BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/21/16**
SECTION: DRUGS	**LAST REVIEW DATE: 1/18/18**
	LAST CRITERIA REVISION DATE: 1/18/18
	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.

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.)

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 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.

NINLARO® (ixazomib) oral capsule (cont.)

Ninlaro (ixazomib)

Medication class:
Antineoplastic Agent, Proteasome Inhibitor

FDA-approved indication(s):
- Treatment of multiple myeloma (in combination with lenalidomide and dexamethasone) in patients who have received at least 1 prior therapy

Recommended Dose:
- 4 mg once on days 1, 8, and 15 of a 28-day treatment cycle (in combination with lenalidomide and dexamethasone)
  - The starting dose of lenalidomide is 25 mg daily on Days 1-21 of a 28-day treatment cycle
  - The starting dose of dexamethasone is 40 mg on Days 1, 8, 15, and 22 of a 28-day treatment cycle

Maximum dosage
- Not stated

Available Dosage Forms:
- 2.3 mg, 3 mg, and 4 mg capsules

Warnings, Precautions, and other Clinical Information:
- Consider antiviral prophylaxis while on Ninlaro to decrease risk of herpes zoster reactivation
- Before each new cycle the ANC should be at least 1,000/mm^3 and the platelet count should be at least 75,000/mm^3
- Reduce the starting dose of Ninlaro to 3 mg in patients with moderate (total bilirubin > 1.5-3x ULN) or severe (total bilirubin > 3x ULN) hepatic impairment
- Reduce the starting dose of Ninlaro to 3 mg in patients with severe renal impairment (CrCl < 30 mL/min) or end-stage renal disease
- Discontinue Ninlaro in patients on 2.3 mg who experience further adverse reactions
- Discontinue all treatment for life-threatening rash or peripheral neuropathy
- Avoid simultaneous use with CYP3A inducers (carbamazepine, phenytoin, rifampin, St. John's wort)
- Woman of child bearing potential should be warned against becoming pregnant
- Woman of childbearing potential should use effective contraception
- Woman who use hormonal contraception should also use a barrier method of contraception
- Woman who is breast feeding an infant or child should stop breast feeding
- Male on Ninlaro who has a female partner of child bearing potential should use effective contraception
- The mean absolute bioavailability of Ninlaro is 58%

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 for MM and Ninlaro will be used in combination with lenalidomide (Revlimid) and dexamethasone
     - Relapsed or refractory MM who has received at least **ONE** prior therapy to treat MM
  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:
       - Severe rash
         - Signs and symptoms may include: progressive skin rash, hives, blistering, oral ulcers
       - Peripheral neuropathy
         - Signs and symptoms may include: numbness, tingling, pain, burning sensation in hands, legs, or feet, hypoesthesia, hyperesthesia, paresthesia, weakness
       - Thrombocytopenia
         - Signs and symptoms may include: bleeding and easy bruising

  Renewal duration: 12 months

NINLARO® (ixazomib) oral capsule (cont.)

Resources:

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

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:	Dosage Form:
Directions for Use:	Quantity: / Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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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:

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.