HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XPOVIO safely and effectively. See full prescribing information for XPOVIO.

XPOVIO® (selinexor) tablets, for oral use

Initial U.S. Approval: 2019

----------RECENT MAJOR CHANGES----------

Indications and Usage, Diffuse Large B-Cell Lymphoma (1.2)	06/2020
Dosage and Administration (2.2, 2.3, 2.5)	06/2020
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5, 5.6)	06/2020

----------INDICATIONS AND USAGE----------

XPOVIO is a nuclear export inhibitor indicated:

- In combination with dexamethasone for the treatment of adult patients with relapsed or 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 (1.1).
- For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy (1.2).

These indications are approved under accelerated approval based on response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials (1).

----------DOSAGE AND ADMINISTRATION----------

- Multiple Myeloma: Recommended dosage of XPOVIO is 80 mg in combination with dexamethasone taken orally on Days 1 and 3 of each week (2.1).
- DLBCL: Recommended dosage of XPOVIO is 60 mg taken orally on Days 1 and 3 of each week (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 20 mg (3).

----------CONTRAINDICATIONS----------

None (4).

----------WARNINGS AND PRECAUTIONS----------

- Thrombocytopenia: Monitor platelet counts throughout treatment. Manage with dose interruption and/or reduction and supportive care (2.5, 5.1).
- Neutropenia: Monitor neutrophil counts throughout treatment. Manage with dose interruption and/or reduction and granulocyte colony-stimulating factors (2.5, 5.2).
- Gastrointestinal Toxicity: Nausea, vomiting, diarrhea, anorexia, and weight loss may occur. Provide antiemetic prophylaxis. Manage with dose interruption and/or reduction, antiemetics, and supportive care (2.5, 5.3).
- Hyponatremia: Monitor serum sodium levels throughout treatment. Correct for concurrent hyperglycemia and high serum paraprotein levels. Manage with dose interruption, reduction, or discontinuation, and supportive care (2.5, 5.4).
- Serious Infection: Monitor for infection and treat promptly (5.2, 5.5).
- Neurological Toxicity: Advise patients to refrain from driving and engaging in hazardous occupations or activities until neurological toxicity resolves. Optimize hydration status and concomitant medications to avoid dizziness or mental status changes (5.6).
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential and males with a female partner of reproductive potential, of the potential risk to a fetus and use of effective contraception (5.7, 8.1, 8.3).

----------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence ≥20%) in patients with multiple myeloma are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection (6.1).
- The most common adverse reactions (incidence ≥20%) in patients with DLBCL, excluding laboratory abnormalities, are fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia. Grade 3-4 laboratory abnormalities (≥15%) are thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Karyopharm Therapeutics Inc. at 1-888-209-9326 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

XPOVIO in combination with dexamethasone is indicated for the treatment of adult patients with relapsed or 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.

This indication is approved under accelerated approval based on response rate *[see Clinical Studies (14.1)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

1.2 Diffuse Large B-Cell Lymphoma

XPOVIO is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy.

This indication is approved under accelerated approval based on response rate *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Multiple Myeloma

The recommended dosage of XPOVIO is 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity. Administer dexamethasone 20 mg orally with each dose of XPOVIO on Days 1 and 3 of each week. For additional information regarding the administration of dexamethasone, refer to its prescribing information.

2.2 Recommended Dosage for Diffuse Large B-Cell Lymphoma

The recommended dosage of XPOVIO is 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.

2.3 Recommended Monitoring for Safety

Monitor complete blood count (CBC) with differential, standard blood chemistries, body weight, nutritional status, and volume status at baseline and during treatment as clinically indicated. Monitor more frequently during the first three months of treatment *[see Warning and Precautions (5.1, 5.2, 5.3, and 5.4)]*. Assess the need for dosage modifications of XPOVIO for adverse reactions *[see Dosage and Administration (2.5)]*.

2.4 Recommended Concomitant Treatments

Advise patients to maintain adequate fluid and caloric intake throughout treatment. Consider intravenous hydration for patients at risk of dehydration *[see Warnings and Precautions (5.3, 5.4)]*.

Provide prophylactic antiemetics. Administer a 5-HT3 receptor antagonist and other anti-nausea agents prior to and during treatment with XPOVIO *[see Warnings and Precautions (5.3)]*.

2.5 Dosage Modification for Adverse Reactions

Recommended XPOVIO dosage reduction steps are presented in Table 1.

Table 1: XPOVIO Dosage Reduction Steps for Adverse Reactions

	Multiple Myeloma	Diffuse Large B-Cell Lymphoma
Recommended Starting Dosage	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	100 mg once weekly	40 mg Days 1 and 3 of each week (80 mg total per week)
Second Reduction	80 mg once weekly	60 mg once weekly
Third Reduction	60 mg once weekly	40 mg once weekly
Fourth Reduction	Permanently discontinue	Permanently discontinue

Recommended dosage modifications for hematologic adverse reactions in patients with multiple myeloma and DLBCL are presented in Table 2 and Table 3, respectively. Recommended dosage modifications for non-hematologic adverse reactions are presented in Table 4.

Table 2: XPOVIO Dosage Modification Guidelines for Hematologic Adverse Reactions in Patients with Multiple Myeloma

Adverse Reaction	Occurrence	Action
Thrombocytopenia *[see Warning and Precautions (5.1)]*		
Platelet count 25,000 to less than 75,000/mcL	Any	• Reduce XPOVIO by 1 dose level (see Table 1).
Platelet count 25,000 to less than 75,000/mcL *with* concurrent bleeding	Any	• Interrupt XPOVIO. • Restart XPOVIO at 1 dose level lower (see Table 1) after bleeding has resolved. • Administer platelet transfusions per clinical guidelines.
Platelet count less than 25,000/mcL	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Restart XPOVIO at 1 dose level lower (see Table 1).
Neutropenia *[see Warning and Precautions (5.2)]*		
Absolute neutrophil count of 0.5 to 1 x 10^9/L without fever	Any	• Reduce XPOVIO by 1 dose level (see Table 1).
Absolute neutrophil count less than 0.5 x 10^9/L *OR* febrile neutropenia	Any	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1 x 10^9/L or higher. • Restart XPOVIO at 1 dose level lower (see Table 1).
Anemia		
Hemoglobin less than 8 g/dL	Any	• Reduce XPOVIO by 1 dose level (see Table 1). • Administer blood transfusions per clinical guidelines.
Life-threatening consequences	Any	• Interrupt XPOVIO. • Monitor hemoglobin until levels return to 8 g/dL or higher. • Restart XPOVIO at 1 dose level lower (see Table 1). • Administer blood transfusions per clinical guidelines.

Table 3: XPOVIO Dosage Modification Guidelines for Hematologic Adverse Reactions in Patients with Diffuse Large B-Cell Lymphoma

Adverse Reaction	Occurrence	Action
Thrombocytopenia *[see Warning and Precautions (5.1)]*		
Platelet count 50,000 to less than 75,000/mcL	Any	• Interrupt one dose of XPOVIO. • Restart XPOVIO at the same dose level.
Platelet count 25,000 to less than 50,000/mcL *without* bleeding	1st	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Reduce XPOVIO by 1 dose level (see Table 1).
Platelet count 25,000 to less than 50,000/mcL *with* concurrent bleeding	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Restart XPOVIO at 1 dose level lower (see Table 1), after bleeding has resolved. • Administer platelet transfusions per clinical guidelines.
Platelet count less than 25,000/mcL	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Restart XPOVIO at 1 dose level lower (see Table 1). • Administer platelet transfusions per clinical guidelines.
Neutropenia *[see Warning and Precautions (5.2)]*		
Absolute neutrophil count of 0.5 to less than 1 x 10^9/L without fever	1st occurrence	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1 x 10^9/L or higher. • Restart XPOVIO at the same dose level.
	Recurrence	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1 x 10^9/L or higher. • Administer growth factors per clinical guidelines. • Restart XPOVIO at 1 dose level lower (see Table 1).
Absolute neutrophil count less than 0.5 x 10^9/L *OR* Febrile neutropenia	Any	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1 x 10^9/L or higher. • Administer growth factors per clinical guidelines. • Restart XPOVIO at 1 dose level lower (see Table 1).
Anemia		
Hemoglobin less than 8 g/dL	Any	• Reduce XPOVIO by 1 dose level (see Table 1). • Administer blood transfusions per clinical guidelines.
Life-threatening consequences	Any	• Interrupt XPOVIO. • Monitor hemoglobin until levels return to 8 g/dL or higher. • Restart XPOVIO at 1 dose level lower (see Table 1). • Administer blood transfusions per clinical guidelines.

Table 4: XPOVIO Dosage Modification Guidelines for Non-Hematologic Adverse Reactions

Adverse Reaction	Occurrence	Action
Nausea and Vomiting *[see Warning and Precautions (5.3)]*		
Grade 1 or 2 nausea (oral intake decreased without significant weight loss, dehydration or malnutrition) *OR* Grade 1 or 2 vomiting (5 or fewer episodes per day)	Any	• Maintain XPOVIO and initiate additional anti-nausea medications.
Grade 3 nausea (inadequate oral caloric or fluid intake) *OR* Grade 3 or higher vomiting (6 or more episodes per day)	Any	• Interrupt XPOVIO. • Monitor until nausea or vomiting has resolved to Grade 2 or lower or baseline. • Initiate additional anti-nausea medications. • Restart XPOVIO at 1 dose level lower (see Table 1).
Diarrhea *[see Warning and Precautions (5.3)]*		
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	• Maintain XPOVIO and institute supportive care.
	2nd and subsequent	• Reduce XPOVIO by 1 dose level (see Table 1). • Institute supportive care.
Grade 3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated)	Any	• Interrupt XPOVIO and institute supportive care. • Monitor until diarrhea resolves to Grade 2 or lower. • Restart XPOVIO at 1 dose level lower (see Table 1).

Weight Loss and Anorexia *[see Warning and Precautions (5.3)]*		
Weight loss of 10% to less than 20% *OR* anorexia associated with significant weight loss or malnutrition	Any	• Interrupt XPOVIO and institute supportive care. • Monitor until weight returns to more than 90% of baseline weight. • Restart XPOVIO at 1 dose level lower (see Table 1).
Hyponatremia *[see Warning and Precautions (5.4)]*		
Sodium level 130 mmol/L or less	Any	• Interrupt XPOVIO, evaluate, and provide supportive care. • Monitor until sodium levels return to greater than 130 mmol/L. • Restart XPOVIO at 1 dose level lower (see Table 1).
Fatigue		
Grade 2 lasting greater than 7 days *OR* Grade 3	Any	• Interrupt XPOVIO. • Monitor until fatigue resolves to Grade 1 or baseline. • Restart XPOVIO at 1 dose level lower (see Table 1).
Ocular Toxicity		
Grade 2, excluding cataract	Any	• Perform ophthalmologic evaluation. • Interrupt XPOVIO and provide supportive care. • Monitor until ocular symptoms resolve to Grade 1 or baseline. • Restart XPOVIO at 1 dose level lower (see Table 1).
Grade ≥3	Any	• Permanently discontinue XPOVIO. • Perform ophthalmologic evaluation.
Cataract (Grade ≥2)	Any	• Perform ophthalmologic evaluation. • Reduce XPOVIO by 1 dose level (see Table 1). • Monitor for progression. • Hold XPOVIO dose 24 hours prior to surgery and for 72 hours after surgery.
Other Non-Hematologic Adverse Reactions *[see Warning and Precautions (5.6)]*		
Grade 3 or 4	Any	• Interrupt XPOVIO. • Monitor until resolved to Grade 2 or lower; restart XPOVIO at 1 dose level lower (see Table 1).

2.6 Administration

Each XPOVIO dose should be taken at approximately the same time of day and each tablet should be swallowed whole with water. Do not break, chew, crush, or divide the tablets.

If a dose of XPOVIO is missed or delayed, instruct patients to take their next dose at the next regularly scheduled time.

If a patient vomits a dose of XPOVIO, the patient should not repeat the dose and the patient should take the next dose on the next regularly scheduled day.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg, blue, round, bi-convex, film-coated tablets with “K20” debossed on one side and nothing on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia

XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia is the leading cause of dosage modifications *[see Adverse Reactions (6.1)]*.

In patients with multiple myeloma receiving XPOVIO 80 mg twice weekly (n=202), thrombocytopenia was reported as an adverse reaction in 74% of patients, and severe (Grade 3-4) thrombocytopenia was reported in 61% of patients. The median time to onset of the first event was 22 days. Bleeding occurred in 23% of patients with thrombocytopenia, clinically significant bleeding occurred in 5% of patients with thrombocytopenia, and fatal hemorrhage occurred in <1% of patients.

In patients with DLBCL receiving XPOVIO 60 mg twice weekly (n=134), thrombocytopenia developed or worsened in 86% of patients, including Grade 3-4 thrombocytopenia in 49% of patients (Grade 4, 18%). The median time to first onset was 28 days for any-grade thrombocytopenia and 33 days for Grade 3 or higher thrombocytopenia.

Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)]*.

5.2 Neutropenia

XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection *[see Adverse Reactions (6.1)]*.

In patients with multiple myeloma (n=202), neutropenia was reported as an adverse reaction in 34% of patients and severe (Grade 3-4) neutropenia occurred in 21% of patients treated with XPOVIO. The median time to onset of the first event was 25 days. Febrile neutropenia was reported in 3% of patients.

In patients with DLBCL (n=134), Grade 3 neutropenia developed in 21% of patients and Grade 4 neutropenia developed in 9% of patients. The median time to first onset of Grade 3 or higher neutropenia was 32 days. Febrile neutropenia was reported in 3% of patients.

Obtain white blood cell counts with differential at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)]*.

5.3 Gastrointestinal Toxicity

XPOVIO can cause severe gastrointestinal toxicities *[see Adverse Reactions (6.1)]*. In patients with DLBCL (n=134), gastrointestinal toxicity occurred in 80% of patients with Grade 3 or 4 in 13%.

Nausea/Vomiting

In patients with multiple myeloma (n=202), with use of antiemetic prophylaxis, nausea was reported as an adverse reaction in 72% of patients and Grade 3 nausea occurred in 9% of patients treated with XPOVIO. The median time to first onset of nausea was 3 days. Vomiting was reported in 41% of patients, and Grade 3 vomiting occurred in 4% of patients. The median time to first onset of vomiting was 5 days.

In patients with DLBCL (n=134) with use of antiemetic prophylaxis, nausea occurred in 57% of patients and Grade 3 nausea occurred in 6% of patients. Vomiting occurred in 28% of patients and Grade 3 vomiting occurred in 1.5% of patients. The median time to first onset was 3 days for nausea and 7 days for vomiting.

Provide prophylactic antiemetics. Administer 5-HT3 receptor antagonists and other anti-nausea agents prior to and during treatment with XPOVIO. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)]*. Administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Diarrhea

In patients with multiple myeloma, diarrhea was reported as an adverse reaction in 44% of patients and Grade 3 diarrhea occurred in 6% of patients treated with XPOVIO. The median time to onset of diarrhea was 15 days.

In patients with DLBCL, diarrhea occurred in 37% of patients and Grade 3 diarrhea occurred in 3% of patients treated with XPOVIO. The median time to onset of the first event was 12 days.

Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)]*. Provide standard anti-diarrheal agents, administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Anorexia/Weight Loss

In patients with multiple myeloma, anorexia was reported as an adverse reaction in 53% of patients, and Grade 3 anorexia occurred in 5% of patients treated with XPOVIO. The median time to onset of anorexia was 8 days. Weight loss was reported as an adverse reaction in 47% of patients, and Grade 3 weight loss occurred in 1% of patients treated with XPOVIO. The median time to onset of weight loss was 15 days.

In patients with DLBCL, anorexia was reported as an adverse reaction in 37% of patients and Grade 3 anorexia occurred in 3.7% of patients treated with XPOVIO. Weight loss (Grade 1-2) was reported as an adverse reaction in 30% of patients.

Monitor weight, nutritional status, and volume status at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)]*. Provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

5.4 Hyponatremia

XPOVIO can cause severe or life-threatening hyponatremia *[see Adverse Reactions (6.1)]*.

In patients with multiple myeloma (n=202), hyponatremia was reported as an adverse reaction in 39% of patients and Grade 3 or 4 hyponatremia was reported in 22% of patients treated with XPOVIO. The median time to onset of the first event was 8 days.

In patients with DLBCL (n=134), hyponatremia developed in 62% of patients and Grade 3 hyponatremia developed in 16% of patients treated with XPOVIO. In approximately 63% of cases, hyponatremia occurred in the context of gastrointestinal toxicity such as nausea, vomiting, diarrhea, dehydration, and anorexia.

Monitor sodium level at baseline and throughout treatment. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Assess hydration status and manage hyponatremia per clinical guidelines, including intravenous saline and/or salt tablets as appropriate and dietary review. Interrupt, reduce dose or permanently discontinue based on severity of the adverse reaction *[see Dosage and Administration (2.5)]*.

5.5 Serious Infection

XPOVIO can cause serious and fatal infections. Most of these infections were not associated with Grade 3 or higher neutropenia *[see Adverse Reactions (6.1)]*.

In patients with multiple myeloma (n=202), 52% of patients experienced any grade of infection after XPOVIO. Grade ≥3 infections were reported in 25% of patients, and deaths from infection occurred in 4% of patients within 30 days of last treatment. Upper respiratory tract infection of any grade occurred in 21%, pneumonia in 13%, and sepsis in 6% of patients. The most frequently reported Grade ≥3 infections were pneumonia in 9% of patients, followed by sepsis in 6%. The median time to onset was 54 days for pneumonia and 42 days for sepsis.

In patients with DLBCL (n=134), 25% of patients experienced Grade 3 or higher infection and 21% had an infection-related serious adverse reaction; 49% developed an infection of any grade, most frequently involving the upper or lower respiratory tract. The most frequently reported Grade ≥3 infections were lower respiratory tract infections in 9% of patients (including pneumonia in 6%), followed by sepsis (6%). The median time to onset of Grade ≥3 infection was 42 days.

Atypical infections reported after XPOVIO include, but are not limited to, fungal pneumonia and herpesvirus infection.

Monitor for signs and symptoms of infection, evaluate and treat promptly.

5.6 Neurological Toxicity

XPOVIO can cause life-threatening neurological toxicities *[see Adverse Reactions (6.1)]*.

In patients with multiple myeloma (n=202), neurological adverse reactions, including dizziness, syncope, depressed level of consciousness, and mental status changes (including delirium and confusional state) occurred in 30% of patients and severe events (Grade 3-4) occurred in 9% of patients treated with XPOVIO. The median time to the first event was 15 days.

In patients with DLBCL (n=134), neurological adverse reactions occurred in 25% of patients and severe events (Grade 3-4) occurred in 6% of patients treated with XPOVIO. The most frequent manifestations were dizziness (16%) and mental status changes (11%), including confusion, cognitive disorders, somnolence, hallucination, delirium, and depressed level of consciousness. Syncope occurred in 2.2% of patients. The median time to the first event was 28 days. Among patients with such neurological adverse reactions, 68% recovered with a median time to recovery of 14 days.

Coadministration of XPOVIO with other products that cause dizziness or mental status changes may increase the risk of neurological toxicity.

Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until the neurological toxicity fully resolves. Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes. Institute fall precautions as appropriate.

5.7 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. Selinexor administration to pregnant animals during organogenesis resulted in structural abnormalities and alterations to growth at exposures below those occurring clinically at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in detail in other labeling sections:

- Thrombocytopenia [*see Warnings and Precautions (5.1)]*.
- Neutropenia *[see Warnings and Precautions (5.2)]*.
- Gastrointestinal Toxicity *[see Warnings and Precautions (5.3)]*.
- Hyponatremia *[see Warnings and Precautions (5.4)]*.
- Serious Infection *[see Warnings and Precautions (5.5)]*.
- Neurological Toxicity *[see Warnings and Precautions (5.6)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Multiple Myeloma

The safety of XPOVIO in combination with dexamethasone was evaluated in STORM *[see Clinical Studies (14.1)]*. Patients received XPOVIO 80 mg orally with dexamethasone 20 mg on Days 1 and 3 of every week (n=202). The median duration of XPOVIO treatment was 8 weeks (range: 1 to 60 weeks). The median dose was 115 mg (range: 36 to 200 mg) per week.

Fatal adverse reactions occurred in 9% of XPOVIO treated patients. Serious adverse reactions occurred in 58% of patients.

The treatment discontinuation rate due to adverse reactions was 27%; 53% of patients had a reduction in the XPOVIO dose, and 65% had the dose of XPOVIO interrupted. Thrombocytopenia was the leading cause of dose modification, resulting in dose reduction and/or interruption in >25% of patients. The most frequent adverse reactions requiring permanent discontinuation in 4% or greater of patients who received XPOVIO included fatigue, nausea, and thrombocytopenia.

Table 5 summarizes the adverse reactions in STORM.

Table 5: Adverse Reactions (≥10%) in Patients Who Received XPOVIO in STORM

	XPOVIO 80 mg twice weekly + Dexamethasone (n=202)	
Adverse Reaction	**All Grades (%)**	**Grades ≥3 (%)**
Thrombocytopenia[a]	74	61
Fatigue[b]	73	22
Nausea	72	9
Anemia[c]	59	40
Decreased appetite	53	4.5
Weight decreased	47	0.5
Diarrhea	44	6
Vomiting	41	3.5
Hyponatremia	39	22
Neutropenia[d]	34	21
Leukopenia	28	11
Constipation	25	1.5
Dyspnea[e]	24	3.5[k]
Upper respiratory tract infection[f]	21	3
Cough[g]	16	0
Mental status changes[h]	16	7
Pyrexia	16	0.5
Hyperglycemia	15	7
Dizziness	15	0
Insomnia	15	2
Lymphopenia	15	10
Dehydration	14	3.5
Hypercreatininemia[i]	14	2
Pneumonia[j]	13	9[k]
Epistaxis	12	0.5
Hypokalemia	12	3.5
Dysgeusia	11	0
Vision blurred	10	0.5
Headache	10	0

a. Thrombocytopenia includes thrombocytopenia and platelet count decreased.
b. Fatigue includes fatigue and asthenia.
c. Anemia includes anemia and hematocrit decreased.
d. Neutropenia includes neutropenia and neutrophil count decreased.
e. Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.
f. Upper respiratory tract infection includes upper respiratory tract infection, respiratory tract infection, pharyngitis, nasopharyngitis, bronchitis, bronchiolitis, respiratory syncytial virus infection, parainfluenza virus infection, rhinitis, rhinovirus infection, and adenovirus infection.
g. Cough includes cough, productive cough, and upper-airway cough syndrome.
h. Mental status changes includes mental status changes, confusional state, and delirium.
i. Hypercreatininemia includes hypercreatininemia and hypercreatinemia.
j. Pneumonia includes pneumonia, atypical pneumonia, lung infection, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia aspiration, pneumonia influenzal, and pneumonia viral.
k. Includes fatal event.

Diffuse Large B-Cell Lymphoma

The safety of XPOVIO was evaluated in SADAL *[see Clinical Studies (14.2)]*. Patients received XPOVIO 60 mg orally on Days 1 and 3 of every week (n=134). The study required an absolute neutrophil count ≥1000/μL, platelet count ≥75,000/μL, hepatic transaminases ≤2.5 times upper limit of normal (ULN) unless abnormal from lymphoma, and bilirubin ≤2 times ULN. The study permitted a maximum of 5 prior systemic regimens for DLBCL. Antiemetic prophylaxis with a 5HT-3 receptor antagonist was required. The median duration of XPOVIO treatment was 2.1 months (range: 1 week to 3.7 years) with 38% receiving at least 3 months and 22% receiving at least 6 months of treatment. The median exposure was 100 mg per week.

Fatal adverse reactions occurred in 3.7% of patients within 30 days and 5% of patients within 60 days of last treatment; the most frequent fatal adverse reaction was infection (4.5% of patients). Serious adverse reactions occurred in 46% of patients who received XPOVIO; the most frequent serious adverse reaction was infection (21% of patients).

Discontinuation due to adverse reactions occurred in 17% of patients who received XPOVIO. Adverse reactions which results in discontinuation in ≥2% of patients included: infection, fatigue, thrombocytopenia, and nausea.

Adverse reactions led to XPOVIO dose interruption in 61% of patients and dose reduction in 49%, with 17% of all patients having 2 or more dose reductions. The median time to first dose modification (reduction or interruption) was 4 weeks, with the leading causes being thrombocytopenia (40% of all patients), neutropenia (16%), fatigue (16%), nausea (10%), and anemia (10%). The median time to first dose reduction was 6 weeks, with 83% of first dose reductions occurring within the first 3 months.

The most common adverse reactions, excluding laboratory abnormalities, in ≥20% of patients were fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia. Table 6 summarizes selected adverse reactions in SADAL.

Table 6: Adverse Reactions (≥10%), Excluding Laboratory Terms, in Patients with DLBCL Who Received XPOVIO in SADAL

	XPOVIO 60 mg twice weekly (n=134)	
Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**
General Conditions		
Fatigue[a]	63	15
Pyrexia	22	4.5
Edema[b]	17	2.2
Gastrointestinal		
Nausea	57	6
Diarrhea[c]	37	3.0
Constipation	29	0
Vomiting	28	1.5
Abdominal pain[d]	10	0
Metabolism and Nutrition		
Appetite decrease[e]	37	3.7
Weight decrease	30	0
Respiratory		
Cough[f]	18	0
Dyspnea[g]	10	1.5
Infections		
Upper respiratory tract infection[h]	17	1.5
Pneumonia	10	6
Urinary tract infection[i]	10	3
Nervous System		
Dizziness[j]	16	0.7
Taste disorder[k]	13	0
Mental status changes[l]	11	3.7
Peripheral neuropathy, sensory[m]	10	0
Musculoskeletal		
Musculoskeletal pain[n]	15	2.2
Vascular		
Hypotension	13	3.0
Hemorrhage[o]	10	0.7
Eye Disorders		
Vision blurred[p]	11	0.7

a. **Fatigue** includes fatigue and asthenia.

b. **Edema** includes edema, swelling, swelling face, edema peripheral, peripheral swelling, acute pulmonary edema.

c. **Diarrhea** includes diarrhea, post-procedural diarrhea, gastroenteritis.

d. **Abdominal pain** includes abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort.

e. **Appetite decrease** includes decreased appetite and hypophagia.

f. **Cough** includes cough and productive cough.

g. **Dyspnea** includes dyspnea and dyspnea exertional.

h. **Upper respiratory tract infection** includes upper respiratory tract infection, sinusitis, nasopharyngitis, pharyngitis, rhinitis, viral upper respiratory infection.

i. **Urinary tract infection** includes urinary tract infection and specific types of urinary tract infection.

j. **Dizziness** includes dizziness and vertigo.

k. **Taste disorder** includes taste disorder, dysgeusia, ageusia.

l. **Mental status changes** include confusional state, amnesia, cognitive disorder, hallucination, delirium, somnolence, depressed level of consciousness, memory impairment.

m. **Peripheral neuropathy** includes peripheral neuropathy, peripheral sensory neuropathy, sensory disturbance, paresthesia, neuralgia.

n. **Musculoskeletal pain** includes musculoskeletal pain, back pain, musculoskeletal chest pain, neck pain, pain in extremity, bone pain.

o. **Hemorrhage** includes hemorrhage, hematoma, hematuria, epistaxis, rectal hemorrhage, injection site hematoma, subdural hematoma, upper gastrointestinal hemorrhage, corneal bleeding.

p. **Vision blurred** includes vision blurred, visual acuity reduced, visual impairment.

Clinically relevant adverse reactions in <10% of patients who received XPOVIO included:

- **Injury:** fall (8%)
- **Metabolic and nutrition disorders:** dehydration (7%)
- **Neurologic disorders:** headache (4.5%), syncope (2.2%)
- **Infection:** sepsis (6%), herpesvirus infection (3%)
- **Eye disorders:** cataract (3.7%)
- **Blood and lymphatic disorders:** febrile neutropenia (3%)
- **Cardiac disorders:** cardiac failure (3%)

Table 7 summarizes selected new or worsening laboratory abnormalities in SADAL. Grade 3-4 laboratory abnormalities in ≥15% included thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia. Grade 4 laboratory abnormalities in ≥5% were thrombocytopenia (18%), lymphopenia (5%), and neutropenia (9%).

Table 7: Select Laboratory Abnormalities (≥15%) Worsening from Baseline in Patients with DLBCL Who Received XPOVIO in SADAL

	XPOVIO 60 mg twice weekly	
Laboratory Abnormality	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematologic		
Platelet count decrease	86	49
Hemoglobin decrease	82	25
Lymphocyte count decrease	63	37
Neutrophil count decrease	58	31
Chemistry		
Sodium decrease	62	16
Glucose increase	57[a]	5
Creatinine increase	47	3.9
Phosphate decrease	34	11
Magnesium decrease	30	2.6
Calcium decrease	30	0.9
Potassium increase	26	3.9
Potassium decrease	23	7
CK increase[b]	21	1.9
Hepatic		
ALT increase	29	0.8
Albumin decrease	25	0
AST increase	24	3.1
Bilirubin increase	16	1.6

The denominator used to calculate the rate varied from 107 to 128 based on the number of patients with at least one post-treatment value.

a. Not fasting.

b. CK increase was not associated with reports of myopathy or myalgia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)],* XPOVIO can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures that were below those occurring clinically at the recommended dose *(see Data).* Advise pregnant women of the risks to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

In an embryo-fetal development study in pregnant rats, daily oral administration of selinexor at 0, 0.25, 0.75, or 2 mg/kg throughout organogenesis caused incomplete or delayed ossification, skeletal variations, and reduced fetal weight compared with controls at a dose of 0.75 mg/kg (approximately 0.08-fold of human area under the curve [AUC] at the recommended dose). Malformations were observed at 2 mg/kg, including microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus.

8.2 Lactation

Risk Summary

There is no information regarding the presence of selinexor or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with XPOVIO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

XPOVIO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)].*

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating XPOVIO *[see Use in Specific Populations (8.1)].*

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Males

Advise males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Infertility

Females and Males

Based on findings in animals, XPOVIO may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)].*

8.4 Pediatric Use

The safety and effectiveness of XPOVIO have not been established in pediatric patients.

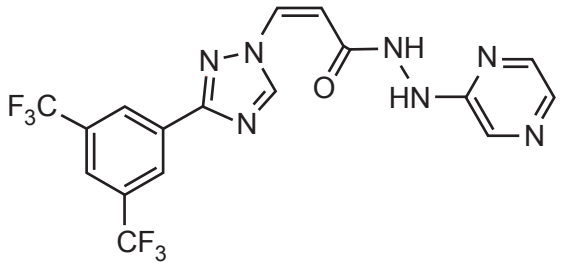
8.5 Geriatric Use

Of the 202 patients with multiple myeloma who received XPOVIO, 49% were 65 years of age and over, while 11% were 75 years of age and over. No overall difference in effectiveness was observed in patients over 65 years of age, including patients over 75 years of age, when compared with younger patients. When comparing patients 75 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (44% vs 27%), higher incidence of serious adverse reactions (70% vs 58%), and higher incidence of fatal adverse reactions (17% vs 9%).

Among 134 patients with DLBCL who received XPOVIO in SADAL, 61% were 65 years of age and older, while 25% were 75 years of age and older. Clinical studies of XPOVIO in patients with relapsed or refractory DLBCL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

Selinexor is a nuclear export inhibitor. Selinexor is (2Z)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-1-yl}-*N*′-(pyrazin-2-yl) prop-2-enehydrazide. It is a white to off-white powder and has the molecular formula $C_{17}H_{11}F_6N_7O$ and a molecular mass of 443.31 g/mol. The molecular structure is shown below:



Each XPOVIO (selinexor) tablet contains 20 mg of selinexor as the active ingredient. XPOVIO tablets are blue, round, bi-convex, film-coated tablets with “K20” debossed on one side and nothing on the other side. The inactive ingredients are colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry 200 clear, Opadry II blue, povidone K30, and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus and 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 cells and showed anti-tumor activity in murine xenograft models of multiple myeloma and diffuse large B cell lymphoma.

12.2 Pharmacodynamics

An increase in selinexor exposure was associated with an increase in the probability of dose modification and some adverse reactions.

Cardiac Electrophysiology

The effect of multiple doses of XPOVIO, up to 175 mg (2.2 times the maximum approved recommended dose) twice weekly, on the QTc interval was evaluated in patients with heavily pretreated hematologic malignancies. XPOVIO had no large effect (i.e. no greater than 20 ms) on QTc interval at the therapeutic dose level.

12.3 Pharmacokinetics

Selinexor C_{max} and AUC increased proportionally over a dose range from 3 mg/m^2 to 85 mg/m^2 (0.06 to 1.8 times the maximum approved recommended dose, based on 1.7 m^2 body surface area). No clinically relevant

accumulation at steady state was observed. Selinexor C_{max} and $AUC_{0\text{-}INF}$ after administration of a single dose of XPOVIO in patients with hematologic malignancies are presented in Table 8.

Table 8: Selinexor C_{max} and AUC After Administration of a Single Dose of XPOVIO

	XPOVIO Dose	
Mean (SD)	60 mg	80 mg
C_{max} (ng/mL)	442 (188)	680 (124)
$AUC_{0\text{-}INF}$ (ng·h/mL)	4,096 (1,185)	5,386 (1,116)

Absorption

The C_{max} is reached within 4 hours following oral administration of XPOVIO.

Effect of Food

Concomitant administration of a high-fat meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) did not affect the pharmacokinetics of selinexor to a clinically significant extent.

Distribution

The apparent volume of distribution of selinexor is 133 L in patients with cancer. The protein binding of selinexor is 95%.

Elimination

Following a single dose of XPOVIO, the mean half-life is 6 to 8 hours. The apparent total clearance of selinexor is 18.6 L/h in patients with cancer.

Metabolism

Selinexor is metabolized by CYP3A4, multiple UDP-glucuronosyl-transferases (UGTs) and glutathione S-transferases (GSTs).

Specific Populations

No clinically significant differences in the pharmacokinetics of selinexor were observed based on age (18 to 94 years old), sex, body weight (36 to 168 kg), ethnicity, mild to severe renal impairment (CL_{CR}: 15 to 89 mL/min, estimated by the Cockcroft-Gault equation), and disease type (hematological non-DLBCL, solid tumor, DLBCL). The effect of end-stage renal disease (CL_{CR} <15 mL/min) or hemodialysis on selinexor pharmacokinetics is unknown. Mild hepatic impairment had no clinically significant effect on the pharmacokinetics of selinexor. The effect of moderate and severe hepatic impairment on selinexor pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

Acetaminophen: No clinically significant differences in selinexor pharmacokinetics were observed when co-administered with acetaminophen (up to 1,000 mg daily dose of acetaminophen).

In vitro Studies

CYP Enzymes: Selinexor does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. Selinexor is not a CYP3A4, CYP1A2, or CYP2B6 inducer.

Non-CYP Enzyme Systems: Selinexor is a substrate of UGTs and GSTs.

Transporter Systems: Selinexor inhibits OATP1B3 but does not inhibit other solute carrier (SLC) transporters. Selinexor is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with selinexor.

Selinexor was not mutagenic in vitro in a bacterial reverse mutation (Ames) assay and was not clastogenic in either the in vitro cytogenetic assay in human lymphocytes or in the in vivo rat micronucleus assay.

Fertility studies in animals have not been conducted with selinexor. In repeat-dose oral toxicity studies, selinexor was administered for up to 13 weeks in rats and monkeys. Reduced sperm, spermatids, and germ cells in epididymides and testes were observed in rats at ≥1 mg/kg, decreased ovarian follicles were observed in rats at ≥2 mg/kg, and single cell necrosis of testes was observed in monkeys at ≥1.5 mg/kg. These dose levels resulted in systemic exposures approximately 0.11, 0.28, and 0.53 times, respectively, the exposure (AUC_{last}) in humans at the recommended human dose of 80 mg.

14 CLINICAL STUDIES

14.1 Relapsed Refractory Multiple Myeloma

The efficacy of XPOVIO plus dexamethasone was evaluated in STORM (KCP-330-012; NCT02336815). STORM was a multicenter, single-arm, open-label study of adults with relapsed or refractory multiple myeloma (RRMM). STORM Part 2 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; and whose myeloma was documented to be refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory agent, an anti-CD38 monoclonal antibody, and to the last line of therapy.

In STORM Part 2, a total of 122 patients received XPOVIO 80 mg orally in combination with dexamethasone 20 mg orally on Days 1 and 3 of every week. Treatment continued until disease progression or unacceptable toxicity. Eighty-three patients had RRMM that was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. Baseline patient demographics and disease characteristics of these 83 patients are summarized in Table 9 and Table 10, respectively.

Efficacy was based on overall response rate (ORR), as assessed by an Independent Review Committee (IRC) based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. The approval of XPOVIO was based upon the efficacy and safety in a prespecified subgroup analysis of the 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, as the benefit-risk ratio appeared to be greater in this more heavily pretreated population than in the overall trial population. Overall response rate results are presented in Table 11. The median time to first response was 4 weeks (range: 1 to 10 weeks). The median duration of response was 3.8 months (95% CI: 2.3, not estimable).

Table 9: Baseline Demographics (STORM)

Demographic	**STORM (n=83)**
Median age, years (range)	65 (40, 86)
Age category, n (%)	
<65 years	40 (48)
65 – 74 years	31 (37)
≥75 years	12 (15)
Sex, n (%)	
Male	51 (61)
Female	32 (39)
Race, n (%)	
White	58 (70)
Black or African American	13 (16)
Asian	2 (2)
Native Hawaiian or other Pacific Islander	1 (1)
Other	6 (7)
Missing	3 (4)

Table 10: Disease Characteristics (STORM)

Parameter	STORM (n=83)
Median years from diagnosis to start of study treatment (range)	7 (1, 23)
Prior treatment regimens, median (range)	8 (4, 18)
Documented refractory status, n (%)	
Lenalidomide	83 (100)
Pomalidomide	83 (100)
Bortezomib	83 (100)
Carfilzomib	83 (100)
Daratumumab	83 (100)
Documented refractory status to specific combinations, n (%)	
Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab	83 (100)
Daratumumab in any combination	57 (69)
Daratumumab as single agent (+/- dexamethasone)	26 (31)
Previous stem cell transplant, n (%)	67 (81)
Revised International Staging System at Baseline, n (%)	
I	10 (12)
II	56 (68)
III	17 (21)
Unknown	0
High-risk cytogenetics[a], n (%)	47 (57)

a. Includes any of del(17p)/p53, t(14; 16), t(4; 14), 1q21.

Table 11: Efficacy Results per IRC in Relapsed or Refractory Multiple Myeloma (STORM)

Response	STORM (n=83)
Overall Response Rate (ORR)[a], n (%)	21 (25.3)
95% CI	16.4, 36
Stringent Complete Response (sCR)	1 (1)
Complete Response (CR)	0
Very Good Partial Response (VGPR)	4 (5)
Partial Response (PR)	16 (19)

a. Includes sCR + CR + VGPR + PR.

14.2 Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The efficacy of XPOVIO monotherapy was evaluated in SADAL (KCP-330-009; NCT02227251). SADAL was a multicenter, single-arm, open-label study of adults with relapsed or refractory DLBCL, not otherwise specified (NOS), after 2 to 5 systemic regimens. Eligible patients were not candidates for autologous hematopoietic stem cell transplantation (HSCT). The study required a minimum of 60 days since last systemic therapy, with a minimum of 98 days in patients with refractory disease (defined as less than partial response) to last systemic therapy.

Patients received XPOVIO 60 mg orally on Days 1 and 3 of each week. Treatment continued until disease progression or unacceptable toxicity.

Of 134 patients evaluated, the median age was 67 years (range: 35-91), 59% were male, 79% were White, and 7% were Asian. Most patients (88%) had an ECOG performance status of 0 or 1. The diagnosis was de novo DLBCL not otherwise specified (NOS) in 75% and transformed DLBCL in 23%. The median number of prior systemic therapies was 2 (range: 1-5), with 63% of patients receiving 2 prior systemic therapies, 24% receiving 3 prior therapies, and 10% receiving 4 or 5 prior therapies. Twenty-eight percent had documented refractory disease to the most recent therapy; 30% had prior autologous HSCT. The median time from last systemic therapy to the start of XPOVIO was 5.4 months overall and 3.6 months in the patients with refractory disease.

Efficacy was based on overall response rate (ORR) and duration of response as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria (Table 12). The median time to first response was 8.1 weeks (range: 6.7-16.4 weeks).

Table 12: Efficacy Results per IRC in Relapsed or Refractory DLBCL (SADAL)

Parameter	XPOVIO 60 mg twice weekly (n=134)
ORR per Lugano criteria, n (%)	39 (29)
95% CI, %	22, 38
Complete Response	18 (13)
Partial Response	21 (16)
Duration of Response	
Patients maintaining response at 3 months, n/N (%)	22/39 (56)
Patients maintaining response at 6 months, n/N (%)	15/39 (38)
Patients maintaining response at 12 months, n/N (%)	6/39 (15)

16 HOW SUPPLIED/STORAGE AND HANDLING

XPOVIO (selinexor) are blue, round, bi-convex, and film-coated 20 mg tablets with "K20" debossed on one side and nothing on the other side. Tablets are packaged in a child-resistant blister pack. Four blister packs are supplied per carton. The following seven dose presentations are available:

Weekly Dose	Strength per tablet	Carton	Blister Pack	NDC
80 mg twice weekly	20 mg	4 blister packs (32 tablets total in the carton)	Each blister has eight 20 mg tablets	Outer carton NDC 72237-101-04 Blister pack NDC 72237-101-14
60 mg twice weekly	20 mg	4 blister packs (24 tablets total in the carton)	Each blister has six 20 mg tablets	Outer carton NDC 72237-101-03 Blister pack NDC 72237-101-13
100 mg once weekly	20 mg	4 blister packs (20 tablets total in the carton)	Each blister has five 20 mg tablets	Outer carton NDC 72237-101-05 Blister pack NDC 72237-101-15
80 mg once weekly	20 mg	4 blister packs (16 tablets total in the carton)	Each blister has four 20 mg tablets	Outer carton NDC 72237-101-02 Blister pack NDC 72237-101-12

Weekly Dose	Strength per tablet	Carton	Blister Pack	NDC
40 mg twice weekly	20 mg	4 blister packs (16 tablets total in the carton)	Each blister has four 20 mg tablets	Outer carton NDC 72237-101-06 Blister pack NDC 72237-101-16
60 mg once weekly	20 mg	4 blister packs (12 tablets total in the carton)	Each blister has three 20 mg tablets	Outer carton NDC 72237-101-01 Blister pack NDC 72237-101-11
40 mg once weekly	20 mg	4 blister packs (8 tablets total in the carton)	Each blister has two 20 mg tablets	Outer carton NDC 72237-101-07 Blister pack NDC 72237-101-17

Store at or below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Dosing Instructions *[see Dosage and Administration (2)]:*

- Instruct patients to take XPOVIO exactly as prescribed.
- Advise patients to swallow the tablet whole with water. The tablet should not be broken, chewed, crushed, or divided.
- If a patient misses a dose, advise them to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of XPOVIO, advise them to take the next dose on the next regularly scheduled day.
- Advise patients that XPOVIO comes in a child-resistant blister pack.
- Advise patients to take their prescribed dexamethasone (if applicable) and prophylactic anti-nausea medications as directed *[see Dosage and Administration (2.1, 2.3)].*
- Advise patients that blood tests and body weight will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first three months of treatment *[see Dosage and Administration (2.3)].*
- Advise patients to maintain appropriate fluid and caloric intake throughout their treatment *[see Dosage and Administration (2.4)].*

Hematologic Adverse Reactions

Thrombocytopenia

Advise patients that they may develop low platelet counts (thrombocytopenia). Symptoms of thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment. Advise patients to report signs of bleeding right away *[see Warnings and Precautions (5.1)].*

Anemia

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath. Advise patients to report signs or symptoms of anemia *[see Adverse Reactions (6.1)].*

Neutropenia

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection *[see Warnings and Precautions (5.2)].* Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

Gastrointestinal Adverse Reactions

Advise patients they may experience nausea/vomiting or diarrhea and to contact their physician if these adverse reactions occur or persist *[see Warnings and Precautions (5.3)].*

Advise patients that they may experience weight loss or decreased appetite. Advise patients to report decreased appetite and weight loss *[see Warnings and Precautions (5.3)].*

Hyponatremia

Advise patients that they may develop low sodium levels (hyponatremia).Most cases of hyponatremia were not associated with specific symptoms. Advise patients that levels of sodium will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first two months of treatment *[see Warnings and Precautions (5.4)].*

Serious Infection

Advise patients of the possibility of serious infections. Instruct patients to immediately report infection-related signs or symptoms (e.g., chills, fever) *[see Warnings and Precautions (5.5)].*

Neurotoxicity

Advise patients that they may experience confusion and dizziness. Advise patients to report symptoms of neurological toxicity right away. Advise patients not to drive or operate hazardous machinery until the neurological toxicity fully resolves. Advise patients to use fall prevention measures as warranted *[see Warnings and Precautions (5.6)].*

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to contact their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)].*

Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the final dose *[see Use in Specific Populations (8.3)].*

Fatigue

Advise patients that they may experience fatigue *[see Adverse Reactions (6.1)].*

Lactation

Advise women not to breastfeed during treatment with XPOVIO and for 1 week after the final dose *[see Use in Specific Populations (8.2)].*

Concomitant Medications

Advise patients to take 5-HT3 antagonist prophylactic treatment and other anti-nausea agents prior to and during treatment with XPOVIO *[see Dosage and Administration (2.4)].*

Advise patients to speak with their physician about other medications they are currently taking and before starting any new medication.

Karyopharm® Therapeutics

Manufactured for and marketed by: Karyopharm Therapeutics Inc., 85 Wells Avenue, Newton, MA, 02459.

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For more information, call 1-888-209-9326 or go to XPOVIO.com

MEDICATION GUIDE
XPOVIO® (x-PO-Vee-O)
(selinexor)
tablets

What is the most important information I should know about XPOVIO?

XPOVIO can cause serious side effects, including:

- **Low platelet counts.** Low platelet counts are common with XPOVIO and can lead to bleeding which can be severe and can sometimes cause death. Your healthcare provider may prescribe platelet transfusions or other treatments for your low platelet counts.

Tell your healthcare provider right away if you have any bleeding or easy bruising during treatment with XPOVIO.

- **Low white blood cell counts**. Low white blood cell counts are common with XPOVIO and can sometimes be severe. You may have an increased risk of getting bacterial infections during treatment with XPOVIO. Your healthcare provider may prescribe antibiotics if you have signs or symptoms of infection, or certain medicines to help increase your white blood cell count, if needed.

Your healthcare provider will do blood tests before you start taking XPOVIO, and often during the first 3 months of treatment, and then as needed during treatment to monitor you for side effects.

Your healthcare provider may change your dose of XPOVIO, stop your treatment for a period of time, or completely stop your treatment if you have certain side effects during treatment with XPOVIO.

See "What are the possible side effects of XPOVIO?" for more information about side effects.

What is XPOVIO?

XPOVIO is a prescription medicine used:

- in combination with dexamethasone to treat adults with multiple myeloma (MM) that has come back (relapsed) or that did not respond to previous treatment (refractory), and
  - who have received at least 4 prior therapies, **and**
  - whose disease did not respond to (refractory) to at least 2 proteasome inhibitor medicines, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody medicine.
- to treat adults with certain types of diffuse large B-cell lymphoma (DLBCL) that has come back (relapsed) or that did not respond to previous treatment (refractory) and who have received at least 2 prior therapies

It is not known if XPOVIO is safe and effective in children less than 18 years of age.

What should I tell my healthcare provider before taking XPOVIO?

Before taking XPOVIO, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had a recent or active infection
- have or have had bleeding problems
- are pregnant or plan to become pregnant. XPOVIO can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider will check to see if you are pregnant before you start taking XPOVIO.
  - You should use effective birth control (contraception) during treatment with XPOVIO and for 1 week after your last dose.
  - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with XPOVIO.

  Males with female partners who are able to become pregnant:
  - You should use effective birth control during treatment with XPOVIO and for 1 week after your last dose.
- are breastfeeding or plan to breastfeed. It is not known if XPOVIO passes into your breast milk.
  - Do not breastfeed during treatment with XPOVIO and for 1 week after your last dose of XPOVIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Talk with your healthcare provider before taking any new medicines.

How should I take XPOVIO?

- Take XPOVIO exactly as prescribed by your healthcare provider.
- If you have multiple myeloma, your healthcare provider will prescribe dexamethasone with your XPOVIO treatment. Take dexamethasone exactly as prescribed.
- Your healthcare provider will tell you how much XPOVIO to take and when to take it. Do not change your dose or stop taking XPOVIO without talking to your healthcare provider first.
- Swallow XPOVIO tablets whole with water. **Do not break, chew, crush, or divide the tablets.**
- Be sure to take any medicines prescribed by your healthcare provider before and during treatment with XPOVIO to help prevent nausea and vomiting. Tell your healthcare provider if the prescribed medicine does not control your nausea and vomiting.
- It is important for you to drink enough fluids to help prevent dehydration and to eat enough calories to help prevent weight loss during treatment with XPOVIO. Talk to your healthcare provider if this is a problem for you. **See "What are the possible side effects of XPOVIO?"**
- If you miss a dose of XPOVIO, take your next dose at your next regularly scheduled day and time.
- If you vomit after taking a dose of XPOVIO, do not take an extra dose. Take your next dose at your next regularly scheduled day and time.
- If you take too much XPOVIO, call your healthcare provider right away.

What should I avoid while taking XPOVIO?

XPOVIO can cause neurologic side effects.

- **See "What are the possible side effects of XPOVIO?" below.**
- If you have any neurologic side effects with XPOVIO, **do not drive or operate heavy or dangerous machinery until your neurologic side effects go away.**
- **Avoid falling.** Use care as needed to avoid falling due to neurologic side effects.

What are the possible side effects of XPOVIO?

XPOVIO can cause serious side effects, including:

- **See "What is the most important information I should know about XPOVIO?"**
- **Nausea and vomiting.** Nausea and vomiting are common with XPOVIO and can sometimes be severe. Nausea and vomiting may affect your ability to eat and drink well. You can lose too much body fluid and body salts (electrolytes) and may be at risk for becoming dehydrated. You may need to receive intravenous (IV) fluids or other treatments to help prevent dehydration. Your healthcare provider will prescribe anti-nausea medicines for you to take before you start and during treatment with XPOVIO. **See "How should I take XPOVIO?"**
- **Diarrhea.** Diarrhea is common with XPOVIO and can sometimes be severe. You can lose too much body fluid and body salts (electrolytes) and may be at risk for becoming dehydrated. You may need to receive IV fluids or other treatments to help prevent dehydration. Your healthcare provider will prescribe anti-diarrhea medicine for you as needed.
- **Loss of appetite and weight loss.** Loss of appetite and weight loss are common with XPOVIO and can sometimes be severe. Tell your healthcare provider if you have a decrease or loss of appetite and if you notice that you are losing weight. Your healthcare provider may prescribe medicines that can help increase your appetite or prescribe other kinds of nutritional support.
- **Decreased sodium levels in your blood.** Decreased sodium levels in your blood is common with XPOVIO but can also sometimes be severe. Low sodium levels in your blood can happen if you have nausea, vomiting, or diarrhea, you become dehydrated, or if you have loss of appetite with XPOVIO. You may not have any symptoms of a low sodium level. Your healthcare provider may talk with you about your diet and prescribe IV fluids for you based on the sodium levels in your blood. Your healthcare provider will do blood tests before you start taking XPOVIO, and often during the first 2 months of treatment, and then as needed during treatment to monitor the sodium levels in your blood.
- **Serious infections.** Infections are common with XPOVIO and can be serious and can sometimes cause death. XPOVIO can cause infections including upper or lower respiratory tract infections, such as pneumonia, and an infection throughout your body (sepsis). **Tell your healthcare provider right away if you have any signs or symptoms of an infection such as cough, chills or fever, during treatment with XPOVIO.**
- **Neurologic side effects.** XPOVIO can cause neurologic side effects that can sometimes be severe and life-threatening.
  - XPOVIO can cause dizziness, fainting, decreased alertness, and changes in your mental status including confusion and decreased awareness of things around you (delirium).
  - In some people, XPOVIO may also cause problems with thinking (cognitive problems), seeing or hearing things that are not really there (hallucinations), and may become very sleepy or drowsy.

Tell your healthcare provider right away if you get any of these signs or symptoms.

What are the possible side effects of XPOVIO? – continued

Your healthcare provider may change your dose of XPOVIO, stop your treatment for a period of time, or completely stop your treatment if you have certain side effects during treatment with XPOVIO.

Common side effects of XPOVIO include:

- tiredness
- low red blood cell count (anemia). Symptoms may include tiredness and shortness of breath.
- constipation
- shortness of breath
- increased blood sugar
- changes in body salt and mineral levels in your blood
- changes in kidney and liver function blood tests

XPOVIO may cause fertility problems in males and females, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of XPOVIO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XPOVIO?

- Store XPOVIO at or below 86°F (30°C).
- XPOVIO comes in a child-resistant blister pack.

Keep XPOVIO and all medicines out of the reach of children.

General information about the safe and effective use of XPOVIO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XPOVIO for a condition for which it was not prescribed. Do not give XPOVIO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about XPOVIO that is written for health professionals.

What are the ingredients in XPOVIO?

Active ingredient: selinexor

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry 200 clear, Opadry II blue, povidone K30, and sodium lauryl sulfate.

Manufactured for and marketed by: Karyopharm Therapeutics Inc., 85 Wells Avenue, Newton, MA, 02459
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For more information, call 1-888-209-9326 or go to XPOVIO.com

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June 2020