated disease: Coverage is limited to eight (8) 28-day treatment cycles

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Ninlaro 2.3 mg capsules: 3 capsules per 28 days
- Ninlaro 3 mg capsules: 3 capsules per 28 days
- Ninlaro 4 mg capsules: 3 capsules per 28 days

B. Max Units (per dose and over time) [HCPCS Unit]:

- 12 mg per 28 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age; **AND**

Universal Criteria [1]

- Patient will avoid concomitant use with strong CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, St. John's Wort, etc.); **AND**

Multiple Myeloma † ‡ Φ [1-3]

- Used as primary therapy or for disease relapse after 6 months following primary induction therapy with the same regimen; **AND**
    - Used as a substitute for carfilzomib; **OR**
- Used for relapsed or progressive disease; **AND**
    - Used in combination with dexamethasone AND either lenalidomide or cyclophosphamide after failure of at least one prior therapy; **OR**
    - Used in combination with dexamethasone and pomalidomide; **AND**
        - Patient has received at least two prior therapies, including an immunomodulatory agent (i.e., lenalidomide or thalidomide) and proteasome inhibitor (i.e., bortezomib, carfilzomib, etc.); **AND**
        - Disease has progressed on or within 60 days of completion of the last therapy; **OR**
    - Used in combination with venetoclax and dexamethasone for patients with t(11:14) translocation

Systemic Light Chain Amyloidosis ‡ [2,4,9]

- Used for relapsed or refractory disease; **AND**
- Used in combination with dexamethasone with or without lenalidomide or cyclophosphamide

Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma ‡ [2,5]

- Used in combination with rituximab and dexamethasone; **AND**
    - Used as primary therapy; **OR**
    - Used for relapsed disease if previously used as primary therapy that was well tolerated and elicited a prolonged response (i.e. 24 or more months); **OR**
    - Used as alternative therapy for previously treated disease; **AND**
        - Patient has persistent symptoms following primary therapy; **OR**
        - Patient has disease that does not respond to primary therapy; **OR**
        - Patient has progressive or relapsed disease

† FDA Approved Indication(s); ‡ Compendia Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria [1,6]

Coverage can be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: gastrointestinal toxicities (i.e., diarrhea, constipation, nausea, vomiting), thrombocytopenia, peripheral neuropathy, peripheral edema, hepatotoxicity, cutaneous reactions (i.e., severe

rash, Stevens-Johnson syndrome, toxic epidermal necrolysis), thrombotic microangiopathy including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), etc.; **AND**

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**

Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma [6,11,12]

- Primary therapy or repeat of primary therapy regimen following relapse after prolonged response may be renewed up to a maximum of six (6) 28-day induction treatment cycles and six (6) 56-day maintenance treatment cycles
- Alternative therapy for previously treated disease may be renewed up to a maximum of eight (8) 28-day treatment cycles

V. Dosage/Administration [1,6,7,9,10-12]

Indication	Dose
Multiple Myeloma	Administer 4 mg orally once a week on Days 1, 8, and 15 of a 28-day cycle. Treatment should be continued until disease progression or unacceptable toxicity.
Systemic Light Chain Amyloidosis	Administer 4 mg orally on Days 1, 8, and 15 of a 28-day cycle
Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma	Primary therapy or repeat of primary therapy regimen following relapse after prolonged response: Induction: Administer 4 mg orally on Days 1, 8, and 15 of a 28-day cycle for a total of 6 cycles Maintenance: Administer 4 mg orally on Days 1, 8, and 15 of a 56-day cycle for a total of 6 cycles Alternative therapy for previously treated disease: Administer 4 mg orally on Days 1, 8, and 15 of a 28-day cycle for a total of 8 cycles

VI. Billing Code/Availability Information

HCPCS code:

- J8999 – Prescription drug, oral, chemotherapeutic, nos

NDC(s):

- Ninlaro 2.3 mg capsules: 63020-0230-xx
- Ninlaro 3 mg capsules: 63020-0390-xx
- Ninlaro 4 mg capsules: 63020-0400-xx

VII. References

1. Ninlaro [package insert]. Lexington, MA; Takeda Pharmaceutical Co. Ltd; March 2024. Accessed April 2024.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ixazomib. National Comprehensive Cancer Network, 2024. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed April 2024
3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Multiple Myeloma Version 3.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed April 2024.
4. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Systemic Light Chain Amyloidosis Version 2.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed April 2024.
5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2024. National Comprehensive Cancer Network, 2024. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed April 2024.
6. Castillo JJ, Meid K, Gustine JN, D et al. Prospective Clinical Trial of Ixazomib, Dexamethasone, and Rituximab as Primary Therapy in Waldenström Macroglobulinemia. Clin Cancer Res. 2018 Jul 15;24(14):3247-3252. Doi: 10.1158/1078-0432.CCR-18-0152.
7. Sanchorawala V, Palladini G, Kukreti V, et al. A phase 1/2 study of the oral proteasome inhibitor ixazomib in relapsed or refractory AL amyloidosis. Blood. 2017 Aug 3;130(5):597-605. Doi: 10.1182/blood-2017-03-771220.
8. Moreau P, Masszi T, Grzasko N, et al; TOURMALINE-MM1 Study Group. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. N Engl J Med. 2016 Apr 28;374(17):1621-34. Doi: 10.1056/NEJMoa1516282.
9. Cohen O, Sharpley F, Gillmore J, et al. Use of ixazomib, lenalidomide and dexamethasone in patients with relapsed amyloid light-chain amyloidosis. Br J Haematol. 2020 May;189(4):643-649. Doi: 10.1111/bjh.16401.

10. Muchtar E, Gertz MA, LaPlant BR, et al. Phase 2 trial of ixazomib, cyclophosphamide, and dexamethasone for previously untreated light chain amyloidosis. Blood Adv. 2022 Sep 27;6(18):5429-5435. doi: 10.1182/bloodadvances.2022007781.
11. Castillo JJ, Meid K, Flynn CA, et al. Ixazomib, dexamethasone, and rituximab in treatment naive patients with Waldenström macroglobulinemia: long-term follow-up. Blood Adv 2020;4:3952-3959.
12. Kersten MJ, Amaador K, Minnema MC, et al. Combining Ixazomib With Subcutaneous Rituximab and Dexamethasone in Relapsed or Refractory Waldenstrom's Macroglobulinemia: Final Analysis of the Phase I/II HOVON124/ECWM-R2 Study. J Clin Oncol 2022;40:40-51.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C88.0	Waldenström macroglobulinemia
C90.00	Multiple myeloma not having achieved remission
C90.01	Multiple myeloma in remission
C90.02	Multiple myeloma in relapse
C90.10	Plasma cell leukemia not having achieved remission
C90.12	Plasma cell leukemia in relapse
C90.20	Extramedullary plasmacytoma not having achieved remission
C90.22	Extramedullary plasmacytoma in relapse
C90.30	Solitary plasmacytoma not having achieved remission
C90.32	Solitary plasmacytoma in relapse
E85.3	Secondary systemic amyloidosis
E85.4	Organ-limited amyloidosis
E85.81	Light chain (AL) amyloidosis
E85.89	Other amyloidosis
E85.9	Amyloidosis unspecified
Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic and related tissues

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

The preceding information is intended for non-Medicare coverage determinations. Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determinations (NCDs) and/or Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. Local Coverage Articles (LCAs) may also exist for claims payment purposes or to clarify benefit eligibility under Part B for drugs which may be self-administered. The following link may be used to search for NCD, LCD, or LCA documents

https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications, including any preceding information, may be applied at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCA/LCD): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC