

09-J2000-51

Original Effective Date: 02/15/16

Reviewed: 06/12/24

Revised: 10/01/24

Subject: Ixazomib (Ninlaro[®]) Capsule

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Ixazomib (Ninlaro) is an oral, reversible proteasome inhibitor that preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome resulting in apoptosis of multiple myeloma cells. It was approved by the FDA in November 2015 for the treatment of patients with multiple myeloma (MM), in combination with lenalidomide and dexamethasone, who have received at least one prior therapy. Ixazomib was reviewed by the FDA under priority review and was granted accelerated approval. Ixazomib was previously granted orphan drug designation by the FDA for the treatment of MM in February 2011. In April 2022, the indication was updated to include a “Limitations of Use” statement, which reads “Ninlaro is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials”. This addition was based on two prospective RCTs for MM in the maintenance setting in which treatment with ixazomib resulted in increased death.

The safety and efficacy of ixazomib leading to its FDA approved indication were evaluated in a multicenter, randomized, double-blind, phase III trial (TOURMALINE-MM1, n = 722). The median progression-free survival time was significantly improved with ixazomib plus lenalidomide and dexamethasone vs. placebo plus lenalidomide and dexamethasone (20.6 months vs. 14.7 months; hazard ratio=0.74; 95% CI, 0.59 to 0.94; p=0.012). The overall response rate was 78% with ixazomib and 72% with placebo. Patients who were refractory to lenalidomide or proteasome inhibitors were excluded from the study. Complete, very good partial, and partial response rates were 12%, 36%, and 30% with ixazomib and 7%, 32%, and 33% with placebo. Median time to response was 1.1 months with ixazomib and 1.9 months with placebo.

The National Comprehensive Cancer Network (NCCN) Guidelines for Multiple Myeloma, Waldenström’s Macroglobulinemia/Lymphoplasmacytic Lymphoma, and Systemic Light Chain Amyloidosis all include

ixazomib regimens as recommended treatment options. For MM, ixazomib can be used as first-line primary therapy, as maintenance therapy, and as treatment for relapse/refractory disease. For primary therapy, the use of ixazomib is only mentioned as a substitute for carfilzomib in select patients. For maintenance therapy, the NCCN lists ixazomib as a category 2B recommendation based on the interim results from the TOURMALINE MM3 and MM4 trials suggesting a potential decrease in overall survival.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of ixazomib (Ninlaro) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1”, “2”, and “3”):

1. The member has **ANY** of the following diagnoses (“a” to “f”), **AND** meets all associated criteria:
 - a. Primary therapy for previously untreated, symptomatic multiple myeloma (MM), and **BOTH** of the following (“i” and “ii”):
 - i. **EITHER** of the following:
 - Ixazomib will be used in combination with **BOTH** lenalidomide (Revlimid) and dexamethasone
 - Ixazomib will be used in combination with **BOTH** cyclophosphamide and dexamethasone
 - Ixazomib will be used in combination with daratumumab (Darzalex/Darzalex Faspro), lenalidomide, and dexamethasone; **AND** the member is a transplant candidate
 - ii. A bortezomib-containing regimen is determined to be clinically inappropriate as first-line primary therapy for the member (the specific reason must be provided)
 - b. Primary therapy for symptomatic multiple myeloma (MM) in members who have had intolerable adverse effects (e.g., severe neuropathy) to their current proteasome inhibitor therapy [i.e., bortezomib or carfilzomib (Kyprolis)] (the specific adverse effect(s) must be provided), and may benefit by switching to ixazomib treatment, **AND EITHER** of the following:
 - i. Ixazomib will be used in combination with **BOTH** lenalidomide and dexamethasone
 - ii. Ixazomib will be used in combination with **BOTH** cyclophosphamide and dexamethasone
 - iii. Ixazomib will be used in combination with daratumumab (Darzalex/Darzalex Faspro), lenalidomide, and dexamethasone; **AND** the member is a transplant candidate
 - c. Relapsed or refractory multiple myeloma (MM), and **BOTH** of the following (“i” and “ii”):
 - i. Member has received at least **ONE** appropriate prior therapy of adequate duration for the treatment of their MM

- ii. **ANY** of the following regimens will be used:
 - Ixazomib in combination with **BOTH** dexamethasone and cyclophosphamide
 - Ixazomib in combination with **BOTH** dexamethasone and lenalidomide
 - Ixazomib in combination with **BOTH** dexamethasone and pomalidomide (Pomalyst), **AND** the member has received at least **TWO** appropriate prior therapies of adequate duration including an immunomodulatory agent and a proteasome inhibitor and demonstrated disease progression on or within 60 days of completion of the last therapy
 - Ixazomib in combination with **BOTH** dexamethasone and venetoclax (Venclexta), **AND** the member has a t(11:14) translocation
- d. Systemic light chain amyloidosis (SLCA), and **BOTH** of the following (“i” and “ii”):
 - i. Member has relapsed/refractory disease
 - ii. One of the following treatment regimens will be used:
 - Ixazomib in combination with dexamethasone
 - Ixazomib in combination with **BOTH** lenalidomide and dexamethasone
 - Ixazomib in combination with **BOTH** cyclophosphamide and dexamethasone
- e. Waldenström’s macroglobulinemia/lymphoplasmacytic lymphoma, **AND** ixazomib will be used in combination with **BOTH** a rituximab product and dexamethasone
- f. Other FDA-approved or NCCN supported diagnosis (not previously listed above), and **ONE** of the following is met (“i” or “ii”):
 - i. Member is diagnosed with a condition that is consistent with an indication listed in the product’s FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the “Indications and Usage” section of the FDA-approved prescribing information (or package insert)
 - ii. Indication **AND** usage are recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
- 2. Ixazomib will **NOT** be used in combination with another proteasome inhibitor [i.e., bortezomib (Velcade) and carfilzomib (Kyprolis)]
- 3. The dosage of ixazomib does not exceed three 4 mg capsules every 28 days [i.e., 4 mg weekly for 3 weeks of every 4-week cycle (day 1, 8, and 15)]

Approval duration: 6 months

Continuation of ixazomib (Ninlaro) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “5”):

1. An authorization or reauthorization for ixazomib has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of multiple myeloma, systemic light chain amyloidosis, Waldenström’s macroglobulinemia/lymphoplasmacytic lymphoma, or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria

2. **ANY** of the following depending on the indication for use (“a”, “b”, “c”, or “d”):
 - a. Indication of MM and **ANY** of the following (“i” to “iv”):
 - i. Ixazomib will be used in combination with **BOTH** dexamethasone and cyclophosphamide
 - ii. Ixazomib will be used in combination with **BOTH** dexamethasone and lenalidomide
 - iii. Ixazomib will be used in combination with **BOTH** dexamethasone and pomalidomide
 - iv. Ixazomib in combination with **BOTH** dexamethasone and venetoclax (Venclexta)
 - b. Indication of SLCA and **EITHER** of the following (“i” or “iii”):
 - i. Ixazomib will be used in combination with dexamethasone
 - ii. Ixazomib will be used in combination with **BOTH** lenalidomide and dexamethasone
 - iii. Ixazomib will be used in combination with **BOTH** cyclophosphamide and dexamethasone
 - c. Indication of Waldenström’s macroglobulinemia/lymphoplasmacytic lymphoma - ixazomib is used in combination with **BOTH** a rituximab product and dexamethasone
 - d. Other FDA-approved or NCCN-supported diagnosis (not listed above) – ixazomib is used in a treatment regimen in accordance with the FDA-approved package labeling or NCCN guideline recommendation for the diagnosis
3. Ixazomib will **NOT** be used in combination with another proteasome inhibitor [i.e., bortezomib (Velcade) and carfilzomib (Kyprolis)]
4. The dosage of ixazomib does not exceed three 4 mg capsules every 28 days [i.e., 4 mg weekly for 3 weeks of every 4-week cycle (day 1, 8, and 15)]
5. Member has had a beneficial response to ixazomib treatment

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER’S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated in combination with lenalidomide (Revlimid) and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
 - Limitations of Use (per package insert): Ixazomib is not recommended for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of controlled clinical trials.
- The recommended starting dose of ixazomib is 4 mg administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle. The recommended starting dose of lenalidomide is 25 mg administered daily on Days 1 through 21 of a 28-day treatment cycle. The recommended starting dose of dexamethasone is 40 mg administered on Days 1, 8, 15, and 22 of a 28-day treatment cycle. Treatment should be continued until disease progression or unacceptable toxicity.

- Ixazomib should be taken once a week on the same day and at approximately the same time for the first three weeks of a four-week cycle. The importance of carefully following all dosage instructions should be discussed with patients starting treatment. Instruct patients to take the recommended dosage as directed, because overdosage has led to deaths. Ixazomib should be taken at least one hour before or at least two hours after food. The whole capsule should be swallowed with water. The capsule should not be crushed, chewed or opened.
- Prior to initiating a new cycle of therapy:
 - Absolute neutrophil count should be at least 1,000/mm³
 - Platelet count should be at least 75,000/mm³
 - Non-hematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or Grade 1 or lower
- Consider antiviral prophylaxis to decrease the risk of herpes zoster reactivation

Dose Adjustments

- **Hepatic impairment:** Reduce the starting dose to 3 mg in patients with moderate (total bilirubin greater than 1.5-3 × ULN) or severe (total bilirubin greater than 3 × ULN) hepatic impairment
- **Renal impairment:** Reduce the starting dose to 3 mg in patients with severe renal impairment (creatinine clearance less than 30 mL/min) or end-stage renal disease requiring dialysis. Ixazomib is not dialyzable and therefore can be administered without regard to the timing of dialysis.
- **Dose Reductions due to Adverse Reactions** – see package insert for more specific information
 - First reduction – 3 mg
 - Second reduction – 2.3 mg

Drug Availability

- 2.3 mg, 3 mg, and 4 mg capsules in a 1-count blister pack in a carton containing 3 blister packs (for a total of 3 capsules per carton – a 28-day supply)
- May be stored at room temperature

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Thrombocytopenia:** Platelet nadirs typically occurring between Days 14 to 21 of each 28-day cycle. Monitor platelet counts at least monthly during treatment and adjust dosing, as needed. Consider more frequent monitoring during the first three cycles.
- **Gastrointestinal toxicities:** Adjust dosing for severe diarrhea, constipation, nausea, and vomiting, as needed.
- **Peripheral neuropathy:** Monitor patients for symptoms of peripheral neuropathy and adjust dosing, as needed.

- **Peripheral edema:** Monitor for fluid retention. Investigate for underlying causes, when appropriate. Adjust dosing, as needed.
- **Cutaneous reactions:** Rash was reported in 27% of patients in the ixazomib regimen and 16% of patients in the placebo regimen. Manage rash with supportive care or with dose modification if Grade 2 or higher. Stevens-Johnson syndrome, including a fatal case, has been reported.
- **Thrombotic Microangiopathy:** Cases, sometimes fatal, of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop ixazomib and evaluate. If the diagnosis of TTP/HUS is excluded, consider restarting. The safety of reinitiating therapy in patients previously experiencing TTP/HUS is not known.
- **Hepatotoxicity:** Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated. Monitor hepatic enzymes during treatment and adjust dosing for Grade 3 or 4 symptoms.
- **Embryo-fetal toxicity:** Ixazomib can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 90 days following the final dose. Women using hormonal contraceptives should also use a barrier method of contraception.
- **Increased Mortality in Patients Treated with Ninlaro in the Maintenance Setting:** In two prospective randomized clinical trials in multiple myeloma in the maintenance setting, treatment with ixazomib resulted in increased deaths. Treatment of patients with ixazomib for multiple myeloma in the maintenance setting is not recommended outside of controlled trials.
- **Lactation:** Discontinue nursing.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8999	Prescription drug, oral, chemotherapeutic, NOS
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ICD-10 Diagnosis Codes That Support Medical Necessity

C88.00	Waldenström's macroglobulinemia not having achieved remission
C90.00 – C90.02	Multiple myeloma
C90.10 – C90.12	Plasma cell leukemia
C90.20 – C90.22	Extramedullary plasmacytoma
C90.30 - C90.32	Solitary plasmacytoma
E85.3	Secondary systemic amyloidosis
E85.4	Organ-limited amyloidosis
E85.81	Light chain (AL) amyloidosis
E85.89	Other amyloidosis
E85.9	Amyloidosis, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

DEFINITIONS:

Heavy chain – the larger component of an immunoglobulin. There are five types: IgG, IgA, IgM, IgD, and IgE.

Immunoglobulins (a.k.a., antibodies) – proteins made by normal plasma cells that have an important role in fighting infection as part of the humoral immune response. Antibodies are composed of two heavy chains and two light chains that form a larger complex. Each plasma cell produces only one type of heavy chain and one type of light chain.

Light chain – the smaller component of an immunoglobulin. There are two types: kappa and lambda.

Minimal response (MR) (according to the Revised Uniform Response Criteria by the International Myeloma Working Group) – ALL of the following:

- $\geq 25\%$ but $\leq 49\%$ reduction of serum M-protein
- Reduction in 24-hour urine M-protein by 50% to 89%
- In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required
- No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response).

Myeloma Protein (M-Protein) – a nonfunctional immunoglobulin protein or protein fragment produced by malignant plasma cells (or myeloma cells). Since myeloma cells are monoclonal, the M-proteins for a given patient are structurally identical. Both portions of an immunoglobulin (the heavy chain and light chain) can be found in the serum, while only light chains can be found in the urine.

Plasma cell - a fully differentiated B lymphocyte (a type of white blood cell) that is specialized for immunoglobulin production and is found primarily in bone marrow.

Primary refractory MM - patients who never achieve at least a MR to initial induction therapy and progress while on therapy

Progressive MM - at least a 25% increase from nadir in the serum M-protein (absolute increase must be ≥ 0.5 g/dL) or urine M-protein (absolute increase must be ≥ 200 mg/24 hours), or in the difference between involved and uninvolved serum-free light-chain (FLC) levels (with an abnormal FLC ratio and FLC difference >100 mg/L).

Relapsed and refractory MM - patients who never achieve at least a MR or who progress within 60 days of their last therapy

Serum free light chain assay (SFLCA) – a test that detects the amount of unbound or free light chains (i.e., not attached to a heavy chain) in the serum. Normal values - kappa: 3.3 to 19.4 mg/L, lambda: 5.71 to 26.3 mg/L, kappa/lambda ratio: 0.26–1.65 (0.37–3.1 if renal impairment).

Serum Protein Electrophoresis (SPEP) – a test that detects and quantifies the amount of M-protein in the serum. An serum M-protein of greater than 30 g/L is consistent with a diagnosis of MM.

Smoldering (Asymptomatic) myeloma: defined as M-protein in serum of 30 g/dL or more and/or bone marrow clonal plasma cells of 10% or more, but no related organ or tissue impairment (no end organ damage, including bone lesions) or symptoms.

RELATED GUIDELINES:

[Allogeneic Bone Marrow and Stem Cell Transplantation, 02-38240-01](#)

[Carfilzomib \(Kyprolis\) IV, 09-J1000-81](#)

[Chimeric Antigen Receptor \(CAR\) T-Cell Therapies, 09-J3000-94](#)

[Daratumumab \(Darzalex\) Infusion and Daratumumab-Hyaluronidase-fihj \(Darzalex Faspro\), 09-J2000-49](#)

[Doxorubicin HCl Liposome \(Doxil\) IV, 09-J0000-91](#)

[Elotuzumab \(Empliciti\) IV, 09-J2000-50](#)

[Elranatamab-bcmm \(Elrexfio\) Injection, 09-4000-64](#)

[Isatuximab \(Sarclisa\) Injection, 09-J3000-67](#)

[Oral Oncology Medications, 09-J3000-65](#)

[Talquetamab-tgvs \(Talvey\) Injection, 09-J4000-63](#)

[Teclistamab \(Tecvayli\) Injection, 09-J4000-46](#)

[Thalidomide \(Thalomid\) Capsules, 09-J1000-56](#)

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 06/12/24.

GUIDELINE UPDATE INFORMATION:

03/15/16	New Medical Coverage Guideline.
04/15/16	Revision to guideline consisting of clarifying the position statement.
12/15/16	Review and revision to guidelines consisting of updating the lab requirements, clarification on switching proteasome inhibitor therapy in the first-line setting, and removal of monotherapy in the position statement.
02/16/17	Revision: Update to Position Statement.
07/15/17	Review and revision to guidelines consisting of updating the description section, position statement, and references.
10/01/17	New ICD-10 codes.
07/15/18	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, and references.
12/15/18	Revision to guideline consisting of updates to the description, position statement, and references based on updated NCCN Guidelines for SLCA.
07/15/19	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, and references.
01/15/19	Revision to guideline consisting of updates to the description, position statement, billing/coding, and references based on updated NCCN Guidelines for Waldenström's Macroglobulinemia.
07/15/20	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, related guidelines, and references.
07/15/21	Review and revision to guidelines consisting of updating the description section, position statement, dosage/administration, precautions, billing/coding information, related guidelines, and references.
07/15/22	Review and revision to guidelines consisting of updating the description section, position statement, billing/coding information, and references.
07/15/23	Review and revision to guidelines consisting of updating the description section, dosage/administration, precautions, related guidelines, and references per NCCN and FDA label updates.
07/15/24	Review and revision to guidelines consisting of updating the description section, position statement, related guidelines, and references per NCCN updates. New combination regimens added for MM and SLCA.
10/01/24	Revision: ICD-10 code updates.