FULL PRESCRIPTION INFORMATION

NAME OF THE MEDICINAL PRODUCT

Xpovio®

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 20 mg of selinexor

PHARMACEUTICAL FORM
Tablet, PER OS

1. INDICATIONS AND USAGE

1.1 Multiple Myeloma

Xpovio in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

Xpovio in combination with dexamethasone is indicated for the treatment of adult patients with relapsed refractory multiple myeloma (RRMM) who have received at least three prior therapies and whose disease is refractory to at least one proteasome inhibitor (PI), at least one immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody (mAb).

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.

2. DOSAGE AND ADMINISTRATION

2.1 **Recommended Dosage for Multiple Myeloma**

In Combination with Bortezomib and Dexamethasone (SVd)

The recommended dosage of XPOVIO is 100 mg taken orally once weekly on Day 1 of each week until disease progression or unacceptable toxicity in combination with:

• Bortezomib 1.3 mg/m2 administered subcutaneously once weekly on Day 1 of each week for 4 weeks followed by 1 week off.

• Dexamethasone 20 mg taken orally twice weekly on Days 1 and 2 of each week.

Refer to Clinical Studies (14.1) and the prescribing information of bortezomib and dexamethasone for additional dosing information.

In Combination with Dexamethasone(Sd)

The recommended dosage of Xpovio is 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity. In combination with dexamethasone 20 mg orally taken 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

Recommended Starting Dosage	**Multiple Myeloma In Combination with Bortezomib and Dexamethasone (SVd)**	**Multiple Myeloma In Combination with Dexamethasone (Sd)**	**Diffuse Large B-Cell Lymphoma**
	100mg once weekly	80 mg Days 1 and 3 of each week (160 mg total per week)	60 mg Days 1 and 3 of each week (120 mg total per week)
First Reduction	80 mg once weekly	100 mg once weekly	40 mg Days 1 and 3 of each week (80 mg total per week)
Second Reduction	60 mg once weekly	80 mg once weekly	60 mg once weekly
Third Reduction	40 mg once weekly	60 mg once weekly	40 mg once weekly
Fourth Reduction	Permanently discontinue	Permanently discontinue	Permanently discontinue

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, excluding cataract	Any	• Permanently discontinue Xpovio. • Perform ophthalmologic evaluation.
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 film, coated bi-convex round tablet debossed with "K20" on one side and nothing on the other.

4. CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 8.

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 (7.1, 7.3)]*.

5.8 Cataract

New onset or exacerbation of cataract has occurred during treatment with XPOVIO *[see Adverse Reactions (6.1)].* In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, 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. Treatment of cataracts usually requires surgical removal of the cataract.

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)].*
- Cataract [see Warnings and Precautions (5.8)].

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

XPOVIO in Combination with Bortezomib and Dexamethasone (SVd)

The safety of XPOVIO in combination with bortezomib and dexamethasone was evaluated in BOSTON *[see Clinical Studies (14.1)].* Patients were randomized to receive XPOVIO 100 mg orally once weekly in combination with bortezomib and dexamethasone (SVd) (n=195) or bortezomib and dexamethasone (Vd) (n=204). Among patients who received XPOVIO, the median duration of XPOVIO treatment was 29 weeks (range: 1 to 120 weeks) and the median dose was 80 mg (range: 30 to 137 mg) per week.

Serious adverse reactions occurred in 52% of patients who received XPOVIO in combination with bortezomib and dexamethasone. Serious adverse reactions in >3% of patients included pneumonia (14%), sepsis, diarrhea and vomiting (4% each). Fatal adverse reactions occurred in 6% of patients within 30 days of last treatment, including pneumonia (n=3) and sepsis (n=3).

Grade ≥2 peripheral neuropathy, a pre-specified key secondary endpoint, was lower in the SVd arm (21%) compared to the Vd arm (34%); odds ratio 0.50 [95% CI: 0.32, 0.79]. The median treatment duration was 30 weeks (range: 1-120 weeks) in patients who received once weekly SVd as compared to 32 weeks (range: 1-122 weeks) in patients who received twice weekly Vd.

Permanent discontinuation of XPOVIO due to an adverse reaction occurred in 19% of patients. Adverse reactions which resulted in permanent discontinuation of XPOVIO in >2% of patients included fatigue (3.6%), nausea (3.1%), thrombocytopenia, decreased appetite, peripheral neuropathy and vomiting (2.1% each).

Dosage interruptions of XPOVIO due to an adverse reaction occurred in 83% of patients. Adverse reactions which required dosage interruption in >5% of patients included thrombocytopenia (33%), fatigue (13%), asthenia (12%), pneumonia (11%), upper respiratory tract infection (10%), decreased appetite (9%), neutropenia (8%), pyrexia (8%), nausea (7%), bronchitis (7%), diarrhea (6%), weight decreased (6%) and anemia (5%).

Dose reductions of XPOVIO due to an adverse reaction occurred in 64% of patients. Adverse reactions which required dose reductions in >5% of patients included thrombocytopenia (31%), decreased appetite (8%), nausea, fatigue, decreased weight (7% each) and asthenia (6%).

The most common adverse reactions (≥20% with a difference between arms of >5% compared to Vd) were fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, weight decrease, cataract, and vomiting. Grade 3-4 laboratory abnormalities (≥10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia.

Table 5 summarizes the adverse reactions in BOSTON.

Table 5: Adverse Reactions (≥10%) in Patients with Multiple Myeloma Who Received XPOVIO in Combination with Bortezomib and Dexamethasone (SVd) with a Difference Between Arms of >5% Compared to Vd in BOSTON

Adverse Reaction	Weekly SVd (n=195)		Twice Weekly Vd (n=204)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal				
Nausea	50	8	10	0
Diarrhea	32	6	25	<1
Vomiting	21	4.1	4.4	0
General Conditions				
Fatigue[a]	59	28	21	5
Pyrexia	15	1.5	11	1
Metabolism and Nutrition				
Appetite decrease	35	3.6	5	0
Weight decrease	26	2.1	12	1
Nervous System				
Peripheral neuropathy[b]	32	4.6	47	9
Dizziness	12	<1	3.9	0
Infections				
Upper respiratory tract infection[c]	29	3.6	22	1.5
Eye Disorders				
Cataract	22	9	6	1.5
Vision blurred[d]	13	<1	6	0

Key: S=selinexor, Vd=bortezomib-dexamethasone

a. Fatigue includes fatigue and asthenia.
b. Peripheral neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, polyneuropathy, peripheral sensorimotor neuropathy, toxic neuropathy and peripheral motor neuropathy.
c. Upper respiratory tract infection includes upper respiratory infection, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, and viral upper respiratory tract infection.
d. Vision blurred includes blurred vision, visual acuity reduced and visual impairment.

Clinically relevant adverse reactions in <10% of patients who received XPOVIO in combination with bortezomib and dexamethasone included:

- **Neurologic disorders:** mental status changes (9%) and syncope (3.6%)

Table 6 summarizes selected laboratory abnormalities in BOSTON.

Table 6: Select Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with Multiple Myeloma Who Received XPOVIO in Combination with Bortezomib and Dexamethasone (SVd) in BOSTON

Laboratory Abnormality	Weekly SVd		Twice Weekly Vd	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic				
Platelet count decrease	92	43	51	19
Lymphocyte count decrease	77	38	70	27
Hemoglobin decrease	71	17	51[a]	12
Neutrophil count decrease	48	12	19	7
Chemistry				
Glucose increase	62	3.8	47	4.1
Phosphate decrease	61	23	42	11
Sodium decrease	58	14	25	3
Calcium decrease	55	2.1	47	1
Blood urea nitrogen increase	41	5	40	5
Creatinine increase	28	3.6	24	1.5
Potassium decrease	27	6	22	3.5
Magnesium decrease	27	<1	23	1.5
Potassium increase	18	4.1	21	2.5
Hepatic				
ALT increase	33	3.1	30	<1
Albumin decrease	27	<1	35	<1
AST increase	24	1.5	19	<1
Bilirubin increase	16	1	13	2
ALP increase	12	0	16	<1

The denominator used to calculate the rate varied from 91 to 201 based on the number of patients with at least one post-treatment value.
a. Includes one fatal anemia.

XPOVIO in Combination with Dexamethasone (Sd)

The safety of Xpovio in combination with dexamethasone was evaluated in STORM *[see Clinical Studies (11.1)]*. 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 7 summarizes the adverse reactions in STORM.

Table 7: Adverse Reactions (≥10%) in Patients Who Received Xpovio in STORM

Adverse Reaction	Xpovio 80 mg twice weekly + Dexamethasone (n=202)	
	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 (11.2)].* 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 8: 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] Pneumonia	17 10	1.5 6
Urinary tract infection[i]	10	3

Nervous System		
Dizziness[j]		
Taste disorder[k]	16	0.7
Mental status changes[l]	13	0
Peripheral neuropathy,	11	3.7
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 9 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

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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/
In addition, suspected adverse events can be reported to the Registration Holder's Patient Safety Unit at: drugsafety@neopharmgroup.com

7. USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

Based on findings in animal studies and its mechanism of action *[see Clinical Pharmacology (9.1)]*, 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.

7.2 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.

7.3 Females and Males of Reproductive Potential

Xpovio can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (7.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating Xpovio *[see Use in Specific Populations (7.1)]*.

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 (10.1)]*.

7.4 Pediatric Use

Xpovio is not indicated for children and adolescents under 18 years old

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

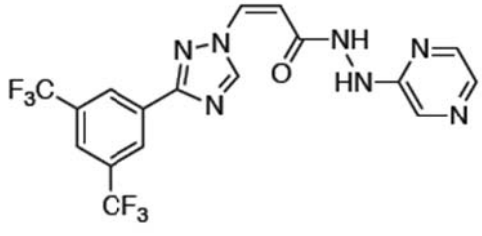
7.5 Geriatric Use

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.

8. DESCRIPTION

Selinexor is a nuclear export inhibitor. Selinexor is (2*Z*)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-1yl}-*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 film coated bi-convex round tablet debossed with “K20” on one side and nothing on the other. The inactive ingredients are microcrystalline cellulose (Avicel® PH-101), microcrystalline cellulose (Avicel® PH-102), croscarmellose sodium, povidone K30, Opadry® II blue, sodium lauryl sulfate, colloidal silicon dioxide, Opadry® 200 clear and magnesium stearate.

9. CLINICAL PHARMACOLOGY

9.1 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. The combination of selinexor and dexamethasone or bortezomib demonstrated synergistic cytotoxic effects in multiple myeloma in vitro and increased anti-tumor activity in murine xenograft multiple myeloma models in vivo, including those resistant to proteasome inhibitors.

9.2 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.

9.3 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 10: Selinexor C_{max} and AUC After Administration of a Single Dose of Xpovio

	Xpovio Dose		
Mean (SD)	60 mg	80 mg	100 mg
Cmax (ng/mL)	442 (188)	680 (124)	693 (201)
$AUC_{0\text{-}INF}$ (ng·h/mL)	4,096 (1,185)	5,386 (1,116)	6,998 (818)

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-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 (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.

10. NONCLINICAL TOXICOLOGY

10.1 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.

11. CLINICAL STUDIES

11.1 Relapsed or Refractory Multiple Myeloma

XPOVIO Combination with Bortezomib and Dexamethasone (SVd)

The efficacy of XPOVIO in combination with bortezomib and dexamethasone was evaluated in BOSTON (NCT03110562). BOSTON was a global, randomized, open label, active-controlled trial in adult patients who had received 1 to 3 prior anti-MM regimens. Prior treatment with bortezomib or other PI was allowed. Patients with Grade 2 or higher peripheral neuropathy at study entry were excluded.

Patients were randomized to receive one of the following:

- XPOVIO 100 mg orally once weekly on Days 1, 8, 15, 22, 29 in combination with bortezomib 1.3 mg/m^2 administered subcutaneously once weekly on Days 1, 8, 15, 22 and dexamethasone 20 mg taken orally twice weekly on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle [SVd arm] or
- Bortezomib 1.3 mg/m^2 administered subcutaneously twice weekly on Days 1, 4, 8, 11 and dexamethasone 20 mg taken orally four times weekly on Days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for the first 8 cycles, followed by bortezomib 1.3 mg/m^2 administered subcutaneously once weekly on Days 1, 8, 15, 22 and dexamethasone 20 mg taken orally twice weekly on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle (Cycle ≥9) [Vd arm].

Treatment continued in both arms until disease progression or unacceptable toxicity. Randomization was stratified based on prior proteasome inhibitor therapies exposure (yes versus no), number of prior regimens (1 versus >1), Stage (III versus I or II) according to the Revised-International Staging System (RISS) and region. Upon confirmed progressive disease (PD), patients in the Vd arm could receive XPOVIO in combination with bortezomib and dexamethasone (SVd) or XPOVIO 100 mg taken orally on Days 1, 8, 15, 22, 29 with dexamethasone 20 mg taken orally on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30 of each 35-day cycle.

A total of 402 patients were randomized: 195 to SVd arm and 207 to Vd arm. Baseline patient demographics and disease characteristics are summarized in Table 11 and Table 12, respectively.

Table 11: Baseline Demographics (BOSTON)

Characteristic	SVd (n=195)	Vd (n=207)
Median age, years (range)	66 (40, 87)	67 (38, 90)
Age distribution, n (%)		
<65 years	86 (44)	75 (36)
65 – 74 years	75 (38)	85 (41)
≥75 years	34 (17)	47 (23)
Sex, n (%)		
Male	115 (59)	115 (56)
Female	80 (41)	92 (44)
Race, n (%)		
White	161 (83)	165 (80)
Black or African American	4 (2)	7 (3)
Asian	25 (13)	25 (12)
Other	0	1 (0.5)
Missing	5 (3)	9 (4)

Table 12: Disease Characteristics (BOSTON)

Parameter	SVd (n=195)	Vd (n=207)
Median years from diagnosis to randomization (range)	3.81 (0.4,23.0)	3.59 (0.4, 22.0)
ECOG performance status score, n (%)		
0-1	175 (90)	191 (92)
≥2	20 (10)	16 (8)
Creatinine Clearance, n (%), mL per minute		
<30	3 (1.5)	10 (5)
30 to 59	53 (27)	60 (29)
≥60	139 (71)	137 (66)

Revised International Staging System at Baseline, n (%)		
I	56 (29)	52 (25)
II	117 (60)	125 (60)
III	12 (6)	16 (8)
Unknown	10 (5)	14 (7)
Number of Prior Therapies, n (%)		
1	99 (51)	99 (48)
2	65 (33)	64 (31)
3	31 (16)	44 (21)
Type of known prior therapy, n (%)		
Stem Cell transplantation	76 (39)	63 (30)
Lenalidomide	77 (39)	77 (37)
Pomalidomide	11 (6)	7 (3)
Bortezomib	134 (69)	145 (70)
Carfilzomib	20 (10)	21 (10)
Daratumumab	11 (6)	6 (3)
Median weeks since end of last prior therapy, (range)	48 (1, 1088)	42 (2, 405)
Known high-risk cytogenetics[a], n (%)	97 (50)	95 (46)

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

Efficacy was based on progression free survival (PFS) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma, as assessed by an Independent Review Committee (IRC). Efficacy results based on a preplanned PFS interim analysis, are shown in Table 13 and Figure 1.

Table 13: Efficacy Results per IRC in Multiple Myeloma (BOSTON)

	SVd (n=195)	**Vd (n=207)**
Progression Free Survival (PFS)[a]		
Hazard Ratio [95% CI]	0.70 [0.53, 0.93]	
One-sided p-value[b]	0.0075	
Median PFS in months [95% CI]	13.9 (11.7, Not Reached)	9.5 (7.6, 10.8)
Overall Response Rate (ORR)[c], n (%)	149 (76.4)	129 (62.3)
95% CI	(69.8, 82.2)	(55.3, 68.9)
One-sided p-value	0.0012	
Stringent Complete Response (sCR)	19 (10)	13 (6)
Complete Response (CR)	14 (7)	9 (4)
Very Good Partial Response (VGPR)	54 (28)	45 (22)
Partial Response (PR)	62 (32)	62 (30)
≥ VGPR Response Rate[d], n (%)	87 (44.6)	67 (32.4)
95% CI	(37.5, 51.9)	(26.0, 39.2)
One-sided p-value	0.0082	

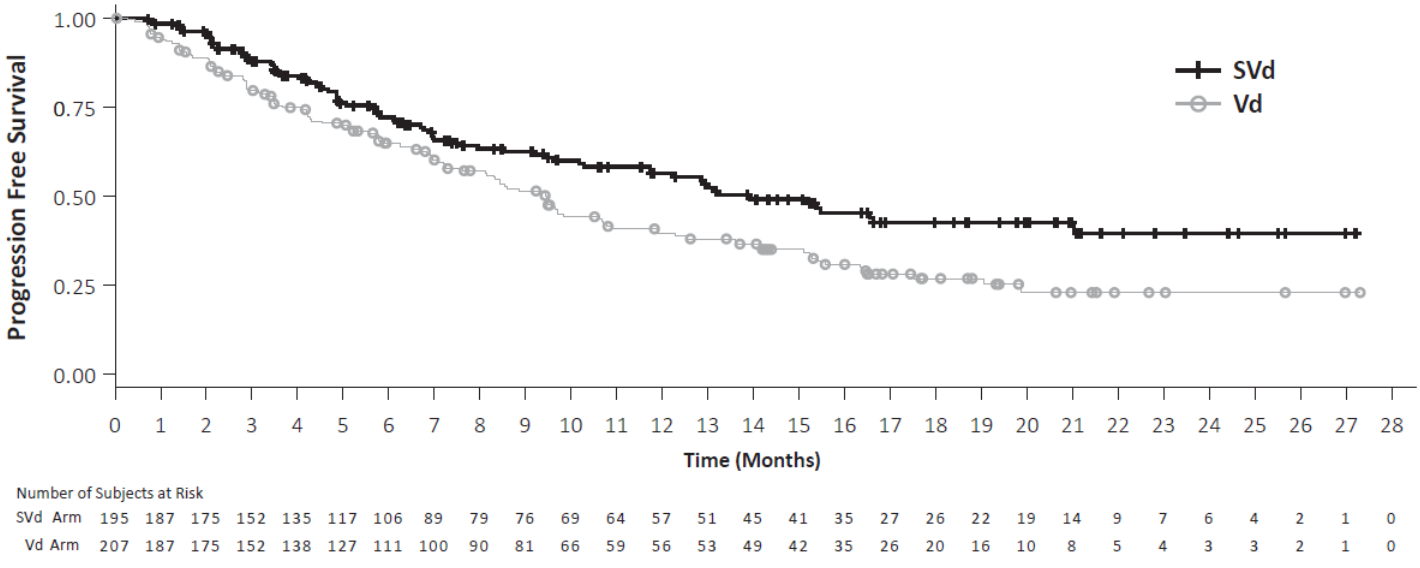
a. Hazard ratio is based on stratified Cox's proportional hazard regression modeling, p-value based on stratified log-rank test. Median follow up of 15.1 months at the time of the analysis.

a. The pre-planned PFS interim analysis boundary of statistical significance was defined as a p-value <0.0103.

b. Includes sCR + CR + VGPR + PR, p value based on Cochran-Mantel-Haenszel test.

c. Includes sCR + CR + VGPR, p value based on Cochran-Mantel-Haenszel test.

Figure 1: Kaplan-Meier Curve of PFS (BOSTON)



The median time to response was 1.4 months in the SVd arm and 1.6 months in the Vd arm. The median duration of response, among responding patients, was 20.3 months and 12.9 months in the SVd and Vd arms, respectively.

XPOVIO Combination with Dexamethasone (Sd)

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 antimyeloma 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 14: 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)

Table 15: 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 16: 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.

11.2 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 17: 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)

12. 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
80 mg twice weekly	20 mg	4 blister packs (32 tablets total in the carton)	Each blister has eight 20 mg tablets
60 mg twice weekly	20 mg	4 blister packs (24 tablets total in the carton)	Each blister has six 20 mg tablets
100 mg once weekly	20 mg	4 blister packs (20 tablets total in the carton)	Each blister has five 20 mg tablets
80 mg once weekly	20 mg	4 blister packs (16 tablets total in the carton)	Each blister has four 20 mg tablets
40 mg twice weekly	20 mg	4 blister packs (16 tablets total in the carton)	Each blister has four 20 mg tablets
60 mg once weekly	20 mg	4 blister packs (12 tablets total in the carton)	Each blister has three 20 mg tablets
40 mg once weekly	20 mg	4 blister packs (8 tablets total in the carton)	Each blister has two 20 mg tablets

Not all pack sizes may be marketed.

Shelf life

Store at or below 30°C.
The expiry date of the product is indicated on the packaging materials.

13. MANUFACTURER

Karyopharm Therapeutics Inc.,
85 Wells Avenue, Newton Massachusetts 02549, USA

14. REGISTRATION HOLDER

Promedico Ltd.,
Hashiloach 6, POB 7063, Petach-Tikva 4917001

15. REGISTRATION NUMBER

167-04-36451-99

Revised on February 2022 according to MOH guidelines