PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **XPOVIO®**

selinexor tablets

Tablets, 20 mg, Oral

Antineoplastic Agent

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Date of Initial Authorization:
MAY 31, 2022

Submission Control Number: 253182

RECENT MAJOR LABEL CHANGES

None at the time of authorization

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

XPOVIO® (selinexor) is indicated:

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

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. When comparing patients 65 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction and a higher incidence of serious adverse reactions (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics, 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

- XPOVIO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- Advise patients to maintain adequate fluid and caloric intake throughout treatment. Consider intravenous hydration for patients at risk of dehydration (see 7 WARNINGS AND PRECAUTIONS).
- Provide prophylactic antiemetics. Administer a 5-HT3 receptor antagonist and other anti-nausea agents prior to and during treatment with XPOVIO (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Adjustment

- The recommended starting dose of XPOVIO in combination with bortezomib and dexamethasone in a 35-day cycle is as follows:
    - XPOVIO 100 mg (five 20 mg tablets) taken orally once weekly on Day 1 of each week.
    - bortezomib 1.3 mg/m^2 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.
- Treatment is administered until disease progression or unacceptable toxicity.
- For additional information regarding the administration of bortezomib and dexamethasone, refer to their respective Product Monographs.

Dose Modification in Patients with Hepatic Impairment

There is limited data to determine the best dosing options for patients with moderate or severe hepatic impairment; these patients should be closely monitored for safety and efficacy (see 10.3 Pharmacokinetics and refer to bortezomib Product Monograph).

Table 1 XPOVIO Dosage Reduction Steps for Adverse Reactions

	Multiple myeloma in combination with bortezomib and dexamethasone (SVd)
Recommended starting dosage	100 mg once weekly
First reduction	80 mg once weekly
Second reduction	60 mg once weekly
Third reduction	40 mg once weekly
Fourth reduction*	Permanently discontinue

*If symptoms do not resolve, treatment should be discontinued.

Recommended dosage modifications for hematologic adverse reactions are presented in Table 2. Recommended dosage modifications for non-hematologic adverse reactions are presented in Table 3.

Table 2 XPOVIO Dosage Modification Guidelines for Hematologic Adverse Reactions

Adverse Reaction	**Occurrence**	**Action**
Thrombocytopenia		
Platelet count 25 x 10^9/L to less than 75 x 10^9/L	Any	• Reduce XPOVIO by 1 dose level (see Table 1).
Platelet count 25 x 10^9/L to less than 75 x 10^9/L 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 x 10^9/L	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50 x 10^9/L. • Restart XPOVIO at 1 dose level lower (see Table 1).
Neutropenia		
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).

Adverse Reaction	Occurrence	Action
Anemia		
Hemoglobin less than 80 g/L	Any	• Reduce XPOVIO by 1 dose level (see Table 1). • Administer blood transfusions and/or other treatments per clinical guidelines.
Life-threatening consequences	Any	• Interrupt XPOVIO. • Monitor hemoglobin until levels return to 80 g/L or higher. • Restart XPOVIO at 1 dose level lower (see Table 1). • Administer blood transfusions and/or other treatments per clinical guidelines.

Table 3 XPOVIO Dosage Modification Guidelines for Non-Hematologic Adverse Reactions

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 or baseline. • Initiate additional anti-nausea medications. • Restart XPOVIO at 1 dose level lower (see Table 1).
Diarrhea		
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	• Interrupt XPOVIO and institute supportive care. • Monitor until diarrhea resolves to Grade 1 or lower. • Restart XPOVIO at current dose.
	2nd and subsequent	• Interrupt XPOVIO and institute supportive care. • Monitor until diarrhea resolves to Grade 1 or lower. • Restart XPOVIO at 1 dose level lower (see Table 1).
Grade 3 or higher	Any	• Interrupt XPOVIO and institute supportive care.

Adverse Reaction	Occurrence	Action
(increase of 7 stools or more per day over baseline; hospitalization indicated)		• Monitor until diarrhea resolves to Grade 1 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 – 120 mmol/L	Any	• Maintain XPOVIO dose and provide appropriate supportive care. • Monitor sodium levels.
Sodium level 120 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	1st	• Interrupt XPOVIO. • Monitor until fatigue resolves to Grade 1 or baseline. • Restart XPOVIO at current dose.
	2nd and subsequent	• 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.

Adverse Reaction	Occurrence	Action
Cataract (Grade ≥2)	Any	• Perform ophthalmologic evaluation. • Reduce XPOVIO by 1 dose level (see Table 1). • Monitor for progression. • Hold XPOVIO dose 24 hours prior to surgery and for 72 hours after surgery.
Other Non-Hematologic Adverse Reactions		
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).

[§]Ocular toxicities may include blindness, cataracts, visual acuity reduced, vision blurred and visual impairment.

Health Canada has not authorized an indication for pediatric use (see 1 INDICATIONS, Pediatrics).

4.3 Administration

Each XPOVIO dose should be taken orally 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.

XPOVIO can be taken with or without food.

4.4 Missed Dose

If a XPOVIO dose is missed or delayed or a patient vomits after a dose of XPOVIO, the patient should not repeat the dose. Patients should take the next dose on the next regularly scheduled day.

5 OVERDOSAGE

In general, doses of up to 300 mg selinexor/week have been associated with similar side effects to those reported for standard dosing and have generally been reversible within 1 week.

Potential acute symptoms of overdosage include nausea, vomiting, diarrhea, dehydration and confusion. Potential signs include low sodium levels, elevated liver enzymes, and low blood counts. Patients should be monitored closely and provided supportive care as appropriate. No fatalities due to overdose have been reported to date.

In the event of an overdose, the patient should be monitored, specifically for adverse reactions listed in section 8 ADVERSE REACTIONS of the Product Monograph and appropriate symptomatic treatment should be provided immediately.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 20 mg	Colloidal silicon dioxide, croscarmellose sodium, FD&C Blue #2/Indigo Carmine Aluminum Lake, FD&C Blue #1 Brilliant Blue FCF Aluminum Lake, glycerol monostearate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, polyvinyl alcohol-partially hydrolyzed, polyvinylpyrrolidone, sodium lauryl sulfate, talc, titanium dioxide.

XPOVIO tablets are supplied in blister packaging: one carton of 20 tablets (4 blister cards of 5 tablets each).

Selinexor tablets are formulated as blue, round, bi-convex, film-coated tablets with “K20” debossed on one side and nothing on the other side.

7 WARNINGS AND PRECAUTIONS

General

Consult the Product Monographs for bortezomib and dexamethasone when given in combination with XPOVIO, prior to initiating treatment.

Patients should be advised to maintain adequate fluid and caloric intake throughout treatment. Intravenous hydration should be considered for patients at risk of dehydration.

Driving and Operating Machinery

Fatigue, confusional state and dizziness have been reported in patients taking XPOVIO (see 8 ADVERSE REACTIONS). Patients should exercise caution when driving or using machines.

Endocrine and Metabolism

XPOVIO can cause severe or life-threatening hyponatremia.

Monitor sodium level at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >8.3 mmol/L) and high serum paraprotein levels. Hyponatremia should be treated as per clinical guidelines (intravenous saline and/or salt tablets), including dietary review. Patients may require XPOVIO dose interruption and/or modification based on severity of adverse reaction (See 4 DOSAGE AND ADMINISTRATION and 8 ADVERSE REACTIONS).

Gastrointestinal

Nausea / Vomiting / Diarrhea

Nausea, vomiting, diarrhea, which sometimes can be severe and require the use of antiemetic and anti-diarrheal medicinal products (see 8 ADVERSE REACTIONS). Provide prophylactic 5-HT3 antagonists and/or other anti-nausea agents, prior to and during treatment with XPOVIO.

Nausea/vomiting can be managed by dose interruption, reduction and/or discontinuation, and/or initiation of other antiemetic medicinal products as clinically indicated. Manage diarrhea by dose modifications and/or standard anti-diarrheal agents; administer intravenous fluids to prevent dehydration in patients at risk (see 4 DOSAGE AND ADMINISTRATION).

Anorexia / Weight Loss

XPOVIO can cause weight loss and anorexia. Monitor patient weight, nutritional status and volume status at baseline, and throughout treatment and as clinically indicated. Monitor more frequently during the first three months of treatment. Interrupt, reduce dose or permanently discontinue based on severity of adverse reactions (see 4 DOSAGE AND ADMINISTRATION). Provide nutritional support, fluids and electrolyte repletion as clinically indicated.

Hematologic

Thrombocytopenia

XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage (see 8 ADVERSE REACTIONS). Thrombocytopenia is the leading cause of dosage modifications (see 4 DOSAGE AND ADMINISTRATION).

In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, n=195), decreased platelet count was reported in 92% (All Grades) and 43% (Grade 3 or 4) of patients. The median time to first onset of any grade thrombocytopenia was 22 days and 43 days for Grade 3 or 4 thrombocytopenia. Bleeding occurred in 16% of patients with thrombocytopenia, clinically significant bleeding (Grade ≥3 bleeding) occurred in 4% of patients with thrombocytopenia, and fatal hemorrhage occurred in 2% of patients with thrombocytopenia. Permanent discontinuations of XPOVIO due to thrombocytopenia occurred in 2% of patients.

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 4 DOSAGE AND ADMINISTRATION).

Neutropenia

XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection (see 8 ADVERSE REACTIONS).

In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, n=195), decreased neutrophil count was reported in 48% (All Grades) and 12% (Grade 3 or 4) of patients. The median time to onset of the first event for any grade neutropenia was 23 days and 40 days for Grade 3-4 neutropenia. Febrile neutropenia was reported in <1% 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). Reduce dose, interrupt, or permanently discontinue treatment based on severity of adverse reaction (see 4 DOSAGE AND ADMINISTRATION).

Tumour Lysis Syndrome

There were no cases of tumour lysis syndrome (TLS) in the SVd arm of the BOSTON study. However, in supportive studies, the incidence of TLS was ~0.3% in patients with MM; thus, a causal relationship between selinexor treatment and TLS cannot be completely excluded. In the supportive studies, the event onset latency ranged from 3 to 8 days (median 4 days). The total selinexor dose prior to event onset ranged from 40 to 320 mg (median 160 mg). Close monitoring and management of patients with hematological malignancies, including MM, for potential signs and symptoms of TLS are recommended.

Immune

Serious and fatal infections have occurred in patients treated with XPOVIO combination therapy. Grade 3 or higher infections occurred in 31% of patients and deaths from infections occurred in 3.1% of patients treated with XPOVIO in the BOSTON clinical trial. The most common Grade 3 or higher infections were pneumonia (14%), sepsis (4.1%) and upper respiratory tract infection (3.6%) in patients treated with XPOVIO combination therapy (see 8 ADVERSE REACTIONS).

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

Monitor patients for signs and symptoms of infection and treat promptly and appropriately.

Monitoring and Laboratory Tests

Platelet counts, hemoglobin, and white blood cell count with differential should be monitored at baseline and throughout treatment with XPOVIO. Consider more frequent monitoring during the first 3 months of treatment.

Sodium level, patient weight, nutritional status and volume status should be monitored at baseline, throughout treatment and as clinically indicated. Monitor sodium level more frequently during the first 2 months of treatment.

Neurologic

XPOVIO can cause life-threatening neurological toxicities including confusional state and dizziness (see 8 ADVERSE REACTIONS).

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

Optimise hydration status, haemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes. Institute fall precautions as appropriate.

Patients should be instructed to avoid situations where dizziness or confusional state may be a problem and to not take other medicinal products that may cause dizziness or confusional state without adequate medical advice. Patients should be advised not to drive or operate heavy machinery.

Ophthalmologic

New onset or exacerbation of cataract has occurred during XPOVIO therapy (see 8 ADVERSE REACTIONS). Manage cataracts per standard clinical guidelines. Monitor for signs and symptoms of cataract, perform ophthalmic evaluation, reduce dose and monitor for progression. If surgery is warranted, hold XPOVIO dose 24 hours prior to cataract surgery and for 72 hours after surgery (see

4 DOSAGE AND ADMINISTRATION).

Reproductive Health: Female and Male Potential

- **Fertility**

  Based on findings in animals, XPOVIO may impair fertility in females and males of reproductive potential (see 16 NON-CLINICAL TOXICOLOGY).

- **Teratogenic Risk**

  XPOVIO can cause fetal harm when administered to a pregnant woman (see 7.1 SPECIAL POPULATIONS).

  Advise females of reproductive potential to use effective contraception during 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.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of XPOVIO in pregnant women. Studies in animals have shown selinexor can cause fetal harm (see 16 NON-CLINICAL TOXICOLOGY). XPOVIO is not recommended during pregnancy or in females of childbearing potential not using contraception.

If the patient becomes pregnant while taking XPOVIO, XPOVIO should be immediately discontinued, and the patient should be apprised of the potential hazard to the fetus.

Based on findings in animal studies and its mechanism of action (see 10 CLINICAL PHARMACOLOGY), 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. Developmental defects were seen with daily exposure in pregnant rats at systemic exposures below the exposure (AUC_{last}) in humans at the recommended human dose of 100 mg. Advise pregnant women of the risks to a fetus.

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 and above. The NOAEL for maternal and embryo-fetal developmental toxicity was 0.25 mg/kg/day (approximately 0.02x the human exposure (AUC_{last}) of the recommended dose of 100 mg). Malformations were observed at 2 mg/kg, including microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus.

7.1.2 Breast-feeding

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.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

In BOSTON, of the 195 patients with multiple myeloma who received XPOVIO in combination with bortezomib and dexamethasone, 56% were 65 years of age and older, while 17% were 75 years of age and older. No overall differences in effectiveness were observed between these patients and younger patients. When comparing patients 65 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (28% vs 13%) and a higher incidence of serious adverse reactions (56% vs 47%).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety data described in this section are based on the BOSTON study, a global, randomized, open-label clinical trial in patients with previously treated multiple myeloma (n=399). In BOSTON, once-weekly XPOVIO 100 mg was administered with once-weekly bortezomib 1.3 mg/m^2 and twice-weekly oral dexamethasone 20 mg (SVd) and compared to twice-weekly bortezomib 1.3 mg/m^2 with twice-weekly dexamethasone 20 mg (Vd) (see 14 CLINICAL TRIALS).

The most frequent treatment-emergent adverse events (TEAEs) in >10% of SVd patients were thrombocytopenia, nausea, fatigue, anemia, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, weight decreased, asthenia, cataract, vomiting, cough, pneumonia, constipation, insomnia, back pain, pyrexia, neutropenia, dyspnea, vision blurred, bronchitis, dizziness, peripheral edema, headache, hypokalemia and taste disorder.

Severe (Grade 3 or higher) TEAEs were reported in 85% and 61% of SVd- and Vd-treated patients, respectively. Severe (Grade 3 or higher) TEAEs with at least a 5% greater incidence in the SVd arm compared to the Vd arm were thrombocytopenia (39% vs 17%), anemia (16% vs 10%), cataract (9% vs 2%), diarrhea (6% vs 0.5%), nausea (8% vs 0%) and fatigue (13% vs 1%). Serious adverse events (resulting in death or disability, requiring or prolonging hospitalization, or are life-threatening) were reported in 52% and 38% of SVd- and Vd-treated patients, respectively. Serious adverse events with at least a 2% greater incidence in the SVd arm compared to the Vd arm were diarrhea (4% vs 0%), vomiting (4% vs 0%), cataract (2% vs 0%), nausea (2% vs 0%), urinary tract infection (2% vs 0%), and sepsis (4% vs 0%). There was a similar number of fatal adverse events in the SVd (12 patients; 6.2%) and in the Vd (11 patients; 5.4%) arms within 30 days of last treatment. The most frequent fatal adverse events in SVd-treated patients were pneumonia and sepsis (3 patients [1.5%] each).

A statistically significant reduction in All Grades and ≥ Grade 2 peripheral neuropathy was noted in patients receiving SVd (32% and 21%) compared with patients receiving Vd (47% and 34%) [odds ratio 0.52 and 0.50, one-sided $p<0.0013$]. A nominal reduction in severe neuropathy (≥ Grade 3) was also observed in SVd-treated patients (5% SVd vs. 9% Vd).

Permanent discontinuation of XPOVIO due to an adverse event occurred in 19% of patients. Adverse events 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 event occurred in 83% of patients. Adverse events 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 event occurred in 64% of patients. Adverse events which required dose reductions in >5% of patients included thrombocytopenia (31%), decreased appetite (8%), nausea, fatigue, decreased weight (7% each) and asthenia (6%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Adverse Reactions and Laboratory Abnormalities described below reflect exposure to XPOVIO for a median treatment duration of 30 weeks (range: 1 to 120 weeks) and a median dose of 80 mg/week (range: 30 to 137) for the SVd patient group (n=195) and a median treatment duration of 32 weeks (range: 1 to 122 weeks) for the Vd patient group (n=204).

Table 5 Adverse Reactions with an All Grades Incidence ≥1% in the SVd Group by MedDRA System Organ Class in the BOSTON Study

	SVd N = 195		**Vd N = 204**	
MedDRA System Organ Class[a] Preferred Term	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Blood and lymphatic system disorders				
Thrombocytopenia	117 (60)	77 (39)	55 (27)	35 (17)
Anemia[b]	71 (36)	31 (16)	47 (23)	21 (10)
Neutropenia	29 (15)	17 (9)	12 (6)	7 (3.4)
Lymphopenia	11 (6)	7 (3.6)	4 (2)	3 (1.5)
Leukopenia	10 (5)	1 (0.5)	3 (1.5)	1 (0.5)
Cardiac disorders				
Tachycardia	10 (5)	0	3 (1.5)	0
Ear and Labyrinth Disorders				
Vertigo	6 (3.1)	0	1 (0.5)	0
Eye Disorders				
Cataract	42 (22)	17 (9)	13 (6)	3 (1.5)
Vision Blurred[§]	25 (13)	1 (0.5)	13 (6)	0

	SVd N = 195		Vd N = 204	
MedDRA System Organ Class[a] Preferred Term	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Gastrointestinal disorders				
Nausea	98 (50)	15 (8)	20 (10)	0
Diarrhea	63 (32)	12 (6)	51 (25)	1 (0.5)
Vomiting	40 (21)	8 (4.1)	9 (4.4)	0
Constipation	33 (17)	0	35 (17)	3 (1.5)
Abdominal pain	15 (8)	0	12 (6)	3 (1.5)
Dyspepsia	8 (4.1)	0	5 (2.5)	1 (0.5)
Dry mouth	4 (2.1)	0	1 (0.5)	0
Flatulence	3 (1.5)	0	1 (0.5)	0
General disorders and administration site conditions				
Fatigue	82 (42)	26 (13)	37 (18)	2 (1.0)
Asthenia	48 (25)	16 (8)	27 (13)	9 (4.4)
Pyrexia	30 (15)	3 (1.5)	22 (11)	2 (1.0)
Edema peripheral	23 (12)	1 (0.5)	26 (13)	0
General physical health deterioration	3 (1.5)	3 (1.5)	1 (0.5)	1 (0.5)
Malaise	3 (1.5)	0	0	0
Infections and infestations				
Upper respiratory tract infection[§]	57 (29)	7 (3.6)	44 (22)	3 (1.5)
Pneumonia[c]	35 (18)	27 (14)	34 (17)	24 (12)
Bronchitis[d]	24 (12)	4 (2.1)	20 (10)	1 (0.5)
Lower respiratory tract infection	14 (7)	4 (2.1)	10 (5)	4 (2)
Sepsis[§]	8 (4.1)	8 (4.1)	1 (0.5)	1 (0.5)
Injury, poisoning and procedural complications				
Fall	10 (5)	2 (1.0)	8 (3.9)	1 (0.5)
Contusion	6 (3.1)	0	2 (1.0)	0

	SVd N = 195		Vd N = 204	
MedDRA System Organ Class[a] Preferred Term	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Investigations				
Weight decreased	51 (26)	4 (2.1)	25 (12)	2 (1.0)
Alanine aminotransferase increased	13 (7)	3 (1.5)	7 (3.4)	0
Aspartate aminotransferase increased	9 (5)	3 (1.5)	6 (2.9)	1 (0.5)
Metabolism and nutrition disorders				
Decreased appetite	69 (35)	7 (3.6)	11 (5)	0
Hypokalemia	19 (10)	8 (4.1)	10 (5)	5 (2.5)
Hypophosphatemia	16 (8)	10 (5)	6 (2.9)	3 (1.5)
Hypocalcemia	15 (8)	3 (1.5)	5 (2.5)	0
Hyponatremia	15 (8)	9 (5)	3 (1.5)	1 (0.5)
Hypercreatinemia	13 (7.0)	2 (1.0)	7 (3.4)	1 (0.5)
Dehydration	9 (5)	3 (1.5)	2 (1)	1 (0.5)
Hypomagnesemia	7 (3.6)	0	4 (2.0)	0
Hyperkalemia	7 (3.6)	0	4 (2.0)	2 (1.0)
Nervous system disorders				
Neuropathy peripheral[§]	63 (32)	9 (5)	96 (47)	18 (9)
Dizziness	24 (12)	1 (0.5)	8 (3.9)	0
Headache	19 (10)	1 (0.5)	11 (5)	0
Taste disorder[§]	19 (10)	0	4 (2)	0
Syncope	7 (3.6)	2 (1.0)	3 (1.5)	1 (0.5)
Amnesia[§]	5 (2.6)	1 (0.5)	1 (0.5)	0
Balance disorder	3 (1.5)	0	1 (0.5)	0
Psychiatric disorders				
Insomnia	31 (16)	2 (1.0)	32 (16)	4 (2)
Mental status changes[§]	17 (9)	3 (1.5)	3 (1.5)	0

	SVd N = 195		Vd N = 204	
MedDRA System Organ Class[a] Preferred Term	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Renal and urinary disorders				
Acute kidney injury[d]	10 (5)	3 (1.5)	3 (1.5)	2 (1.0)
Respiratory, thoracic and mediastinal disorders				
Cough	35 (18)	1 (0.5)	30 (15)	0
Dyspnea[§]	26 (13)	1 (0.5)	35 (17)	5 (2.5)
Epistaxis	11 (6)	2 (1)	3 (1.5)	1 (0.5)
Skin and subcutaneous tissue disorders				
Alopecia	9 (5)	0	3 (1.5)	0
Night sweats[§]	6 (3.1)	1 (0.5)	1 (0.5)	0
Pruritis	5 (2.6)	0	3 (1.5)	0
Vascular disorders				
Hypotension	11 (6)	4 (2.1)	11 (5)	1 (0.5)

SVd = XPOVIO + bortezomib (VELCADE®) + dexamethasone; Vd = bortezomib (VELCADE®) + dexamethasone.

[a] MedDRA version 22.0

[b] Grade 5 anemia was reported in one patient (0.5%) in the Vd arm.

[c] Grade 5 pneumonia was reported in 3 patients (1.5%) in the SVd arm and 3 patients (1.5%) in the Vd arm. These events were considered to be not related to study treatment.

[d] Includes one (0.5%) Grade 5 event in the SVd arm considered not related to study treatment.

[§] Includes multiple preferred terms:
Neuropathy peripheral represents high level term peripheral neuropathies NEC.
Upper respiratory tract infection includes upper respiratory infection, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, and viral upper respiratory infection.
Vision blurred includes blurred vision, visual acuity reduced and visual impairment.
Dyspnea includes dyspnea and dyspnea exertional.
Mental status changes includes mental status changes, confusional state and delirium.
Taste disorder includes taste disorder, ageusia, and dysgeusia.
Pneumonia includes pneumonia, pneumonia pneumococcal, hemophilus infection, pneumonia bacterial, pneumonia fungal, pneumonia influenza, pneumonia parainfluenzae viral, pneumonia respiratory syncytial viral, and pulmonary sepsis.
Amnesia includes amnesia and memory impairment
Night sweats includes night sweats and hyperhidrosis
Sepsis includes sepsis, septic shock, pulmonary sepsis, staphylococcal sepsis and urosepsis

Cataract

New onset or exacerbation of cataract has occurred during treatment with XPOVIO (see 7 WARNINGS AND PRECAUTIONS). 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. The median time to worsening of cataract in patients presenting with cataract at start of XPOVIO therapy was 237 days. Treatment of cataracts usually requires surgical removal of the cataract.

Gastrointestinal Events

Among the 195 patients with multiple myeloma who received SVd in the BOSTON study, diarrhea (32%), nausea (50%), and vomiting (21%) were among the most frequent adverse drug reactions associated with selinexor treatment. Most events were Grade 1 or 2 with ≥ Grade 3 events of diarrhea, nausea and vomiting occurring in 6%, 8% and 4% of patients, respectively. These events occurred most frequently in the first 8 weeks of treatment. In the SVd arm, 172 (88.2%) patients were given 5-HT_3 antagonists prophylactically. In the clinical trial, patients with treatment emergent nausea/vomiting could also receive olanzapine or an NK1 antagonist. Permanent treatment discontinuations due to diarrhea and vomiting each occurred in 2% of SVd treated patients.

Anorexia was reported in 35% of patients and Grade 3 anorexia was reported in 3.6% of patients who received XPOVIO 100 mg once weekly in the BOSTON study (n=195). The median time to onset of the first event was 35 days. Permanent discontinuations due to anorexia occurred in 2.1% of patients. Weight loss was reported in 26% of patients and Grade 3 weight loss was reported in 2.1% of patients. The median time to onset of the first event was 58 days. Permanent discontinuation due to weight loss occurred in 1% of patients (see 7 WARNINGS AND PRECAUTIONS).

8.3 Less Common Clinical Trial Adverse Reactions

All adverse reactions occurred at >1% and are presented in Table 5, ADVERSE REACTIONS, Clinical Trial Adverse Reactions.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 6 Select Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients with Multiple Myeloma Receiving SVd or Vd in the BOSTON Trial

Laboratory Abnormality	Weekly SVd		Twice Weekly Vd	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematologic laboratory abnormalities				
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 laboratory abnormalities				
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

Laboratory Abnormality	Weekly SVd		Twice Weekly Vd	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
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 laboratory abnormalities				
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.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

No dedicated clinical drug interaction studies have been conducted.

There are potential drug-drug interactions between selinexor and CYP3A4 inhibitors or inducers. Concomitant use of strong CYP3A4 inducer might lead to lower exposure of selinexor. Patients should be closely monitored for safety and efficacy when initiating therapy with concomitant moderate or strong modulators of CYP3A4.

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.

9.2 Drug-Food Interactions

Interactions with food have not been established.

9.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

In non-clinical settings, selinexor reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of growth promoting (oncogenic) proteins by specifically blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to marked accumulation of TSPs in the nucleus, cell cycle arrest, reductions in several oncoproteins such as c-Myc and cyclin D1, and apoptosis of cancer cells. The combination of selinexor and dexamethasone was evaluated in patients with disease refractory/resistant to dexamethasone and proteasome inhibitors and in cell lines, both of which demonstrated activity and synergy for the combination including when proteasome inhibition was present. The combination of selinexor and bortezomib was evaluated in cells and murine xenograft multiple myeloma models in vivo, including cells and models resistant to proteasome inhibitors.

10.2 Pharmacodynamics

Cardiac electrophysiology

The effect of multiple doses of selinexor up to 175 mg weekly on the QTc interval was evaluated in patients with heavily pre-treated haematologic malignancies. Selinexor had no large effect (i.e. no greater than 20 ms) on QTc interval at the therapeutic dose level.

10.3 Pharmacokinetics

The pharmacokinetics of a single oral dose of 60 mg/m^2 (equivalent to 100 mg) selinexor is shown in Table 7.

Table 7 Summary of Selinexor Pharmacokinetic Parameters (Mean and CV%) in Patients with Hematologic Malignancies

	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng h/mL)	CL/F (L/h/kg)	Vd/F (L/kg)
Single dose mean	693 (29)	1.9 (1.8 – 2.0)	6.0 (30)	6998 (12)	0.19 (25)	1.6 (23)

Absorption

Following oral administration of selinexor peak plasma concentration, C_{max} is reached within 4 hours. Concomitant administration of a high fat meal (800 - 1,000 calories with approximately 50% of total caloric content of the meal from fat) resulted in an increase in AUC_T of 15.7% and an increase in C_{max} of 14.7%. Concomitant administration of a low-fat meal (500 – 600 calories with approximately 20% of total caloric content of the meal from fat) resulted in an increase in AUC_T of 20.0% and an increase in C_{max} of 17.8%. The median T_{max} was delayed from 1.5 to 3.4 hours when the tablets were administered with food.

Distribution

Selinexor is 95.0% bound to human plasma proteins. In a population pharmacokinetic (PK) analysis, the apparent volume of distribution (Vd/F) of selinexor was 133 L in cancer patients.

Metabolism

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

Elimination

Following a single dose of 100 mg selinexor the mean half-life (t1/2) is 6 to 8 hours. In a population PK analysis, the apparent total clearance (CL/F) of selinexor was 18.6 L/h in cancer patients.

Special Populations and Conditions

Based on population pharmacokinetic analyses of 793 patients no clinically significant differences in the pharmacokinetics of selinexor were observed based on age (18 – 94 years old), sex, body weight (36 to 168 kg), and ethnicity.

- **Pediatrics** Selinexor was not studied in patients under 18 years of age.
- **Hepatic Insufficiency** Population PK analysis indicated that mild hepatic impairment (bilirubin >1-1.5 x ULN or AST > ULN, but bilirubin ≤ ULN, n = 119) had no clinically significant effect on the PK of selinexor. In a small number of patients with moderate (bilirubin >1.5-3 x ULN; any AST, n = 10) and severe hepatic impairment (bilirubin >3 x ULN; any AST, n = 3), no clear change in the apparent clearance (CL/F) was observed. However, because of the small number of patients involved in the analysis, patients with moderate or severe hepatic impairment should be treated with caution.
- **Renal Insufficiency** The degree of renal impairment was determined by creatinine clearance (CLcr) as estimated by the Cockcroft-Gault equation. Results from population PK analyses of patients with normal renal function (n=283, CLcr: >=90 mL/min), and mild (n=309, CLcr: 60 to 89 mL/min), moderate (n=185, CLcr: 30 to 59 mL/min) or severe (n=13, CLcr: 15 to 29 mL/min) renal impairment indicated that creatinine clearance had no impact on the PK of XPOVIO. Therefore, mild, moderate, or severe renal impairment is not expected to alter selinexor PK, and no adjustments in the dose of selinexor are required in patients with renal dysfunction.

11 STORAGE, STABILITY AND DISPOSAL

Store between 2 - 30°C.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

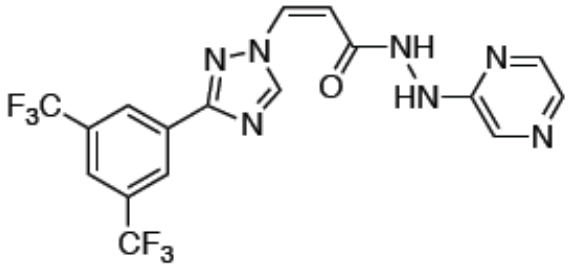
Drug Substance

Proper/Common name: selinexor

Chemical name:
(2*Z*)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-1yl}-*N*'-(pyrazin-2-yl)prop-2-enehydrazide

Molecular formula and molecular mass: $C_{17}H_{11}F_6N_7O$; 443.31 g/mol

Structural formula:



Physicochemical properties: Selinexor is the anhydrous Form A, a white to off-white powder with a pKa of 10.2. The solubility of selinexor in aqueous media decreases over the range pH 1.0 to pH 7.4 from 0.114 mg/mL to 0.009 mg/mL. The melting point is 178°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Relapsed/Refractory Multiple Myeloma

Table 8 Summary of patient demographics for a clinical trial in patients with relapsed or refractory multiple myeloma who had received at least one prior line of therapy (BOSTON)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
KCP-330-023 (BOSTON)	Randomized (1:1), open label, active controlled, Phase 3 study	SVd arm[a]: XPOVIO 100 mg PO once weekly + bortezomib 1.3 mg/m^2 SC once weekly + dexamethasone 20 mg PO twice weekly	195	65.3 (40 - 87) 55.9% ≥ 65 years of age	Male: 59% Female: 41%
		Vd arm[b]: bortezomib 1.3 mg/m^2 SC twice weekly + dexamethasone 20 mg PO four times weekly for first 8 cycles followed by bortezomib 1.3 mg/m^2 SC once weekly + dexamethasone 20 mg PO twice weekly	207	66.7 (38 - 90) 63.8% ≥ 65 years of age	Male: 56% Female: 44%

SVd = selinexor + bortezomib (VELCADE®) + dexamethasone; Vd = bortezomib (VELCADE®) + dexamethasone

[a] XPOVIO was administered on days 1, 8, 15, 22, 29 in combination with bortezomib once weekly on days 1, 8, 15, 22 and dexamethasone on days 1, 2, 8, 9, 15, 16, 22, 23, 29 and 30 of each 35-day cycle.

[b] bortezomib was administered twice weekly on days 1, 4, 8, 11 in combination with dexamethasone on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for the first 8 cycles, followed by bortezomib once weekly on days 1, 8, 15, 22 and dexamethasone on days 1, 2, 8, 9, 15, 16, 22, 23, 29, 30 of each 35-day cycle.

The efficacy of XPOVIO in combination with bortezomib and dexamethasone was evaluated in a global, randomized, open label, active-controlled trial in patients 18 years of age or older who had received 1 to 3 prior anti-MM regimens, BOSTON (KCP-330-023). A total of 402 patients were randomized 1:1 to receive either SVd (n=195) or Vd (n=207). Among these, the median age was 67 years (range 38 to 90 years), 60% of patients were 65 years of age or older, 20% of patients were 75 years of age or older, and 57% were male. 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.

Patients enrolled in the trial had multiple myeloma that was measurable by paraprotein in the serum, urine or via free light chain measurements. Prior treatment with bortezomib or another proteasome inhibitor was allowed. Eligible patients were also required to have an Eastern Cooperative Oncology Group (ECOG) score of ≤ 2 and adequate hepatic, renal and hematopoietic function. Patients were excluded if they had systemic light-chain amyloidosis, CNS involvement, or Grade 2 painful or Grade 2 or higher peripheral neuropathy.

Treatment continued in both arms until disease progression or unacceptable toxicity.

Antiemetic prophylaxis was used in 88% and 36% of patients in the SVd arm and Vd arm, respectively.

Baseline patient and disease characteristics were balanced and comparable between treatment arms and are shown in Table 9.

Table 9 Baseline Patient and Disease Characteristics in BOSTON

	XPOVIO + bortezomib + dexamethasone (N = 195)	**bortezomib + dexamethasone (N=207)**
Median age in years (range)	66 (40 – 87)	67 (38 – 90)
Gender (%) Male / Female	59.0 / 41.0	55.6 / 44.4
Age Group (% [<65 / 65 – 74 / ≥75])	44.1 / 38.5 / 17.4	40.1 / 39.8 / 20.1
Race, n (%) White Black or African American Asian Other or Missing	 161 (82.6) 4 (2.1) 25 (12.8) 5 (2.6)	 165 (79.7) 7 (3.4) 25 (12.1) 10 (4.8)
Median years from diagnosis to randomization (range)	3.81 (0.4, 23.0)	3.59 (0.4, 22.0)
ECOG performance status, n (%) 0 – 1 ≥2	 175 (90) 20 (10)	 191 (92) 16 (8)
Creatinine Clearance, n (%), mL per minute <30 30 to 59 ≥60	 3 (1.5) 53 (27) 139 (71)	 10 (5) 60 (29) 137 (66)

	XPOVIO + bortezomib + dexamethasone (N = 195)	bortezomib + dexamethasone (N=207)
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)
Known high-risk cytogenetics[a], n (%)	97 (50)	95 (46)
del (17p)/p53	21 (11)	16 (8)
t (14;16)	7 (4)	11 (5)
t (4;14)	22 (11)	28 (14)
1q21	80 (41)	71 (34)

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

The primary endpoint of the BOSTON study was 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). Confirmation of progressive disease was required. Progression and disease response were assessed every three weeks up to week 37, then every 5 weeks thereafter. Key secondary efficacy endpoints included overall response rate (ORR), overall survival (OS), and response rate for responses ≥ very good partial response (VGPR) as per IMWG criteria.

BOSTON demonstrated a statistically significant improvement in PFS in the SVd arm compared to the Vd arm; hazard ratio (HR)=0.70 (95% CI: 0.53-0.93; p=0.0075). Efficacy results are shown in Table 10 and Figure 1.

Table 10 Efficacy Results of BOSTON in Patients with Relapsed or Refractory Multiple Myeloma

Endpoint	XPOVIO + bortezomib + dexamethasone (N = 195)	bortezomib + dexamethasone (N=207)
Progression-Free Survival		
Median (months) [95% CI]	13.9 [11.7, Not reached]	9.5 [8.1, 10.8]
Hazard Ratio[a] [95% CI]	0.70 [0.53, 0.93]	
One-sided p-value[b]	0.0075	
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)
Duration of Response		
Median (months) [95% CI]	20.3 (12.6, NE)	12.9 (9.3, 15.8)
≥ 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	
Overall Survival (OS)		
Number of events, n (%)	47	62
Median OS, months (95% CI)	Not reached [NE, NE]	25.0 [23.5, NE]
Hazard Ratio (95% CI)[e]	0.84 [0.58, 1.23]	
One-sided p-value	0.1852	

[a] Hazard ratio is based on stratified Cox's proportional hazard regression modeling. Median follow up of 15.1 months at the time of the analysis.

[b] p-value based on stratified log-rank test. The pre-planned PFS interim analysis boundary of statistical significance was defined as a p-value <0.0103.

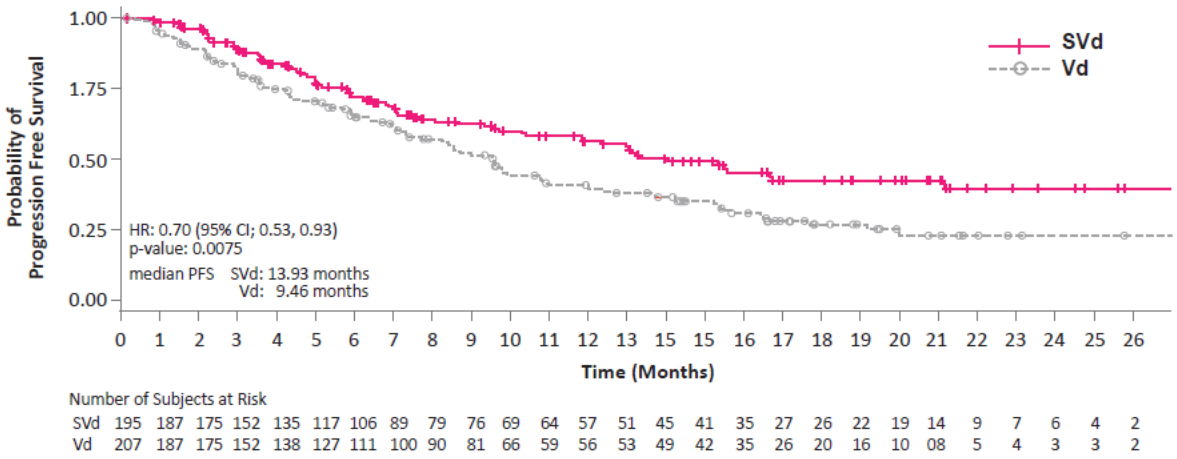
[c] Includes sCR + CR + VGPR + PR, p value based on Cochran-Mantel-Haenszel test.

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

[e] Based on stratified Cox Proportional Hazard model with Efron's Method of handling ties. Stratified for prior PI therapies, number of prior anti-MM regimens and R-ISS Stage at screening.

NE=Not Estimable

Figure 1 BOSTON Kaplan-Meier Curve of Progression-Free Survival (ITT Population)



The median time to response was 1.1 months in the SVd-treated patients and 1.4 months in the Vd-treated patients. The median duration of response was 20.3 months and 12.9 months in the SVd and Vd arms, respectively.

Upon confirmed progressive disease, 74 (36%) patients crossed over from the Vd arm to receive a regimen that included selinexor.

In an ad-hoc updated analysis (15 Feb 2021) with median follow-up time of 22.1 months the median PFS was 13.2 months in the SVd arm and 9.5 months in the Vd arm (hazard ratio (HR)=0.71 (95% CI: 0.54 – 0.93; p=0.0064). The overall response rate remained consistent with the primary analysis (77% and 63% in the SVd and Vd arms, respectively). The median duration of response was 17.3 months in the SVd arm and 12.9 months in the Vd arm. At the time of the updated analysis (median follow-up for survival 28.7 months), the median overall survival was 36.67 (95% CI: 30.19, NE) months in the SVd arm and 32.76 (95% CI: 27.83, NE) months in the Vd arm (HR=0.88 (95% CI: 0.63 – 1.21; p=0.2152).

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, p=0.0013], due to the lower dose of bortezomib in the SVd arm.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Findings in the repeat dose 13-week rat study were decrements in body weight gain and food consumption, and hematopoietic/lymphoid hypoplasia, and male/female reproductive organ effects. All the reproductive organ toxicity was irreversible with cessation of treatment. The NOAEL was considered to be 0.25 mg/kg (approximately 0.02-fold of human area under the curve [AUC_{last}] of an 100 mg dose) in males and 1 mg/kg (approximately 0.14-fold of the area under the curve [AUC_{last}] at the recommended human dose of 100 mg) in females.

In the 13-week monkey study, the treatment-related effects observed included body weight loss,

gastrointestinal effects, and lymphoid/haematologic depletion which were partially/fully reversed with cessation of treatment. Gastrointestinal toxicities, including anorexia, decrements in body weight gain and reduced food consumption were noted to be CNS-mediated. No safety margin for these toxicities could be established. The NOAEL was 1 mg/kg across both genders approximately 0.23- fold to 0.29-fold of the area under the curve (AUC_{last}) at the recommended human dose of 100 mg.

Carcinogenicity: Carcinogenicity studies have not been conducted with selinexor.

Genotoxicity: Selinexor was not mutagenic in vitro in a bacterial reverse mutation (Ames) assay and was not clastogenic in either the in vitro mammalian chromosomal aberration test in human lymphocytes or in the in vivo bone marrow micronucleus assay in rats.

Reproductive and Developmental Toxicology: 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. In other short-term toxicology studies, effects were observed in male and female reproductive organs in monkeys and developmental effects were seen with daily exposure in rats.

Fertility and early embryonic development 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 results were observed at systemic exposures approximately 0.10, 0.29, and 0.49 times, respectively, the exposure (AUC_{last}) in humans at the recommended human dose of 100 mg.

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 and above. The NOAEL for maternal and embryo-fetal developmental toxicity was 0.25 mg/kg/day (approximately 0.02x the human exposure (AUC_{last}) of the recommended dose of 100 mg.

Other Toxicities

A topical challenge to guinea pig in a sensitization assay showed that selinexor at 25% induced a mild grade II dermal contact hypersensitivity response at 24 and 48 hours.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrXPOVIO®

selinexor tablets

Read this carefully before you start taking **XPOVIO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **XPOVIO**.

Your cancer will be treated with XPOVIO in combination with the medicines bortezomib and dexamethasone. Read the leaflets for these medications as well as this one.

What is XPOVIO used for?

XPOVIO is used together with bortezomib and dexamethasone to treat adults with multiple myeloma. You will likely already have received at least one treatment for your cancer.

How does XPOVIO work?

XPOVIO is a XPO1 inhibitor cancer medicine. It blocks the action of a substance called XPO1. XPO1 acts inside cells. It is responsible for carrying important materials into and out of the core of the cell (the nucleus). Some of these materials are responsible for cancer cell growth. By blocking XPO1, XPOVIO can slow down the growth of cancer cells, cause cancer cell death and can stop multiple myeloma from getting worse.

What are the ingredients in XPOVIO?

Medicinal ingredients: selinexor

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, FD&C Blue #2/Indigo Carmine Aluminum Lake, FD&C Blue #1 Brilliant Blue FCF Aluminum Lake, glycerol monostearate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, polyvinyl alcohol-partially hydrolyzed, polyvinylpyrrolidone, sodium lauryl sulfate, talc, titanium dioxide.

XPOVIO comes in the following dosage forms:

Tablets, 20 mg

Do not use XPOVIO if:

- you are allergic to selinexor or any of the other ingredients in XPOVIO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take XPOVIO. Talk about any health conditions or problems you may have, including if you:

- have liver problems
- have eye problems, such as cataracts

Other warnings you should know about:

Female patients – Pregnancy and breastfeeding:

- If you are pregnant, able to get pregnant or think you are pregnant, there are specific risks you should discuss with your healthcare professional.
- Avoid getting pregnant while taking XPOVIO. It may harm your unborn baby.

- If you are able to get pregnant, use an effective method of birth control while you are taking XPOVIO and for at least 1 week after your last dose. This is to ensure you do not become pregnant.
- If you become pregnant, or think you are pregnant, tell your healthcare professional right away.
- It is not known if XPOVIO passes into your breast milk. Do not breast-feed your baby during treatment with XPOVIO and for at least 1 week after your last dose.

Male patients: During your treatment with XPOVIO, use an effective method of birth control each time you have sex with a woman who can get pregnant. Continue this birth control for at least 1 week after your last dose.

Fertility for females and males: Taking XPOVIO may make it more difficult for you to have a child in the future.

XPOVIO can cause serious side effects, including:

- **Problems with your blood including:**
  - **Neutropenia** (low white blood cell count): Low white blood cell counts can sometimes be severe. This may increase your risk for serious **infections** that can cause death. Your healthcare professional will monitor you for signs and symptoms of infection. They may give you antibiotics to treat an infection or other medicines to improve your white blood cell count.
  - **Thrombocytopenia** (low platelet count): This can lead to easy bruising or bleeding. Bleeding may be severe and can sometimes cause death. You may need a platelet transfusion or other medicines to help increase your platelet count. Your healthcare professional will also monitor you for signs of bleeding.
  - **Hyponatremia** (decreased sodium levels): This is when sodium levels in your blood are low. It can be severe or life-threatening. Low sodium levels in your blood can happen if you have nausea, vomiting, diarrhea, you become dehydrated, or if you have loss of appetite with XPOVIO. You may not have any symptoms of a low sodium level.
  - Your healthcare professional will do **blood tests** before you start taking XPOVIO. These tests will be repeated regularly during your treatment. They will be done more often during the first 2 to 3 months of treatment. The results of these tests will tell your healthcare professional how XPOVIO is affecting your white blood cell and platelet counts and your sodium levels. Throughout your treatment your healthcare professional will watch you for signs and symptoms of infection and bleeding. They may also talk to you about your diet and prescribe you fluid through a vein in your arm (intravenous (IV) fluid) if you are dehydrated.
- **Nausea, vomiting and diarrhea:** These can sometimes be severe. Your healthcare professional will prescribe medicines to help prevent or treat your nausea and vomiting as well as your diarrhea. You may also receive treatments to help prevent dehydration including IV fluids. It is important for you to also drink fluids to prevent dehydration.
- **Anorexia** (loss of appetite) and **weight loss:** You may lose your appetite and experience weight loss while you are taking XPOVIO. Your healthcare professional will monitor your weight and ask you questions about how much you are eating. They may adjust your XPOVIO dose if you have these side effects. They may also give you medicines to increase your appetite. It is important for you to also eat enough calories to help prevent weight loss.

- **Neurologic problems** such as dizziness, fainting, confusional state and changes in mood and behaviour. These may be worse if you are taking certain other medications. You should avoid situations that may cause you to become dizzy or cause confusion.
- **Cataracts:** This is an eye problem where the lens of the eye becomes cloudy. XPOVIO may cause cataracts or cause your cataract to get worse. If you notice changes with your vision, your healthcare professional may request an eye examination by an eye specialist (an ophthalmologist). You may need eye surgery to remove the cataract and fix your vision. If you need surgery for your cataracts, do not take XPOVIO for 24 hours before the surgery and for 72 hours (3 days) after.

See the "Serious side effects and what to do about them" table below, for more information on these and other serious side effects.

Driving and using machines: Before you do tasks that may require special attention, wait until you know how you respond to XPOVIO. If you are tired, confused or are dizzy do not drive or use tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with XPOVIO:

- a medicine used to treat bacterial infections called rifampin
- Medicines used to prevent seizures or to treat epilepsy or medicines used to treat a painful condition of the face called trigeminal neuralgia including carbamazepine and phenytoin
- an herbal remedy used to treat depression called St. John's Wort

How to take XPOVIO:

- Exactly as your healthcare provider tells you. Do not decrease, stop, or change your dose on your own.
- XPOVIO will be given with bortezomib and dexamethasone in treatment cycles. Each cycle is 5 weeks (35 days) long.
- Take your XPOVIO on day 1 of each week in the cycle. You will take your XPOVIO only once each week. Take it with or without food.
    - Your healthcare professional will tell you how much and how often you will have each of bortezomib and dexamethasone.
- Swallow your XPOVIO tablets whole with water. Do not break, chew, crush, or divide the tablets.
- On the days you take XPOVIO, take it at about the same time.
- Your healthcare professional may recommend that you take other medicines before and during treatment with XPOVIO to help prevent nausea and vomiting. Take these exactly as you are told. Tell your healthcare professional if these medicines do not control your nausea and vomiting.
- You may also need to increase the amount of fluid you drink and food you eat during your treatment.

Usual dose:

100 mg once per week. This weekly dose is made by taking five 20 mg XPOVIO tablets on Day 1 of each week of the cycle.

If you experience certain side effects while taking XPOVIO your healthcare professional may stop, interrupt or change your dose to one of the following:

- 80 mg once per week: Take four 20 mg tablets on Day 1 of each week of the cycle.
- 60 mg once per week: Take three 20 mg tablets on Day 1 of each week of the cycle.
- 40 mg once per week: Take two 20 mg tablets on Day 1 of each week of the cycle.

Check your dose before starting your treatment. Only take your dose once per week.

Overdose:

If you think you, or a person you are caring for, have taken too much XPOVIO, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of XPOVIO, skip the dose. Take your next dose at the regularly scheduled day and time.

If you vomit after taking a dose of XPOVIO, do not repeat the dose. Take your next dose of XPOVIO on the next scheduled day and time.

What are possible side effects from using XPOVIO?

These are not all the possible side effects you may have when taking XPOVIO. If you experience any side effects not listed here, tell your healthcare professional.

- abdominal pain
- altered taste
- blurry vision
- bruising
- constipation
- cough
- dehydration
- difficulty falling asleep
- dizziness, headache
- dry mouth
- fatigue, lack of energy
- gas
- hair loss
- heartburn
- decreased blood pressure
- night sweats
- nosebleed
- shortness of breath
- swelling of the hands or legs

XPOVIO can cause abnormal blood test results. Your healthcare professional will do blood tests during your treatment and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Anemia (low red blood cells): being short of breath, feeling very tired, loss of energy, weakness, irregular heartbeats, pale complexion		✓	
Cataracts (clouding of the lens of the eye): blurry vision, seeing double, sensitivity to light or glare, symptoms can be new or worsening	✓		
Decreased appetite	✓		
Decreased weight	✓		
Diarrhea: severe, at least 3 loose or liquid bowel movements in a day	✓		
Hyperglycemia (high blood sugar): increased thirst, frequent urination, dry skin, headache, blurred vision, fatigue	✓		
Infections including: **Sepsis** (infection of the blood): fast heart rate, fever, confusion and rapid breathing **Urinary tract infection**: frequent urination, painful urination, blood in the urine **Shingles**: painful skin rash with blisters **Upper and lower respiratory infections**: cough, fatigue, fever, chills, flu-like symptoms **Pneumonia** (a lung infection) and **bronchitis** (inflammation of the airway): cough, fever, chills, shortness of breath that may only occur when climbing stairs, difficult and painful breathing		✓	
Nausea: feeling the need to vomit		✓	
Neurologic problems: dizziness, fainting, confusion, decreased awareness of things around you (delirium), problems thinking,		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
seeing or hearing things that are not really there (hallucinations), sleepiness, drowsiness, memory problems, balance problems			
Neutropenia (low white blood cells): fever, fatigue, aches and pains, flu-like symptoms		✓	
Peripheral neuropathy (damage to nerves outside of the brain and spinal cord): weakness, numbness, pain, tingling, usually in the hands and feet		✓	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue, weakness		✓	
Vomiting		✓	
COMMON			
Acute kidney injury: very little or no urine		✓	
Hyponatremia (low sodium level in blood): tiredness, weakness, confusion, achy, stiff or uncoordinated muscles		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store XPOVIO between 2 and 30 °C.

Keep out of reach and sight of children.

If you want more information about XPOVIO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.forustherapeutics.com, or by calling 1-866-542-7500.

This leaflet was prepared by FORUS Therapeutics Inc.

Last Revised May 31, 2022

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