



PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

ORIGINAL EFFECTIVE DATE: 01/21/16
LAST REVIEW DATE: 02/21/19
LAST CRITERIA REVISION DATE: 02/21/19
ARCHIVE DATE:

NINLARO® (ixazomib) oral capsule

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as “Description” defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as “Criteria” defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. All requested data must be provided. Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

NINLARO® (ixazomib) oral capsule (cont.)

Criteria:

- **Criteria for initial therapy:** Ninlaro (ixazomib) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
1. Prescriber is an Oncologist
 2. Individual is 18 years of age and older
 3. A confirmed diagnosis of multiple myeloma (MM) and **ONE** of the following:
 - Primary therapy in combination with lenalidomide (Revlimid) and dexamethasone
 - In combination with dexamethasone with or without lenalidomide for patients who have received at least one prior therapy
 - In combination with pomalidomide (Pomalyst) and dexamethasone for patients who have received at least 2 prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have disease progression on or within 60 days of completion of the last therapy
 - Relapsed or refractory Systemic Light Chain Amyloidosis with or without dexamethasone
 - 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. **ALL** of the following tests have been completed before initiation of treatment:
 - Complete blood count with differential
 - Liver Function
 - Comprehensive metabolic panel

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Ninlaro (ixazomib) is considered *medically necessary* and will be approved when **ALL** of the following criteria are met:
1. Individual continues to be seen by an Oncologist
 2. Individual's condition has not worsened while on therapy
 - Worsening is defined as:
 - Cancer progression
 3. Individual has been adherent with the medication
 4. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use
 - Significant adverse effect such as:

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- Severe rash
- Peripheral neuropathy
- Thrombocytopenia

Renewal duration: 12 months

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.

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 ubiquitinated 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 (hypercalcemia, renal dysfunction, anemia, and bone 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

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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.

Resources:

NCCN Drugs & Biologics Compendium Ninlaro accessed 02-02-19

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.

Ninlaro. Package Insert. Reference ID 101155/1. Revised by manufacturer 11/2015. Accessed 12-04-2015, 12-01-2016

Ninlaro. Package Insert. Revised by manufacturer 11/2016. Accessed 12-27-2017

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 3.2018, Nov 22, 2017.
https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature:	Date:
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Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.