PHARMACY COVERAGE GUIDELINE

NINLARO® (ixazomib) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Ninlaro (ixazomib) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Multiple myeloma (MM), used in combination with Revlimid (lenalidomide) and dexamethasone for individuals who has received at least one prior therapy

b. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. Request is **NOT** for use in the maintenance setting or in newly diagnosed multiple myeloma in combination with lenalidomide and dexamethasone outside of clinical controlled trials

5. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Negative pregnancy test in a woman of childbearing potential
   b. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2

6. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance, to the generic should be reported to the FDA] (see Definitions section)

7. Individual is **not** currently taking any other drugs which cause severe adverse reactions or any significant drug interactions requiring discontinuation such as use with strong CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and St. John's Wort)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Ninlaro (ixazomib) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual's condition has responded while on therapy with response defined as no evidence of disease progression or unacceptable toxicity

3. Individual has been adherent with the medication

4. There have been **no more than** 2 dose reductions due to adverse effects

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance, to the generic should be reported to the FDA] (see Definitions section)

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Life-threatening rash such as Stevens-Johnson syndrome
   b. Life-threatening peripheral neuropathy
   c. Thrombotic microangiopathy including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)

7. Individual is **not** currently taking any other drugs which cause severe adverse reactions or any significant drug interactions requiring discontinuation such as use with strong CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and St. John's Wort)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Ninlaro (ixazomib) is a proteasome inhibitor indicated in combination with linalidomide and dexamethasone for the treatment of patients with multiple myeloma (MM) who have received at least one prior therapy. Ninlaro (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 ubiquitin-proteasome complex plays a critical role in signal transduction pathways important for tumor cell growth and survival, cell-cycle control, transcriptional regulation, and the modulation of cellular stress responses to endogenous and exogenous stimuli. The proteasome is responsible for degradation of ubiquinated peptides within the cell. For a protein to be recognized by the proteasome, ubiquitin must be conjugated to the target protein; this is carried out by a cascade of enzymes. Agents that inhibit this complex have been found to be useful in cancer cells that are dependent on this pathway, such as multiple myeloma.

Ixazomib is a reversible proteasome inhibitor that preferentially binds and inhibits the chymotrypsin-like activity of the proteasome. It has demonstrated *in vitro* cytotoxicity against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone. The combination of ixazomib and lenalidomide demonstrated synergistic cytotoxic effects in MM cell lines.

MM is the second most common hematologic cancer. Despite treatment advances, it remains a disease with poor long-term survival as a result of relapse and/or resistance to treatment. MM is a malignancy of plasma cells in the bone marrow. Malignant monoclonal plasma cells accumulate in the bone marrow and produce a monoclonal protein (usually IgG or IgA which are often referred to as M [or myeloma] proteins) that causes disruption of normal bone marrow function, destruction and invasion of bone surrounding the bone marrow cavity, production and release of M-proteins from the myeloma cells into the blood stream and/or into the urine, and a reduction of normal immune function. MM makes up 10-15% of all hematologic malignancies.

MM is a genetically complex disease that develops through several steps over time and as a result has various clinical presentations or phases. The earliest phase is monoclonal gammopathy of undetermined significance (MGUS). The next phase is smoldering multiple myeloma (SMM), distinguished from MGUS by a greater tumor cell content of >10% and an average risk of progression to myeloma of 10% per year for the first five years. The myeloma phase is recognized when malignant clones cause clinically relevant end-organ damage such as the

features of CRAB (hyper**c**alcemia, **r**enal dysfunction, **a**nemia, and **b**one lesions, including bone pain and fractures). Other manifestations include infection, neurologic symptoms (lethargy, headaches, confusion, depression and other), clotting abnormalities and hyperviscosity. The final phase is plasma cell leukemia (PCL). MM is characterized by multiple relapses and progressive refractoriness to available therapies. There is no cure. The choice of primary therapy is based on whether a patient is a candidate for a stem cell transplant. Drug therapy is used to bridge eligible patients to an autologous stem cell transplant (ASCT). Agents from several different classes are combined with one another or with corticosteroids and/or various generic chemotherapy medications to make up a MM drug regimen. Medication drug classes include: *Chemotherapy:* liposomal doxorubicin (Doxil), melphalan, cyclophosphamide, vincristine, etoposide, cisplatin, others; *HDAC inhibitor:* panobinostat (Farydak); *Immunomodulators:* lenalidomide (Revlimid), pomalidomide (Pomalyst), thalidomide (Thalomid); *Proteasome inhibitors:* bortezomib (Velcade), carfilzomib (Kyprolis), and ixazomib (Ninlaro).

Regimens may contain two or three drug combinations for selected patients undergoing hematopoietic cell transplantation (HCT). Maintenance therapy includes use of one agent. Selection of therapy for relapse or progressive disease is based on the context of the clinical relapse and use of prior regimens. There are numerous combinations of agents that are used for relapse or progressive MM, combinations may contain 2 or more agents.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Ninlaro (ixazomib) cap product information, revised by Takeda Pharmaceuticals America, Inc. 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed December 05, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Multiple Myeloma Version 1.2025 – Updated September 17, 2024. Available at https://www.nccn.org. Accessed February 01, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.