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

----------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 (RRMM) 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial (1).

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

Recommended starting dosage of XPOVIO is 80 mg in combination with dexamethasone 20 mg taken orally on Days 1 and 3 of each week (2.1).

- Manage adverse reactions using dose modifications and supportive care (2.4, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6).

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

Tablets: 20 mg (3).

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

None (4).

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

- Thrombocytopenia: Monitor platelet counts at baseline, during treatment, and as clinically indicated. Manage with dose interruption, reduction, and supportive care (2.4, 5.1).
- Neutropenia: Monitor neutrophil counts at baseline, during treatment, and as clinically indicated. Manage with dosage interruption and/or reduction and granulocyte colony-stimulating factors (G-CSFs) (2.4, 5.2).
- Gastrointestinal Toxicity: Nausea, vomiting, diarrhea, anorexia, and weight loss may occur. Provide antiemetic prophylaxis. Manage with dosage interruption and/or reduction, antiemetics, and supportive care (2.4, 5.3).
- Hyponatremia: Monitor serum sodium levels at baseline, during treatment, and as clinically indicated. Correct for concurrent hyperglycemia and high serum paraprotein levels (2.4, 5.4).
- Infections: Monitor for signs/symptoms of infection and treat promptly (5.2, 5.5).
- Neurological Toxicity: Avoid taking XPOVIO with other medications that may cause dizziness or confusion. Avoid situations where dizziness or confusional state may be a problem. Optimize hydration status, blood counts, and concomitant medications to avoid dizziness or confusion (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%) are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection (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: 07/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

XPOVIO is indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended starting dosage of XPOVIO is 80 mg (four 20-mg tablets) taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*.

The recommended starting dosage of dexamethasone is 20 mg taken

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.

Each XPOVIO dose should be taken at approximately the same time, 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.

2.2 Recommended Monitoring for Safety

Monitor complete blood count (CBC), standard blood chemistry, and body weight at baseline and during treatment as clinically indicated. Monitor more frequently during the first two months of treatment *[see Warning and Precautions (5.1, 5.2, 5.3, and 5.4)].*

2.3 Recommended Concomitant Treatments

Advise patients to maintain adequate fluid and caloric intake throughout treatment.

Consider intravenous hydration for patients at risk of dehydration.

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

2.4 Dosage Modification for Adverse Reactions

Recommended XPOVIO dosage reductions and dosage modifications for adverse reactions are presented in Table 1 and Table 2, respectively.

Refer to the dexamethasone prescribing information for dexamethasone dosage modifications due to adverse reactions.

Table 1: XPOVIO Dosage Reduction Steps for Adverse Reactions

Recommended Starting Dose	First Reduction	Second Reduction	Third Reduction	
80 mg Days 1 and 3 of each week (160 mg total per week)	100 mg once weekly	80 mg once weekly	60 mg once weekly	Discontinue

Table 2: XPOVIO Dosage Modification Guidelines for Adverse Reactions

Adverse Reaction[a]	Occurrence	Action
Hematologic Adverse Reactions		
Thrombocytopenia		
Platelet count 25,000 to less than 75,000/mcL	Any	• Reduce XPOVIO by 1 dose level (see Table 1). • Interrupt XPOVIO If there is concurrent bleeding, then after bleeding has resolved, restart XPOVIO at 1 dose level lower.
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		
Absolute neutrophil count of 0.5 to 1.0 x 109/L without fever	Any	• Reduce XPOVIO by 1 dose level (see Table 1).
Absolute neutrophil count less than 0.5 x 109/L or febrile neutropenia	Any	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1.0 x 109/L or higher. • Restart XPOVIO at 1 dose level lower (see Table 1).
Anemia		
Hemoglobin level less than 8.0 g/dL	Any	• Reduce XPOVIO by 1 dose level (see Table 1). • Administer blood transfusions and/or other treatments per clinical guidelines.
Life-threatening consequences (urgent intervention indicated)	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 and/or other treatments per clinical guidelines.
Non-Hematologic Adverse Reactions		
Hyponatremia		
Sodium level 130 mmol/L or less	Any	• Interrupt XPOVIO and provide appropriate supportive care. • Monitor until sodium levels return to 130 mmol/L or higher. • 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).

Nausea and Vomiting		
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		
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		
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).
Other Non-Hematologic Adverse Reactions		
Grade 3 or 4 (life threatening)	Any	• Interrupt XPOVIO. • Monitor until resolved to Grade 2 or lower, restart XPOVIO at 1 dose level lower (see Table 1).

a. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

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 thrombocytopenia, leading to potentially fatal hemorrhage. Thrombocytopenia was reported as an adverse reaction in 74% of patients, and severe (Grade 3-4) thrombocytopenia occurred in 61% of patients treated with XPOVIO. 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.

Monitor platelet counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two 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 and/or reduce dosage, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.4) and Adverse Reactions (6.1)]*.

5.2 Neutropenia

XPOVIO can cause neutropenia, potentially increasing the risk of infection. 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.

Obtain neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF). Interrupt and/or reduce dosage, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.4) and Adverse Reactions (6.1)]*.

5.3 Gastrointestinal Toxicity

Gastrointestinal toxicities occurred in patients treated with XPOVIO *[see Adverse Reactions (6.1)]*.

Nausea/Vomiting

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 onset of the first nausea event was 3 days.

Vomiting was reported in 41% of patients, and Grade 3 vomiting occurred in 4% of patients treated with XPOVIO. The median time to onset of the first vomiting event was 5 days.

Provide prophylactic concomitant treatment of 5-HT3 antagonists and/or other anti-nausea agents, prior to and during treatment with XPOVIO. Manage nausea/vomiting by dosage interruption, reduction, and/or discontinuation. Administer intravenous fluids and replace electrolytes to prevent dehydration in patients at risk. Use additional anti-nausea medications as clinically indicated *[see Dosage and Administration (2.4)]*.

Diarrhea

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.

Manage diarrhea by dosage modifications and/or standard anti-diarrheal

agents; administer intravenous fluids to prevent dehydration in patients at risk *[see Dosage and Administration (2.4)]*.

Anorexia/Weight Loss

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.

Monitor patient weight at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Manage anorexia and weight loss with dosage modifications, appetite stimulants, and nutritional support *[see Dosage and Administration (2.4)]*.

5.4 Hyponatremia

XPOVIO can cause hyponatremia; 39% of patients treated with XPOVIO experienced hyponatremia, 22% of patients experienced Grade 3 or 4 hyponatremia. The median time to onset of the first event was 8 days.

Monitor sodium level at baseline, during treatment, and as clinically indicated. 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. Treat hyponatremia per clinical guidelines (intravenous saline and/or salt tablets), including dietary review. Interrupt and/or reduce dosage, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.4) and Adverse Reactions (6.1)]*.

5.5 Infections

In patients receiving XPOVIO, 52% of patients experienced any grade of infection. Upper respiratory tract infection of any grade occurred in 21%, pneumonia in 13%, and sepsis in 6% of patients. Grade ≥3 infections were reported in 25% of patients, and deaths resulting from an infection occurred in 4% of patients. The most commonly 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. Most infections were not associated with neutropenia and were caused by non-opportunistic organisms *[see Adverse Reactions (6.1)]*.

5.6 Neurological Toxicity

Neurological toxicities occurred in patients treated with XPOVIO *[see Adverse Reactions (6.1)]*.

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. Median time to the first event was 15 days.

Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes.

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)]*.
- Infections *[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.

The data described below reflect exposure to XPOVIO plus dexamethasone in 202 patients with RRMM who received XPOVIO 80 mg in combination with dexamethasone 20 mg on Days 1 and 3 of every week.

The median duration of XPOVIO treatment was 8 weeks (range: 1 to 60 weeks). The median dose was 115.4 mg (range: 36 to 200 mg) per week.

The treatment discontinuation rate due to adverse reactions was 27%; 53% of patients had a reduction in the XPOVIO dose, and 65.3% had the dose of XPOVIO interrupted. The most frequent adverse reactions requiring permanent discontinuation in 4% or greater of patients who received XPOVIO included fatigue, nausea, and thrombocytopenia. The rate of fatal adverse reactions was 8.9%.

The population had a median age of 64 years (range: 35 to 86 years), 54% were male, and the majority (73%) were White (17% were Black or African American).

Table 3 summarizes the most common (≥10% of patients) adverse reactions reported in patients with RRMM who received XPOVIO and dexamethasone.

Table 3: Adverse Reactions with XPOVIO 80 mg and Dexamethasone 20 mg Administered Twice Weekly

Adverse Reaction	Any Grade (N = 202) n (%)	Grade ≥3 (N = 202) n (%)
Thrombocytopenia[a]	149 (74)	124 (61)
Fatigue[b]	147 (73)	44 (22)
Nausea	146 (72)	18 (9)
Anemia[c]	119 (59)	81 (40)
Decreased appetite	108 (53)	9 (4.5)
Weight decreased	95 (47)	1 (0.5)
Diarrhea	89 (44)	13 (6)
Vomiting	82 (41)	7 (3.5)
Hyponatremia	78 (39)	44 (22)
Neutropenia[d]	68 (34)	43 (21)
Leukopenia	57 (28)	23 (11)
Constipation	50 (25)	3 (1.5)
Dyspnea[e]	48 (24)	7 (3.5)[k]
Upper respiratory tract infection[f]	42 (21)	6 (3)

Cough[g]	33 (16)	0
Mental status changes[h]	33 (16)	14 (7)
Pyrexia	32 (16)	1 (0.5)
Hyperglycemia	31 (15)	15 (7)
Dizziness	30 (15)	0
Insomnia	30 (15)	4 (2)
Lymphopenia	30 (15)	20 (10)
Dehydration	28 (14)	7 (3.5)
Hypercreatininemia[i]	28 (14)	4 (2)
Pneumonia[j]	26 (13)	18 (9)[k]
Epistaxis	25 (12)	1 (0.5)
Hypokalemia	25 (12)	7 (3.5)
Dysgeusia	22 (11)	0
Vision blurred	21 (10)	1 (0.5)
Headache	20 (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.

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

Pregnancy Testing

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

Contraception

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

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

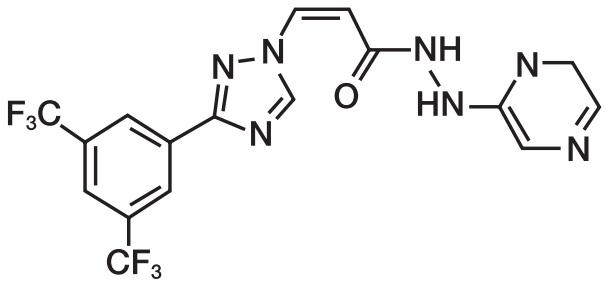
Of the 202 patients with RRMM who received XPOVIO, 49% were 65 years of age and over, while 11% were 75 years of age and over. No overall difference in safety or effectiveness was observed in patients over 65 years of age, including patients over 75 years of age, when compared with younger patients.

11 DESCRIPTION

XPOVIO (selinexor) is an orally available nuclear export inhibitor.

Selinexor is (2*Z*)-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, 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.

12.2 Pharmacodynamics

XPOVIO exposure-response relationships and the time course of pharmacodynamic responses are unknown.

Cardiac Electrophysiology

The effect of multiple doses of XPOVIO, up to 175 mg (2.2 times the 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 dosage level.

12.3 Pharmacokinetics

Following a single-dose administration of XPOVIO 80 mg, the mean (standard deviation) peak plasma concentration (C_{max}) was 680 (124) ng/mL and the mean AUC was 5386 (1116) ng•h/mL. Selinexor C_{max} and AUC increased proportionally over doses from 3 mg/m^2 to 85 mg/m^2 (0.06 to 1.8 times the approved recommended dose based on 1.7 m^2 body surface area). No clinically relevant accumulation at steady state was observed.

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 125 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 17.9 L/h in patients with cancer.

Metabolism

Selinexor is metabolized by CYP3A4, multiple UDP-glucuronosyltransferases (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, ethnicity, mild to severe renal impairment (CL_{CR}: 15 to 89 mL/min, estimated by the Cockcroft-Gault equation). The effect of end-stage renal disease (CLCR <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

No dedicated drug interaction studies have been performed with XPOVIO.

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. Selinexor is a substrate of CYP3A4.

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 patients with 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 were treated with XPOVIO (80 mg) in combination with dexamethasone (20 mg) on Days 1 and 3 of every week. 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 4 and Table 5, respectively. Treatment continued until disease progression, death, or unacceptable toxicity.

The major efficacy outcome measure was 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 6. 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 4: 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 5: 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 6: Overall Response (STORM) as Assessed by the IRC per IMWG Criteria

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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

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 four 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
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
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

16.2 Storage

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 and prophylactic anti-nausea medications exactly as prescribed *[see Dosage and Administration (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 two months of treatment. *[see Dosage and Administration (2.2)].*
- Advise patients to maintain appropriate fluid and caloric intake throughout their treatment *[see Dosage and Administration (2.3)].*

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 2 months of treatment *[see Warnings and Precautions (5.1)].*

Anemia

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath *[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 platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 2 months of treatment.

Gastrointestinal Adverse Reactions

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

Fatigue

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

Anorexia/Weight Loss

Advise patients that they may experience weight loss *[see Warnings and Precautions (5.3)].*

Confusional State and Dizziness

Advise patients that they may experience confusion and dizziness. Advise patients not to operate motorized vehicles until they know how XPOVIO affects their abilities *[see Adverse Reactions (6.1)].*

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)].*

Infections

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

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with XPOVIO *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)].*

Females and Males of Reproductive Potential

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 of XPOVIO *[see Use in Specific Populations (8.3)].*

Lactation

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

Concomitant Medications

Advise patients to take 5-HT3 antagonist prophylactic treatment and/or other anti-nausea agents prior to and during treatment with XPOVIO *[see Dosage and Administration (2.3)].*

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

Karyopharm® Therapeutics

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