selinexor (Xpovio™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO086

Description

Selinexor (Xpovio) is an oral nuclear export inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
selinexor (Xpovio)	80 mg tablet twice weekly carton	Relapsed or refractory multiple myeloma (MM)	1 carton (32 tablets)/28 days
	100 mg tablet once weekly carton		1 carton (20 tablets)/28 days
	80 mg tablet once weekly carton		1 carton (16 tablets)/28 days
	60 mg tablet once weekly carton		1 carton (12 tablets)/28 days
	40 mg tablet once weekly carton		1 carton (8 tablets)/28 days
	60 mg tablet twice weekly carton	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	1 carton (24 tablets)/28 days
	40 mg tablet twice weekly carton		1 carton (16 tablets)/28 days

Initial Evaluation

I. Selinexor (Xpovio) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. Not used in combination with any other oncology therapy unless outlined below; **AND**
   D. A diagnosis of **multiple myeloma** when **ONE** of the following are met:
      1. The provider attests to the following:
         i. The member has received ONE, but no more than THREE previous therapies; **AND**

a. Previous treatments included at least one of the following medications:
    i. Bortezomib (Velcade)
    ii. Carfilzomib (Kyprolis)
    iii. Ixazomib (Ninlaro)
    iv. Daratumumab (Darzalex)
    v. Immunomodulatory agent (e.g., lenalidomide, pomalidomide); **AND**
b. Selinexor (Xpovio) will be used in combination with bortezomib (Velcade) AND dexamethasone; **OR**

ii. The member has received **FOUR** or more previous therapies; **AND**
a. Refractory to ALL of the following medications:
    i. TWO proteasome inhibitors (e.g., bortezomib, carfilzomib)
    ii. TWO immunomodulatory medications (e.g., lenalidomide, pomalidomide)
    iii. An anti-CD38 monoclonal antibody (e.g., daratumumab); **AND**
b. Selinexor (Xpovio) will be used in combination with dexamethasone.

II. Selinexor (Xpovio) is considered investigational when used for all other conditions, including but not limited to:
A. Multiple myeloma when given as part of a quadruplet ("quad") regimen
B. Diffuse large B-cell lymphoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
I. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
II. Clinical documentation of response to treatment such as stabilization or improvement in disease or symptoms; **AND**
III. Provider attests to the following:
A. The member has received ONE, but no more than THREE previous therapies; **AND**
    1. Selinexor (Xpovio) will be used in combination with bortezomib (Velcade) AND dexamethasone; **OR**
B. The member has received **FOUR** or more previous therapies; **AND**
    1. Selinexor (Xpovio) will be used in combination with dexamethasone.

Supporting Evidence

I. As of February 2021, selinexor (Xpovio) has three FDA-approved indications:
- In combination with bortezomib and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy
- In combination with dexamethasone in adult patients with multiple myeloma who have previously received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (penta-refractory)
- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

II. Multiple myeloma (MM)
- Selinexor (Xpovio) is indicated for use in two different multiple myeloma settings: (1) received at least one prior therapy (*BOSTON trial*) and (2) received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody *(STORM trial*).
- Selinexor (Xpovio) for treatment in the setting of penta-refractory MM was approved via the accelerated approval pathway, and continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. Results from the BOSTON trial confirmed continued approval for use in the setting of penta-refractory MM.
  i. **STORM**: Phase 2, open-label trial of 79 patients in combination with dexamethasone only. No other oncolytic therapies were included in the drug regimen. Patients included were previously treated with glucocorticoids, an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb **and** refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.
     1. The primary endpoint was objective response rate (ORR), which occurred in 21%. Secondary outcomes included progression free survival (PFS) and overall survival (OS), which resulted in 2.3 and 9.3 months, respectively.
     2. The safety profile is as follows: Sixty percent of patients in the trial experienced grade 3-4 adverse events including thrombocytopenia, anemia, and neutropenia. Additionally, other serious adverse events occurred such as febrile neutropenia, serious infections, and fatal serious bleeding.
     3. Selinexor (Xpovio) has not been sufficiently studied in the penta-refractory setting with further clinical evaluation of safety and efficacy needed to confirm a net health benefit and place in therapy for this medication.
  ii. **BOSTON**: Phase 3, randomized, open-label trial of 402 patients in combination with bortezomib and dexamethasone (N= 195 SEL-BTZ-Dex) compared to a combination with bortezomib and dexamethasone only (N=207 BTZ-Dex). Patients included had

received one to three previous different regimens for multiple myeloma. Patients who previously received proteasome inhibitors (mono- or combination therapy) were required to have had at least a partial response and at least a 6-month interval since their last proteasome inhibitor therapy, with no history of discontinuation of bortezomib due to Grade 3+ AEs.

1. The primary efficacy endpoint was progression free survival (PFS), which was 13.93 months in the SEL-BTZ-Dex arm versus 9.46 months in the BTZ-Dex arm. Key secondary endpoints were overall survival (OS), which was not reached in the SEL-BTZ-Dex arm versus 25 months in the BTZ-Dex arm; overall response rate (ORR) of 76.4% in the SEL-BTZ-Dex arm versus 62.3% in the BTZ-Dex arm; duration of response (DoR) of 20.3 months in the SEL-BTZ-Dex arm versus 12.9 months in the BTZ-Dex arm; time to response (TTR) of 1.1 months in the SEL-BTZ-Dex arm versus 1.4 months in the BTZ-Dex arm.
2. Safety results were analyzed in all patients who received at least one dose of the study drug (N=195 SEL-BTZ-Dex, N=204 BTZ-Dex). The most common adverse events (≥20% incidence) included thrombocytopenia, anemia, nausea, fatigue, decreased appetite, diarrhea, peripheral neuropathy, weight loss, asthenia, cataract, and vomiting. Selinexor (Xpovio) showed an 81% treatment discontinuation rate: 21% due to adverse events versus 16% in the BTZ-Dex arm.

- Recommended dosage for MM:
    i. In combination with bortezomib and dexamethasone is selinexor (Xpovio) 100 mg taken orally once weekly on Day 1 of each week until disease progression or unacceptable toxicity.
    ii. In combination with dexamethasone is selinexor (Xpovio) 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for previously treated multiple myeloma has included selinexor (Xpovio) in combination with bortezomib and dexamethasone as “Other Recommended Regimens” (Category 1 recommendation). Additionally, NCCN recommends selinexor (Xpovio) in combination with dexamethasone as “Useful in Certain Circumstances” for patients with relapsed/refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (Category 2A recommendation).

III. Diffuse large B-cell lymphoma (DLBCL)

- **SADAL**: Phase 2, an open-label, single-arm, multi-cohort trial of 127 patients with de novo DLBCL or DLBCL transformed from previously diagnosed indolent lymphoma,

previously treated with two to five lines of therapy and progressed after, or were not candidates for autologous stem-cell transplantation were included. Previous systemic regimens permitted included at least one course of anthracycline-based chemotherapy (unless contraindicated due to cardiac dysfunction, in which case, other active drugs such as etoposide, bendamustine, or gemcitabine were given) and at least one course of anti-CD20 immunotherapy such as rituximab. Low dose dexamethasone (4 mg) was permitted as it does not show anti-lymphoma activity. FDA approval was based on the overall response rate (ORR).

i. The primary efficacy endpoint was overall response rate (ORR), which occurred in 28%, and the secondary endpoint was duration of response (DoR), which was 9.3 months. Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.

ii. Safety results were analyzed in all patients who received at least one dose of selinexor (Xpovio) (N=125). The most common adverse events (≥20% incidence) included thrombocytopenia, nausea, fatigue, anemia, decreased appetite, diarrhea, constipation, neutropenia, weight loss, vomiting, pyrexia, and asthenia. There are no specific contraindications to selinexor (Xpovio); however, warnings and precautions include: thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, serious infection, neurological toxicity, and embryo-fetal toxicity. Selinexor (Xpovio) showed a 93% treatment discontinuation rate: 63% due to disease progression, 10% withdrawal by patient, 7% death, 6% physician decision, and 7% due to adverse events.

- Selinexor (Xpovio) for treatment in the setting of DLBCL received accelerated approval from the FDA based on ORR and DoR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 2/3 trial underway to assess rituximab + gemcitabine + dexamethasone + platinum (R-GDP) with or without selinexor (Xpovio) in patients with relapsed/refractory diffuse large B-cell lymphoma.
- Recommended dosage for DLBCL:
    i. Selinexor (Xpovio) 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for B-cell lymphomas has included selinexor (Xpovio) as third-line and subsequent treatment with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

I. Selinexor (Xpovio) has not been sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Quadruple ("quad") regimen
      i. Although triplet regimens remain the standard of care for multiple myeloma, there is growing interest in quad regimens which may include the addition of monoclonal antibodies (e.g., daratumumab [Darzalex], elotuzumab [Empliciti]) to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.
   B. Diffuse large B-cell lymphoma
      i. Refer to SADAL trial information under Supporting Evidence

Appendix

Table 1: Classification of Medications used for Multiple Myeloma

Proteasome Inhibitors	Immunomodulatory Agents	Monoclonal Antibodies	Histone Deacetylase Inhibitors	B-cell Maturation Antigen-Directed Antibody	Chemotherapy
• bortezomib • carfilzomib • ixazomib	• thalidomide • lenalidomide • pomalidomide	• elotuzumab • daratumumab • isatuximab-irfc	• panobinostat	• belantamab mafodotin-blmf	• cyclophosphamide • doxorubicin • cisplatin • etoposide • melphalan • bendamustine

Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions

	MM In combination with Bortezomib and Dexamethasone	MM In combination with Dexamethasone	DLBCL
Recommended Starting Dosage	100 mg once weekly	80 mg Days 1 and 3 of each week (160 mg total per week)	60 mg Days 1 and 3 of each week (120 mg total per week)
First Reduction	80 mg once weekly	100 mg once weekly	40 mg Days 1 and 3 of each week (80 mg total per week)
Second Reduction	60 mg once weekly	80 mg once weekly	60 mg once weekly
Third Reduction	40 mg once weekly	60 mg once weekly	40 mg once weekly

Fourth Reduction	Permanently discontinue	Permanently discontinue	Permanently discontinue

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added split fill management, length of authorization. Updated quantity limits to include 40 mg tablet once weekly carton, as well as DLBCL dosage forms. Updated penta-refractory MM indication from E/I to allow criteria coverage. Added criteria coverage for new MM indication of at least one prior therapy. Added new DLBCL indication and quad-regimen for MM as E/I. Added additional supporting evidence to include more details surrounding all three indications. Added "Table 1: Classification of Medications used for Multiple Myeloma" and "Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions" under Appendix.	02/2021
Policy created	08/2019