BlueCross BlueShield of Arizona
An Independent Licensee of the Blue Cross and Blue Shield Association

PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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XPOVIO™ (selinexor) oral tablet

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.**

XPOVIO™ (selinexor) oral tablet

Criteria:

- **Criteria for initial therapy:** Xpovio (selinexor) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in cancer or is in consultation with an Oncologist

  2. Individual is 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:
     - Used in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma (RRMM) in an individual who has received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

     - 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 baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
     - Complete blood count with differential
     - Basic metabolic panel
     - Body weight
     - Negative pregnancy test in a woman of child bearing potential

  5. Will not be used in a patient with end-stage renal disease (Cockcroft-Gault CrCl < 15 mL/min) or a patient on hemodialysis

  6. Will not be used in a patient with moderate to severe hepatic impairment

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Xpovio (selinexor) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in cancer or is in consultation with an Oncologist

  2. Individual's condition responded while on therapy
     - Response is defined as:
       - No evidence of disease progression
       - Documented evidence of efficacy, disease stability and/or improvement

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:
     - Thrombocytopenia (platelet count < 50,000/mcL)
     - Hemorrhage or hemoglobin < 8 g/dL
     - Neutropenia (absolute neutrophil count < 1 x 10^9/L)
     - Fatigue lasting more than 7 days despite dose reduction
     - Severe nausea or vomiting such that cannot maintain adequate caloric and fluid intake or vomits 6 or more times per day despite antiemetic therapy
     - Severe diarrhea, continues to have 7 or more stools per day despite treatment with anti-diarrheal agents or needing hospitalization for treatment
     - Severe anorexia and weight loss such that weight cannot be maintained at least 90% of baseline weight or continues to have anorexia associated weight loss or malnutrition despite appetite stimulants and nutritional support
     - Severe hyponatremia, (sodium < 130 mmol/L)
     - Has had 3 dose reductions for toxicity and the toxicity still has not resolved

5. Will not be used in a patient with end-stage renal disease (Cockcroft-Gault CrCl < 15 mL/min) or a patient on hemodialysis

6. Will not be used in a patient with moderate to severe hepatic impairment

7. There are no significant interacting drugs

Renewal duration: 12 months

- Xpovio (selinexor) for all other indications not previously listed or if above criteria not met is considered ***experimental or investigational*** based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing or frequency outside the FDA-approved dosing and frequency

XPOVIO™ (selinexor) oral tablet

Description:

Xpovio (selinexor) is an oral nuclear export inhibitor indicated to be used in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma (RRMM) in an individual who has received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody.

In nonclinical studies, selinexor reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1, also known as chromosome region maintenance 1 [CRM1]). XPO1 is the major mammalian export protein that facilitates the transport of large macromolecules including RNA and protein across the nuclear membrane to the cytoplasm thereby facilitating proteins out of the nucleus. XPO1 inhibition by leads to accumulation of TSPs in the nucleus, reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells. Selinexor demonstrated pro-apoptotic activity in vitro in multiple myeloma cell lines and patient tumor samples, and in murine xenograft models.

Definitions:

Proteasome Inhibitors:
- Velcade (bortezomib) injection
- Kyprolis (carfilzomib) injection
- Ninlaro (ixazomib) oral capsule

Anti-CD38 monoclonal antibody:
- Darzalex (daratumumab) injection

Immunomodulatory agents:
- Revlimid (lenalidomide)
- Pomalyst (pomalidomide)
- Thalomid (thalidomide)

An alkylating agent:
- Bendamustine
- Cisplatin
- Cyclophosphamide
- Alkeran (melphalan)

Other agents used in MM:
- Adriamycin (doxorubicin)
- Empliciti (elotuzumab)
- Etoposide
- Doxil (liposomal doxorubicin)
- Farydak (panobinostat)

XPOVIO™ (selinexor) oral tablet

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE
U.S. department of Health and Human Services, National Institutes of Health, and National Cancer Institute	

Medication class:
- Antineoplastic Agent, Nuclear Export Inhibitor

FDA-approved indication(s):
- Treatment of relapsed or refractory multiple myeloma (in combination with dexamethasone) in adults who have received ≥ 4 prior therapies and whose disease is refractory to ≥ 2 proteasome inhibitors, ≥ 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody

Limitations of use:
- This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial

Recommended Dose:
- 80 mg on days 1 and 3 of each week with dexamethasone 20 mg with each dose of Xpovio

Maximum dosage
- Bullet 2
- There are no well-established maximum doses for the approved indications according to the prescribing information

Available Dosage Forms:
- 20 mg tablet

Warnings, Precautions, and other Clinical Information:
- Prior to and during treatment Provide prophylactic concomitant treatment with a 5-HT3 antagonist and/or other anti-nausea agents
- Maintain adequate fluid and caloric intake throughout treatment, consider IV hydration for patients at risk for dehydration
- Discontinue Xpovio after 3 dose reductions have occurred and no resolution of toxicity
- Package label does not provide any data on metabolism and elimination other than it is metabolized by CYP3A4, multiple UDP-glucuronosylftransferases (UGTs) and glutathione S-transferases (GSTs)
- Package label does not provide any data on drug interactions other than saying it does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5 and that it does not induce CYP3A4, CYP1A2, or CYP2B6 and that it inhibits OATP1B3 but does not inhibit other solute carrier transporters
- Label also says it is a substrate for CYP3A4 and not a substrate for P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K

XPOVIO™ (selinexor) oral tablet

Clinical Studies section information:

- Efficacy was evaluated in a multi-center, single arm, open label study STORM
  - Part 1 of STORM?
  - Part 2 of STROM included 122 patients with RRMM who had previously received three or more anti-myeloma treatment regimens including:
    - An alkylating agent, glucocorticoids, bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody
    - Also refractory to refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory agent, an anti-CD38 monoclonal antibody, and to the last line of therapy
    - 83 patients had RRMM that was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab
    - Study included high-risk cytogenetics (47 Pt [57%])
      - del(17p)/p53, t(14; 16), t(4; 14), 1q21
    - Approval of Xpovio was based on efficacy and safety analysis of the 83 patients
  - Outcome measure was overall response rate (ORR)
    - Median time to first response was 4 weeks (1-10)
    - Median duration of response was 3.8 months
    - ORR was 21 patients (25.3%)
      - Stringent complete response (sCR) 1 [1.2%]
      - Complete response (CR) 0
      - Very good partial response (VGPR) 4 [4.8%]
      - Partial response (PR) 16 [19.3%]
      - Response: Minimal, None, Death? 62 [74.6%]

Resources:

Xpovio (selinexor) product information accessed 07-30-19 at DailyMed

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.

NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 3.2019, June 19, 2019.

UpToDate: Multiple myeloma: Overview of management. Current through June 2019

UpToDate: Multiple myeloma: Selection of initial chemotherapy for symptomatic disease. Current through June 2019

UpToDate: Multiple myeloma: Regimens used for relapsed or refractory disease. Current through June 2019

UpToDate: Multiple myeloma: Treatment of relapsed or refractory disease. Current through June 2019