Clinical Policy: Ixazomib (Ninlaro)

Reference Number: CP.PHAR.302
Effective Date: 02.01.17
Last Review Date: 08.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Ixazomib (Ninlaro®) is a proteasome inhibitor.

FDA Approved Indication(s)

Ninlaro is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy.

Limitation(s) of use: Ninlaro is not recommended for use in the maintenance setting or in newly diagnosed MM in combination with lenalidomide and dexamethasone outside of controlled clinical trials.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Ninlaro is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Multiple Myeloma (must meet all)**:**

1. Diagnosis of MM;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member has received at least one prior therapy (*see Appendix B*);
5. Prescribed in one of the following ways (a, b, c, or d):
   a. In combination with dexamethasone with either lenalidomide or cyclophosphamide;*
   b. Member is lenalidomide- or anti-CD-38-refractory (e.g., Darzalex®, Darzalex Faspro™, Sarclisa®) and all of the following (i, ii, and iii):
      i. Prescribed in combination with dexamethasone and Pomalyst®;*
      ii. Member has received at least two prior therapies including an immunomodulatory agent (e.g., Revlimid®, Pomalyst, Thalomid®) and a proteasome inhibitor (e.g., bortezomib, Kyprolis®);
      iii. Member has demonstrated disease progression on or within 60 days of completion of the last therapy;
   c. In combination with Venclexta® and dexamethasone for patients with t(11:14);*

**Prior authorization may be required for Revlimid, Pomalyst, cyclophosphamide, or Venclexta.*

d. As primary treatment or when used for disease relapse after 6 months following primary induction therapy with the same regimen for non-transplant candidates in case of intolerance/logistical reasons as a substitute for bortezomib or carfilzomib;

6. Request meets one of the following (a or b):*
   a. Dose does not exceed 4 mg (1 tablet) per week for 3 weeks of a 28-day (4-week) treatment cycle;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

B. Systemic Light Chain Amyloidosis (off-label) (must meet all)**:**

1. Diagnosis of relapsed or refractory systemic light chain amyloidosis;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed in one of the following ways (a, b, or c):
   a. In combination with dexamethasone;
   b. In combination with dexamethasone and lenalidomide;*
   c. In combination with dexamethasone and cyclophosphamide;

   **Prior authorization may be required for lenalidomide*
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

C. Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma (off-label) (must meet all)**:**

1. Diagnosis of Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Prescribed in combination with rituximab* and dexamethasone;

   **Prior authorization may be required for rituximab.*
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 6 months
Commercial – 12 months or duration of request, whichever is less

D. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Ninlaro for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 4 mg (1 tablet) per week for 3 weeks of a 28-day (4-week) treatment cycle;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use *(prescriber must submit supporting evidence)*.

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
MM: multiple myeloma
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
bortezomib/ lenalidomide (Revlimid®) /dexamethasone	Varies	Varies
bortezomib/cyclophosphamide/dexamethasone	Varies	Varies
bortezomib/doxorubicin (or liposomal doxorubicin)/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib)/ lenalidomide (Revlimid) /dexamethasone	Varies	Varies
Kyprolis® (carfilzomib)/cyclophosphamide/ dexamethasone	Varies	Varies
bortezomib/dexamethasone	Varies	Varies
bortezomib/Thalomid® (thalidomide)/dexamethasone	Varies	Varies
cyclophosphamide/ lenalidomide (Revlimid)/dexamethasone	Varies	Varies
lenalidomide (Revlimid)/dexamethasone	Varies	Varies
VTD-PACE (dexamethasone/Thalomid® (thalidomide)/cisplatin/doxorubicin/ cyclophosphamide/etoposide/bortezomib)	Varies	Varies
lenalidomide (Revlimid)/low-dose dexamethasone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/bortezomib/melphan/ prednisone	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Darzalex (daratumumab) or Darzalex Faspro (daratumumab/hyaluronidase-fihj)/Revlimid (lenalidomide)/ dexamethasone	Varies	Varies
Sarclisa® (isatuximab-irfc)/bortezomib/ Revlimid (lenalidomide)/dexamethasone	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: General Information

- NCCN includes a category 2B recommendation for use of Ninlaro as maintenance therapy. The prescribing information for Ninlaro states that in two prospective randomized clinical trials in MM in the maintenance setting, treatment with Ninlaro resulted in increased deaths. Treatment of patients with Ninlaro for MM in the maintenance setting is not recommended outside of controlled trials.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MM	4 mg PO on Days 1, 8, and 15 of a 28-day cycle. See Ninlaro Prescribing Information for lenalidomide and dexamethasone dosing.	4 mg/week for 3 weeks of a 28-day (4-week) treatment cycle

VI. Product Availability

Capsules: 2.3 mg, 3 mg, 4 mg

VII. References

1. Ninlaro Prescribing Information. Cambridge, MA: Millennium Pharmaceuticals, Inc.; July 2024. Available at https://www.ninlaro.com/sites/default/files/resources/ninlaro-prescribing-information.pdf. Accessed April 14, 2025.
2. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at www.nccn.org. Accessed April 29, 2025.
3. National Comprehensive Cancer Network. Multiple Myeloma Version 2.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed April 29, 2025.
4. National Comprehensive Cancer Network. Systemic Light Chain Amyloidosis Version 2.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf. Accessed April 29, 2025.
5. National Comprehensive Cancer Network. Waldenstrom Macroglobulinemia / Lymphoplasmacytic Lymphoma Version 3.2025. Available at https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed April 29, 2025.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
3Q 2021 annual review: no significant changes; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated.	04.02.21	08.21
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	01.20.22	05.22
3Q 2022 annual review: for MM removed use as a single agent for subsequent therapy in transplant candidates as this has been downgraded to a NCCN category 2B recommendation; clarified combination use with dexamethasone and Pomalyst requires two prior therapies per NCCN; RT4: added limitations of use for maintenance therapy and newly diagnosed MM per updated prescribing information, for MM added requirement that member has received at least one prior therapy, removed maintenance use as a single agent after prior autologous stem cell transplant; for systemic light chain amyloidosis added requirements for use as a single agent or in combination per NCCN; references reviewed and updated.	05.12.22	08.22
Template changes applied to other diagnoses/indications.	09.21.22	
3Q 2023 annual review: per NCCN for MM removed option for use in combination with dexamethasone alone (without lenalidomide or cyclophosphamide), for systemic light chain amyloidosis removed option for use as a single-agent; revised references from Revlimid to lenalidomide; references reviewed and updated.	04.14.23	08.23
3Q 2024 annual review: per NCCN Compendium for MM added additional use in combination with Venclexta and dexamethasone for patients with t(11:14); for systemic light chain amyloidosis added additional use in combination with cyclophosphamide and dexamethasone; references reviewed and updated.	05.06.24	08.24
3Q 2025 annual review: added NCCN Compendium supported use as primary treatment as a substitute for bortezomib or carfilzomib; clarified for combination with dexamethasone and Pomalyst, member is lenalidomide- or anti-CD-38-refractory; references reviewed and updated.	04.14.25	08.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical

practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.