XPOVIO™ tablets 20mg (selinexor)

ETC (Orphan drug)

■ **The ingredients :** 1 tablet (167.2mg)
Active ingredient : selinexor ··· 20.0 mg
Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry 200 clear, Opadry II blue, povidone K30, and sodium lauryl sulfate

■ **Appearance**
blue, round, film-coated tablets

■ **INDICATIONS AND USAGE**

1. 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.

2. XPOVIO is indicated 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.

■ **DOSAGE AND 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.

1. Recommended Dosage

1) 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 : The recommended dosage of this drug is 80 mg taken orally on Days 1 and 3 of each week (twice a week). The recommended dosage of dexamethasone is 20 mg taken orally with each dose of this drug on Days 1 and 3 of each week (twice a week).

2) 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. : The recommended dosage of this drug is 60 mg taken orally on Days 1 and 3 of each week (twice a week).

2. Dosage Modification for Adverse Reactions

Recommended XPOVIO dosage reduction steps for Adverse Reactions are presented in Table 1.

Table 1: XPOVIO Dosage Reduction Steps for Adverse Reactions -USPI 18dec20 Table 1

Adverse Reaction	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

Refer to Tables 2 and 3 for recommended dose adjustment according to adverse hematologic reactions in patients with multiple myeloma and diffuse large B-cell lymphoma.

Table 2: XPOVIO Dosage Modification Guidelines for Hematologic Adverse Reactions in Patients with Multiple Myeloma -USPI 18dec20 Table 2

Adverse Reaction	Occurrence	Action
Thrombocytopenia		
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		
Absolute neutrophil count of 0.5 to 1.0 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 8.0 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 -USPI 18dec20 Table 3

Adverse Reaction	Occurrence	Action
Thrombocytopenia		
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		
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.

Recommended dosage modifications for non- hematologic adverse reactions are presented in Table 4.

Table 4: XPOVIO Dosage Modification Guidelines for Non-Hematologic Adverse Reactions
-USPI 18dec20 Table 4

Adverse Reaction	Occurrence	Action
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. • 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).
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).
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, excluding cataract	Any	• Permanently discontinue XPOVIO. • Perform ophthalmologic evaluation
Other Non-Hematologic Adverse Reactions		
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).

■ WARNINGS AND PRECAUTIONS

1. Do not administer to the following patients
Patients with hypersensitivity to the active ingredients and additives of this drug

2. Adverse Reactions

1) patients with Multiple Myeloma

The most common adverse reactions (≥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.

2) patients with DLBCL

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

The safety of XPOVIO in combination with dexamethasone was evaluated in STORM. 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 common adverse reactions observed in patients treated with this drug in STORM.

Table 5: Adverse Reactions (≥10%) in Patients Who Received XPOVIO in STORM -USPI 18dec20 Table 7

Adverse Reactions	XPOVIO 80 mg and Dexamethasone 20 mg Administered Twice Weekly (n=202)	
	Any Grade (%)	Grade ≥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 influenza, and pneumonia viral
k. Includes fatal event.

Diffuse Large B-Cell Lymphoma

The safety of XPOVIO was evaluated in SADAL. 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 the common adverse reactions observed in patients treated with this drug in SADAL.

Table 6: Adverse Reactions (≥10%), Excluding Laboratory Terms, in Patients with DLBCL Who Received XPOVIO in SADAL -USPI 18dec20 Table 8

Adverse Reaction	XPOVIO 60 mg twice weekly (n=134)	
	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 decreasee	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 thrombocytope nia, 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 -USPI 18dec20 Table 9

Laboratory Abnormality	XPOVIO 60 mg twice weekly	
	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.

3. WARNINGS AND PRECAUTIONS

1) Thrombocytopenia

XPOVIO can cause thrombocytopenia, leading to potentially fatal hemorrhage. Thrombocytopenia is the main factor of dosage modification. [see Dosage and Administration]

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), thrombocytopenia was reported as an adverse reaction in 74% 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 who received XPOVIO 60 mg twice weekly (SADAL, 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 4 thrombocytopenia.

Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first three months of treatment

2) Neutropenia

XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection [see 2. Adverse Reactions].

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

In patients with DLBCL (SADAL, 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 4 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.

3) Gastrointestinal Toxicity

XPOVIO can cause severe gastrointestinal toxicities [see 2. Adverse Reactions].

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 receiving XPOVIO 80 mg twice weekly (STORM, 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%. 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 (SADAL, 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 at baseline and throughout treatment.

Diarrhea

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), diarrhea was reported as an adverse reaction in 44% of patients and Grade 3 diarrhea occurred in 6% of patients. The median time to onset of diarrhea was 15 days.

In patients with DLBCL (SADAL, n=134), 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.

Anorexia/Weight Loss

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM n=202), anorexia was reported as an adverse reaction in 53% of patients and Grade 3 anorexia occurred in 5% of patients. 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.

4) Hyponatremia

XPOVIO can cause severe or life-threatening hyponatremia [see 2. Adverse Reactions].

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, 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. The median time to onset of the first event was 8 days.

In patients with DLBCL (SADAL, 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.

5) Serious Infection

XPOVIO can cause serious and fatal infections. Most of these infections were not associated with Grade 3 or higher neutropenia [see 2. Adverse Reactions].

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), 52% of patients experienced any grade of infection. Grade ≥3 infections were reported in 25% of patients, and deaths from infections 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 (SADAL, 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, 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.

6) Neurotoxicity

XPOVIO can cause life-threatening neurological toxicities [see 2. Adverse Reactions].

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, 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. The median time to the first event was 15 days.

In patients with DLBCL (SADAL, 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.

7) Cataract

New onset or exacerbation of cataract has occurred during treatment with XPOVIO [see 2. Adverse Reactions].

In patients with multiple myeloma who received XPOVIO 100 mg once weekly (n=195), the incidence of new onset or worsening cataracts requiring clinical intervention was reported in 22% of patients. The median time to new onset of cataract was 228 days and was 237 days for worsening of cataract in patients presenting with cataract at start of XPOVIO therapy.

8) PMS (Post Market Surveillance)

Potential risks (TLS(tumor lysis syndrome), ACS(acute cerebellar syndrome), Medication error) and missing information (Use in patients with severe renal impairment, Use in patients with severe hepatic impairment) should be taken as follows.

1. In the criteria of the PMS, there is no restriction on the number of patients used, so measures are taken so that the patient group of important safety review can be collected without omission. 2. In the baseline survey items of the PMS, potential risks or missing information were initially investigated, and measures were taken so that they could be compared. 3. In case that important safety and efficacy review items are collected, they are classified and analyzed as AESIs(adverse events of special interest) during the PMS reporting and reported to the MFDS on a regular basis. The confirmed adverse events that have been reported after completion of domestic and international PMS are periodically updated.

4. Interaction studies

1) Clinical studies

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

2) 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.

5. USE IN SPECIFIC POPULATIONS

1) Pregnancy

Based on findings in animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant woman to inform the drug-associated risk. 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.

2) Lactation

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.

3)Females and Males of Reproductive Potential

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

6. Pediatric Use

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

7. Geriatric Use

In STORM, of the 202 patients with multiple myeloma who received XPOVIO, 49% were 65 years of age and older, while 11% were 75 years of age and older. No overall difference in effectiveness was observed in patients over 65 years of age. 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. No overall difference in effectiveness was observed in patients over 65 years of age.

8. Use in patients with renal/liver impairment

It has not been studied in patients with moderate/severe renal or hepatic impairment.

9. Treatment in case of overdose - Local PI

In general, overdose has side effects similar to those reported with standard doses and can usually be reversed within a week. Potential acute symptoms include nausea, vomiting, diarrhea, dehydration, and confusion. Potential signs include low sodium levels, high liver enzymes, and low blood count.

10. Precautions for storage and handling

1) Keep XPOVIO and all medicines out of the reach of children.
2) Store XPOVIO at or below 30°C.

11. Information for Professional

1) Clinical pharmacology

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.

② 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 Cmax and AUC After Administration of a Single Dose of XPOVIO -USPI 18dec20 Table10

Mean (SD)	XPOVIO Dose	
	60 mg	80 mg
Cmax (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.

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.

- Distiribution

The apparent volume of distribution of selinexor is 133L in patients with canc er. 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-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, body weight (36 to 168 kg), ethnicity, mild to severe renal impairment (CLCR: 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 (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.

③ 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 per dose (2.2 times the maximum approved recommended dose), 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.

2) Clinical studies

① **Relapsed Refractory Multiple Myeloma**

The efficacy of XPOVIO plus dexamethasone was evaluated in STORM (KCP-330-012; NCT02336815). STORMwas 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. 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 demographicsand disease characteristics of these 83 patients are summarized in Table 9 and Table 10, respectively.

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 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) -USPI 18dec20 Table 14

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) -USPI 18dec20 Table 15

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 del(17p)/p53, t(14; 16), t(4; 14), 1q21

Table11:Overall Response (STORM) as Assessed by the IRC per IMWG Criteria -USPI 18dec20 Table 16

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.

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) -USPI 18dec20 Table 17

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)

3) **NONCLINICAL TOXICOLOGY**

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) as say 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.

■ **Shelf-life**
36 months from the date of manufacture

■ **Storage**
Tight container, Store at 1~30℃

■ **Packaging unit**
16T(4T/PTP×4), 20T(5T/PTP×4), 24T(6T/PTP×4), 32T(8T/PTP×4)

Imported by
Antengene Korea Co., Ltd.
The Executive Center 41st floor, Gangnam finance Center, 152 Teheran-ro, Gangnam-gu, Seoul, Korea

Manufacturer
Karyopharm Therapeutics Inc., USA
85 Wells Ave Ste 210, Newton, MA 02459

Manufacturer: (subcontracter1 for partial manufacturing process)
Catalent CTS, LLC, USA
10245 Hickman Mills Dr, Kansas City, MO 64137 (raw material weighing ~ coating)

Manufacturer: (subcontracter 2 for packaging)
Carton Service Incorporated, USA
341 JD Yarnell Industrial Parkway Clinton, TN 37716 (Packaging Process)

Local PI
※ Please check the attached document before taking it.
※ Please keep out of reach of children.
※ Do not use medicines that have passed the expiration date or expiration date.
※ Drugs that have passed the expiration date or the expiration date, deteriorated, deteriorated, contaminated or damaged, will be exchanged only to the pharmacy founder, the seller of safe and standing medicine, and the drug seller.
※ For detailed drug information, please refer to the Integrated Drug Information System of the Ministry of Food and Drug Safety (http://nedrug.mfds.go.kr).
※ If adverse event occurs while taking or using medicines, please inform your doctor, pharmacist or Korea Pharmaceutical Safety Management Agency (Tel: 1644-6223, www.drugsafe.or.kr).
※ You can apply for side effects damage relief at the Korea Pharmaceutical Safety Management Agency (Tel: 1644-6223, www.drugsafe.or.kr).

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