09-J2000-51

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Reviewed: 06/12/19

Revised: 07/15/19

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.

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. Ixazomib also has an orphan drug designation for the treatment of systemic light chain amyloidosis granted in March 2012.

The safety and efficacy of ixazomib 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 MM (Version 2.2019) list the triplet regimen of ixazomib + lenalidomide (Revlimid) + dexamethasone under “Other Recommended Regimens” as a primary therapy option for transplant candidates (category 2B recommendation) and non-transplant candidates (category 2A). In contrast to ixazomib, several bortezomib-containing options are listed under “Preferred Regimens” with either a category 1 or 2A recommendation. For patients with previously treated MM, the triplet regimen of ixazomib + lenalidomide + dexamethasone is listed as a

category 1 “Preferred Regimen”. Two footnotes are included for the previously treated MM regimen stating, “indicated for the treatment of patients who have received at least one prior therapy” and “clinical trials with these regimens primarily included patients who were lenalidomide-naïve or with lenalidomide-sensitive MM.” There are numerous other category 1 preferred regimens listed by NCCN for previously treated MM. Ixazomib + dexamethasone doublet therapy and ixazomib + pomalidomide (Pomalyst) + dexamethasone triplet therapy are listed under ‘Other Recommended Regimens” as category 2A recommendations for therapy of previously treated MM. The ixazomib + dexamethasone regimen includes a footnote stating, “indicated for the treatment of patients who have received at least one prior therapy”. The triplet pomalidomide regimen includes a footnote for pomalidomide stating, “indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy”. Ixazomib monotherapy is no longer recommended by NCCN. The NCCN Guidelines for Systemic Light Chain Amyloidosis (Version 1.2019) list the treatment regimen of ixazomib with or without dexamethasone as a Category 2A recommendation for relapsed/refractory disease.

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”, “3”, and “4”):

1. The member has **ANY** of the following diagnoses (“a”, b”, “c”, “d”, or “e”), **AND** meets all associated criteria:
    a. Previously untreated, active (symptomatic) multiple myeloma (MM), and **BOTH** of the following (“i” and “ii”):
        i. Ixazomib will be used in combination with **BOTH** lenalidomide (Revlimid) **AND** dexamethasone as primary therapy for the member’s MM
        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. First-line treatment of active (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)] and may benefit by switching to ixazomib treatment, **AND** ixazomib will be used in combination with **BOTH** lenalidomide **AND** dexamethasone as primary therapy for the member’s MM
    c. Relapsed or refractory multiple myeloma (MM), and **BOTH** of the following (“i” and “ii”):
        i. Member has received at least **ONE** prior therapy for treatment of their MM
        ii. **ANY** of the following regimens will be used:
            - Ixazomib in combination with dexamethasone
            - Ixazomib in combination with both dexamethasone and lenalidomide (Revlimid)

- Ixazomib in combination with both dexamethasone and pomalidomide (Pomalyst), **AND** the member has received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy

d. Relapsed or refractory systemic light chain amyloidosis (SCLA), and **ALL** of the following ("i" "ii", "iii", and "iv"):

   i. The diagnosis has been validated by confirming the presence of amyloid deposits in tissue **AND** the deposits are composed of light chains

   ii. Member has received one or more prior lines of NCCN-recommended therapy for their for their disease

   iii. Member was **NOT** previously refractory to bortezomib (Velcade) treatment (i.e., disease progression on treatment or progression within 60 days after the last dose of a given therapy)

   iv. Ixazomib will be used as either monotherapy OR in combination with dexamathasone.

e. 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 is 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)]
4. **ANY** of the following depending on the indication for use ("a", "b", or "c"):

   a. MM - The member's baseline (i.e., within 90 days prior to initiating treatment with ixazomib) serum monoclonal protein (M-protein) level, as detected by serum protein electrophoresis (SPEP), is provided*

   b. SLCA - The member's baseline (i.e., within 90 days prior to initiating treatment with ixazomib) serum free light chains (SFLC), as detected by serum free light chain assay (SFLCA), is provided

   c. Other FDA-approved or NCCN supported diagnosis – no additional requirement

   **If the M-protein is undetectable by SPEP, documentation of a baseline SFLC must also be provided*

Approval duration: 6 months

Continuation of ixazomib (Ninlaro) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

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, or other FDA-approved or NCCN-supported diagnosis; **OR** the member previously met **ALL** indication-specific initiation criteria
2. **EITHER** of the following depending on the indication for use ("a", "b", or "c"):

   a. Indication of MM and **ANY** of the following ("i", "ii", or "iii"):

i. Ixazomib will be used in combination with dexamethasone

ii. Ixazomib will be used in combination with **BOTH** dexamethasone and lenalidomide

iii. Ixazomib will be used in combination with **BOTH** dexamethasone and pomalidomide

b. Indication of SLCA and **EITHER** of the following ("i" or "ii"):

i. Ixazomib will be used as monotherapy

ii. Ixazomib will be used in combination with dexamethasone

c. 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 meets **EITHER** of the following depending on the indication for treatment ("a" or "b"):

a. Multiple myeloma or systemic light chain amyloidosis, and **EITHER** of the following based on duration of treatment:

i. If less than 18 months of treatment

- MM - a serum M-protein level decrease of 25% or more* compared to baseline, or M-protein is undetectable; **AND** no increase in the size or number of lytic bone lesions after at least two cycles of treatment with ixazomib[†,#]
- SLCA - there has been a reduction (improvement) in the member's SFLC level as compared to baseline[¥] after at least two cycles of treatment with ixazomib - laboratory documentation of the SFLC level must be submitted

ii. 18 months or more of treatment - provider attestation that the member has not had disease progression during ixazomib treatment

**If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a decrease of 25% or more in the difference between the light chain produced by the myeloma cells (lambda or kappa) and the other light chain must be achieved*

[†]If the M-protein was undetectable by SPEP at baseline and a baseline SFLC level is available, a follow-up SFLC level must be submitted

*[#]An exception is permitted if a baseline M-protein level **AND** SFLC level are unavailable. In these cases the physician may provide an attestation of a beneficial clinical response which must include no increase in the size or number of lytic bone lesions.*

[¥]An exception is permitted if a baseline SFLC value is unavailable. Follow-up laboratory documentation of the SFLC level still must be submitted. The physician must provide an attestation of a beneficial clinical response.

b. Other FDA-approved or NCCN-supported diagnosis (not previously listed above) - provider attestation that the 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.
- 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 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/mm^3
    - Platelet count should be at least 75,000/mm^3
    - 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 either a 1-count or 3-count blister pack
- 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 19% of patients. Monitor patients for rash and manage rash with supportive care or with dose modification if Grade 2 or higher.
- **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.
- **Lactation**: Discontinue nursing.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY)
J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity

C90.00	Multiple myeloma not having achieved 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
E85.81	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: BCBSF 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:

- ≥25% but ≤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 dose 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 ≥200mg/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

Bortezomib (Velcade) IV, 09-J0000-92

Carfilzomib (Kyprolis) IV, 09-J1000-81

Daratumumab (Darzalex) IV, 09-J2000-49

Doxorubicin HCl Liposome (Doxil) IV, 09-J0000-91

Elotuzumab (Empliciti) IV, 09-J2000

Lenalidomide (Revlimid), 09-J0000-80

Panobinostat (Farydak), 09-J2000-37

Pomalidomide (Pomalyst) Capsule, 09-J1000-95

Thalidomide (Thalomid) Capsules, 09-J1000-56

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 06/12/19.

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.