▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems

AUSTRALIAN PRODUCT INFORMATION – XPOVIO (SELINEXOR) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

Selinexor

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of Selinexor.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Blue, round, bi-convex, round, film-coated tablets with “K20” debossed on one side and nothing on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment must be initiated and monitored under supervision of physicians experienced in the management of multiple myeloma.

Dosage

In combination with bortezomib and dexamethasone (SVd)

The recommended starting dose of XPOVIO in combination with bortezomib and dexamethasone is based on a 35-day cycle as follows:

- XPOVIO 100 mg (five 20 mg tablets) is taken orally once weekly on Days 1, 8, 15, 22 and 29.
- Bortezomib 1.3 mg/m2 is administered subcutaneously once weekly on Days 1, 8, 15 and 22.
- Dexamethasone 20-mg is taken orally on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30.

Treatment is administered until disease progression or unacceptable toxicity, for additional information regarding the administration of bortezomib and dexamethasone, refer to their respective prescribing information

In combination with dexamethasone (Sd)

The recommended starting dose is 80 mg (four 20 mg tablets) of XPOVIO on Days 1 and 3 of each week.

The recommended starting dose of dexamethasone is 20 mg taken orally on Days 1 and 3 of each week with XPOVIO. For additional information regarding the administration of dexamethasone, refer to its Product Information.

Treatment should be continued until disease progression or unacceptable toxicity.

Dose modifications for Adverse Reactions

Continued treatment of XPOVIO may require appropriate dose modifications (reductions and/or interruptions) in the event of adverse reactions. Dose modifications utilised in clinical trials are presented in Tables 1-4.

Recommended XPOVIO dose reduction steps for adverse reactions are presented in Table 1.

Recommended dosage modifications for hematologic adverse reactions in patients with multiple myeloma (both SVd and Sd) is presented in Table 2.

Recommended dosage modifications for non-hematologic adverse reactions in all XPOVIO treated patients are presented in Table 3

Table 1: Xpovio Dosage Reduction Steps for Adverse Reactions

	Multiple myeloma in combination with bortezomib and dexamethasone (SVd)	**Multiple myeloma in combination with dexamethasone (Sd)**	
Recommended starting dosage	100 mg once weekly	80 mg Days 1 and 3 of each week (160 mg total per week)	
First reduction	80 mg once weekly	100 mg once weekly	
Second reduction	60 mg once weekly	80 mg once weekly	
Third reduction	40 mg once weekly	60 mg once weekly	
Fourth reduction*	Discontinue	Discontinue	

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

For information regarding dosage modification of drugs given in combination with XPOVIO, see the drugs manufacturer's Product Information.

Table 2: Dose modification guidelines for haematologic adverse reactions in patients with multiple myeloma (both SVd and Sd combinations)

Adverse reaction*	**Occurrence**	**Action**
Haematologic adverse reactions		
Thrombocytopenia		
Platelet count 25,000 to less than 75,000/µL	Any	• Reduce XPOVIO by 1 dose level (see Table 1).
Platelet count 25,000 to less than 75,000/µL with concurrent bleeding	Any	• Interrupt XPOVIO. • Restart XPOVIO at 1 dose level lower (see Table 1), after bleeding has resolved.
Platelet count less than 25,000/µL	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/µL. • Restart XPOVIO at 1 dose level lower (see Table 1).
Neutropenia		
Absolute neutrophil count of 0.5 to 1.0 x 10^9/L without fever	Any	• Reduce XPOVIO by 1 dose level (see Table 1).
Absolute neutrophil count less than 0.5 x 10^9/L *OR* febrile neutropenia	Any	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1.0 x 10^9/L or higher. • Restart XPOVIO at 1 dose level lower (see Table 1).
Anaemia		
Haemoglobin less than 8.0 g/dL	Any	• Reduce XPOVIO by 1 dose level (see Table 1).

Adverse reaction*	Occurrence	Action
Haematologic adverse reactions		
		• Administer blood transfusions and/or other treatments per clinical guidelines.
Life-threatening consequences (urgent intervention indicated)	Any	• Interrupt XPOVIO. • Monitor haemoglobin until levels return to 8 g/dL or higher. • Restart XPOVIO at 1 dose level lower (see Table 1). • Administer blood transfusions and/or other treatments per clinical guidelines.

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

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

Table 3:Dosage modification guidelines for non-haematologic 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			
		Multiple Myeloma (Sd Combination)	Multiple Myeloma (SVd Combination)
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	• Maintain XPOVIO and institute supportive care.	• Interrupt XPOVIO and institute supportive care. • Monitor until diarrhea resolves to Grade 1 or lower. • Restart XPOVIO at current dose.
	2nd and subsequent	• Reduce XPOVIO by 1 dose level (see Table 1). • Institute supportive care.	• 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).

Adverse Reaction	Occurrence	Action	
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 1 or lower. • Restart XPOVIO at 1 dose level lower (see Table 1).	
Weight Loss and Anorexia *[see Special Warning and Precautions for Use (4.4)]*			
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 Special Warning and Precautions for Use (4.4)]*			
		Multiple Myeloma (Sd Combination)	Multiple Myeloma (SVd Combination)
Sodium level 130-120 mmol/L	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).	• 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			
		Multiple Myeloma (Sd Combination)	Multiple Myeloma (SVd Combination)
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 1 dose level lower (see Table 1).	• 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).	
Cataracts* *[see Warning and Precautions (4.4)]*			
Grade 2, excluding cataract	Any	• Perform ophthalmologic evaluation. • Interrupt XPOVIO and provide supportive care. • Monitor until ocular symptoms resolve to Grade 1 or baseline. • Restart XPOVIO at 1 dose level lower (see Table 1).	
Grade ≥3	Any	• Permanently discontinue XPOVIO. • Perform ophthalmologic evaluation.	
Cataract (Grade ≥2)	Any	• Perform ophthalmologic evaluation. • Reduce XPOVIO by 1 dose level (see Table 1). • Monitor for progression.	

Adverse Reaction	Occurrence	Action
		• 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).

* Cataracts includes cataract, cataract subcapsular and cataract cortical

Method of Administration

The tablet should be swallowed whole with water. It should not be crushed, chewed, broken or divided in order to prevent risk of skin irritation from the active substance. It can be taken with or without food.

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.

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

Consider intravenous hydration for patients at risk of dehydration.

Dosage Adjustment

Use in hepatic impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES).

Use in renal impairment

No dosage adjustment of XPOVIO is recommended for patients with mild, moderate or severe renal impairment (see Sections 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.2 PHARMACOKINETIC PROPERTIES).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 LIST OF EXCIPIENTS.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

For medicinal products administered in combination with XPOVIO, the product information of these medicinal products must be consulted prior to initiation of treatment, including for special warnings and precaution for use and recommended concomitant treatments.

Haematologic

Patients should have their complete blood counts (CBC) assessed at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment.

Thrombocytopaenia

XPOVIO can cause life-threatening thrombocytopenia or may increase thrombocytopenia induced by concomitant therapy, leading to potentially fatal haemorrhage

Thrombocytopenia can be managed with dose interruptions, modifications, platelet transfusions, and/or other treatments as clinically indicated. Monitor platelet counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). For dose modification guidelines refer to Table 1, Table 2 and Table 3**Error! Reference source not found.**.

Neutropenia

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

Obtain white blood counts with differential at baseline and throughout, and as clinically indicated. 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 for signs of infection and use of growth factors (e.g., G-CSF). Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction [see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS))].

Gastrointestinal Toxicity

XPOVIO can cause severe gastrointestinal toxicities (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Nausea/Vomiting

Grade 3 or higher nausea/vomiting events have occurred and there have been events that resulted in permanent discontinuation.

Provide prophylactic 5-HT3 antagonists and other anti-nausea agents, prior to and during treatment with XPOVIO. Manage nausea/vomiting by dose interruption, reduction, and/or discontinuation. Administer intravenous fluids and replace electrolytes to prevent dehydration in patients at risk. Use additional anti-nausea medications as clinically indicated (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Diarrhoea

Grade 3 or higher diarrhoea events have occurred and there have been events that resulted in permanent discontinuation.

Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction [see Section 4.2 DOSE AND METHOD OF ADMINISTRATION]. Provide standard anti-diarrheal agents, administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Fatigue, weight loss and anorexia

XPOVIO can cause fatigue, weight loss, and anorexia. Grade 3 fatigue, weight loss and anorexia events have occurred and there have been events that resulted in permanent discontinuation.

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. Provide nutritional support, fluids and electrolyte repletion as clinically indicated. [see Section 4.2 DOSE AND METHOD OF ADMINISTRATION]. For dose modification guidelines refer to Table 1 and Table 3. Patients should be advised not to drive or operate heavy machinery (see Section 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

Neurological Toxicity

XPOVIO can cause life-threatening neurological toxicities including confusional state and dizziness (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Dizziness

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 (see Section 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

Hyponatraemia

XPOVIO can cause severe or life-threatening hyponatraemia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

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 hyperglycaemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Hyponatraemia 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 Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). For dose modification guidelines refer to Table 1, and Table 3.

Serious Infection

XPOVIO can cause serious and fatal infections. Most of these infections were not associated with Grade 3 or higher neutropenia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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.

Cataracts

New onset or exacerbation of cataract has occurred during XPOVIO therapy (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). 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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported in patients receiving therapy with XPOVIO. Patients at a high risk for TLS should be monitored closely. Treat TLS promptly in accordance with clinical guidelines.

Use in hepatic impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment [see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.2 PHARMACOKINETIC PROPERTIES).

Use in renal impairment

No dosage adjustment of XPOVIO is recommended for patients with mild, moderate or severe renal impairment. XPOVIO use in patients requiring dialysis has not been established (see Sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 5.2 PHARMACOKINETIC PROPERTIES, Renal Impairment).

Use in the elderly

Multiple myeloma

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, a higher incidence of serious adverse reactions, and a higher incidence of fatal adverse reactions. See also Section 5.2 PHARMACOKINETIC PROPERTIES, Age, Sex, Race.

Paediatric use

The safety and efficacy of XPOVIO in children below the age of 18 years of age have not been established. No data are available.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Exposure of XPOVIO was not affected by co-administration with paracetamol at a daily dose up to 1000 mg.

Selinexor is a substrate of CYP3A4. Concomitant use of strong CYP3A4 inducer might lead to lower exposure of XPOVIO.

In vitro, selinexor was shown to not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 or 3A4/5, or UGT1A1, 1A3, 1A4, 1A6, 1A9 or 2B7, at clinically relevant concentrations. Selinexor is not an inducer of CYP1A2, 2B6 or 3A4, and is not a substrate of P-glycoprotein, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K. Selinexor inhibits OATP1B3, but not OATP1B1, OAT1, OAT3, OCT2, MATE1 or MATE2-K, at clinically relevant concentrations.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Based on findings in animals, XPOVIO may impair fertility in females and males.

No fertility studies have been conducted with selinexor in animals. Impairment of male and female fertility in patients is suggested by findings in general repeat-dose toxicity studies. Selinexor reduced sperm, spermatids and germ cells in the epididymides and testes in rats at oral doses ≥0.25 mg/kg, decreased ovarian follicles in rats at ≥2 mg/kg, and produced single cell necrosis in the testes of monkeys with treatment at ≥1.5 mg/kg. These doses resulted in systemic exposure (plasma AUC) well below that of patients at the maximum recommended human dose. Reversibility of the male reproductive tract findings was not demonstrated in animals.

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant or abstain from sexual intercourse while being treated with XPOVIO and for at least 1 week following the last dose of XPOVIO. A pregnancy test is recommended for women of childbearing potential prior to initiating XPOVIO treatment.

Male patients of reproductive potential should be advised to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with XPOVIO and for at least 1 week following the last dose of XPOVIO.

Use in pregnancy –Category D

There are no data from the use of XPOVIO in pregnant women. Based on findings in animal studies and its mechanism of action , XPOVIO can cause fetal harm when administered to a pregnant woman.

Administration of selinexor to pregnant rats during organogenesis resulted in reduced fetal weight, impaired ossification and increased fetal skeletal variations at oral doses ≥0.75 mg/kg/day. Malformations (microphthalmia, fetal oedema, malpositioned kidney and persistent truncus arteriosus) were observed at 2 mg/kg/day. These doses yield systemic exposure well below that of patients at the maximum recommended clinical dose (4–16 times lower than the human AUC at 100 mg). At 5 mg/kg/day (estimated to yield 0.6 times the clinical AUC), selinexor was embryolethal in rats.

XPOVIO is not recommended during pregnancy and in women of childbearing potential not using contraception. Verify the pregnancy status of females of reproductive potential prior to initiating XPOVIO.

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

Use in lactation

It is unknown whether XPOVIO or its metabolites are excreted in human milk, or their effects on the breastfed child or milk production. A risk to breast-fed children cannot be excluded. Breast-feeding should be discontinued during treatment with XPOVIO and for 1 week after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

XPOVIO has the potential to have a major influence on the ability to drive and use machines. XPOVIO can cause fatigue, confusional state and dizziness. 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 machines if they experience any of these symptoms.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety data of selinexor have been assessed in patients with multiple myeloma treated with selinexor in combination with dexamethasone (202 patients-STORM trial) or selinexor in combination with bortezomib and dexamethasone (195 patients-BOSTON trial).

In combination with bortezomib and dexamethasone (SVd, BOSTON Trial)

The safety data described are based on the BOSTON study, a global, randomised, 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 1.3mg/m^2 with twice-weekly dexamethasone 20 mg (Vd) (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials and Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Adverse Events (AEs) and Laboratory Abnormalities described in Table 4 and Table 5 below reflect exposure to XPOVIO for a median treatment duration of 30 weeks (range: 1 to 120 weeks) and median dose of 80 mg/week (range: 30 to 137) for the SVd patient group (n=195) and median treatment duration of 32 weeks (range: 1 to 122 weeks) for the Vd patient group (n=204).

The most frequent (≥20%) non-hematologic AEs with a 5% greater incidence in the SVd arm compared to the Vd arm were nausea, fatigue, decreased appetite, diarrhea, upper respiratory tract infection, weight decreased, asthenia, cataract, and vomiting. Serious AEs were reported in 52% and 38% of SVd- and Vd-treated patients, respectively.

There was a similar number of fatal AEs in the SVd (12 patients) and in the Vd (11 patients) arms, within 30 days of last treatment. Fatal AEs occurred in 12 patients in both the SVd and Vd arms, within 60 days of last treatment. The most frequent fatal AEs in SVd-treated patients were pneumonia and septic shock (n=3 each) and it was pneumonia (n=3) in Vd-treated patients.

There were no serious AEs with a 5% greater incidence in the SVd arm compared to the Vd arm. Serious AEs with a 2% greater incidence in the SVd arm compared to the Vd arm were diarrhea (SVd 4% vs Vd 0%), vomiting (SVd 4% vs Vd 0%), cataract (SVd 2% vs Vd 0%), nausea (SVd 2%, Vd 0%), urinary tract infection (SVd 2%, Vd 0%), and septic shock (SVd 2%, Vd 0%).

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, respectively, 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).

The proportion of patients who discontinued any component of the treatment regimen due to AEs was 21% in the SVd arm and 16% in the Vd arm. XPOVIO dose reductions and interruption occurred in 65% and 87% of SVd-treated patients. Bortezomib dose reduction and interruption occurred in 43% and 82% of the SVd-patient group and 45% and 74% of the Vd-patient group. Dexamethasone dose reduction and interruption occurred in 27% and 80% of the SVd-patient group and 36% and 73% of the Vd-patient group.

Table 4: Adverse Events Reported in ≥10% of Patients and With at Least a 5% Greater Difference in Frequency between SVd and Vd Treated Patients in the BOSTON Trial (Safety Population)

	Weekly SVd (N=195)		Twice Weekly Vd (N=204)	
Adverse Event	**Any Grade (%)**	**Grade 3 or 4 (%)**	**Any Grade (%)**	**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	42	13	18	1
Asthenia	25	8	13	4.4

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, sensory[a]	32	4.6	47	9
Dizziness	12	<1	3.9	0
Infections				
Upper respiratory tract infection[b]	29	3.6	22	1.5
Eye Disorders				
Cataract	22	9	6	1.5
Vision blurred[c]	13	<1	6	0

Key: S=selinexor, Vd=bortezomib-dexamethasone

a. **Peripheral neuropathy** represents high level term peripheral neuropathies NEC.
b. **Upper respiratory tract infection** includes upper respiratory infection, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, and viral upper respiratory tract infection.
c. **Vision blurred** includes blurred vision, visual acuity reduced and visual impairment.

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

- **Neurologic disorders:** mental status changes consisting of confusional state and delirium (9%) and syncope (3.6%)

Table 5 summarises selected new or worsening laboratory abnormalities in the BOSTON trial. Grade 3-4 laboratory abnormalities in ≥15% in the XPOVIO combination with bortezomib and dexamethasone (SVd) arm included thrombocytopenia, lymphopenia, anemia, and hypophosphatemia. Grade 4 laboratory abnormalities in ≥5% were thrombocytopenia (13%), and lymphopenia (7%).

Table 5: Select Laboratory Abnormalities (≥15%) Worsening from Baseline in Patients with Multiple Myeloma Receiving SVd or Vd in the BOSTON trial (Safety Population)

	Weekly SVd (N=195)		Twice Weekly Vd (N=204)	
Laboratory Abnormality	**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. Include one fatal anemia.

In combination dexamethasone (Sd; STORM Trial)

The most frequent AEs were nausea (75%), thrombocytopenia (75%), fatigue (66%), anaemia (60%), decreased appetite (56%), decreased weight (49%), diarrhoea (47%), vomiting (43%), hyponatraemia (40%), neutropenia (36%) and leukopenia (30%).

Serious AEs were pneumonia (7.5%), sepsis (6.1%) thrombocytopenia (4.7%), acute kidney injury (3.7%), anaemia (3.3%), hyponatraemia (2.8%), pyrexia (2.8%), and dehydration (2.3%).

Tabulated list of AEs

AEs are presented by MedDRA system organ class and within each SOC and frequency grouping, AEs are presented in order of decreasing seriousness Table 6. Frequency categories are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). AEs presented by Any Grade and Grade are presented in Table 7.

Table 6: AEs with Selinexor 80 mg and Dexamethasone 20 mg in the STORM Trial

System organ class/ preferred term	All AEs/frequency	Grade 3-4 AEs/frequency
Infections and infestations	Very common Pneumonia, upper respiratory tract infection Common Sepsis	Common Pneumonia, sepsis Uncommon Upper respiratory tract infection
Blood and lymphatic system disorders	Very common Thrombocytopenia, anaemia, neutropenia, leukopenia, lymphopenia Common Febrile neutropenia	Very common Thrombocytopenia, anaemia, neutropenia, leukopenia, lymphopenia Common Febrile neutropenia
Metabolism and nutrition disorders	Very common Hyponatraemia, dehydration, decreased appetite, hyperglycaemia, hypokalaemia, hypercreatininaemia Common Hypocalcaemia, hypophosphataemia, hyperkalaemia, hyperuricaemia, hypomagnesaemia, hyperamylasaemia, hyperlipasaemia Uncommon Tumour lysis syndrome	Very common Hyponatraemia Common Dehydration, decreased appetite, hyperglycaemia, hypocalcaemia, hyperuricaemia, hyperkalaemia, hypokalaemia, hyperlipasaemia, hyperamylasaemia, hypophosphataemia Uncommon Tumour lysis syndrome, hypercreatininaemia
Psychiatric disorders	Very common Confusional state, insomnia Common Depression, anxiety, delirium	Common Confusional state, insomnia Uncommon Depression, anxiety, delirium
Nervous system disorders	Very common Dizziness, dysgeusia, headache Common Syncope, peripheral neuropathy, disturbance in attention, ageusia cognitive disorder Uncommon Encephalopathy	Common Syncope Uncommon Peripheral neuropathy, encephalopathy
Eye disorders	Very common Vision blurred	Common Cataract

System organ class/ preferred term	All AEs/frequency	Grade 3-4 AEs/frequency
	Common Visual impairment, cataract	Uncommon Vision blurred, visual impairment
Cardiac disorders	Common Tachycardia	None
Vascular disorders	Common Hypotension	Uncommon Hypotension
Respiratory, thoracic and mediastinal disorders	Very common Dyspnoea, epistaxis, cough	Common Dyspnoea Uncommon Epistaxis
Gastrointestinal disorders	Very common Nausea, diarrhoea, vomiting, abdominal pain, constipation Common Dyspepsia, dry mouth, abdominal discomfort, anal incontinence, flatulence	Common Nausea, diarrhoea, vomiting, constipation Uncommon Abdominal pain
Skin and subcutaneous tissue disorders	Common Alopecia, night sweats	None
Musculoskeletal and connective tissue disorders	Common Muscular weakness, bone pain, muscle spasms, hypercreatinaemia	Uncommon Muscular weakness, bone pain, muscle spasms, hypercreatinaemia
Renal and urinary disorders	Common Acute kidney injury	Common Acute kidney injury
General disorders and administration site conditions	Very common Fatigue, pyrexia, asthenia Common General physical health deterioration, malaise, gait disturbance, chills	Very common Fatigue Common Asthenia, general physical health deterioration Uncommon Pyrexia
Investigations	Very common Weight decreased Common Aspartate aminotransferase increased, alanine aminotransferase increased	Common Alanine aminotransferase increased Uncommon Weight decreased, aspartate aminotransferase increased
Injury, poisoning and procedural complications	Common Fall, contusion	Common Fall

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 include 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.

Table 7: Adverse Events with Selinexor 80 mg and Dexamethasone 20 mg in the STORM Trial, data expressed as Any Grade (reported in >10% of patients) or Grade ≥3.

Adverse Event	Any Grade (N = 202) n (%)	Grade ≥3 (N = 202) n (%)
Thrombocytopaenia[a]	149 (74)	124 (61)
Fatigue[b]	147 (73)	44 (22)
Nausea	146 (72)	18 (9)
Anaemia[c]	119 (59)	81 (40)
Decreased appetite	108 (53)	9 (4.5)
Weight decreased	95 (47)	1 (0.5)
Diarrhea	89 (44)	13 (6)
Vomiting	82 (41)	7 (3.5)
Hyponatremia	78 (39)	44 (22)
Neutropaenia[d]	68 (34)	43 (21)
Leukopenia	57 (28)	23 (11)
Constipation	50 (25)	3 (1.5)
Dyspnea[e]	48 (24)	7 (3.5)k
Upper respiratory tract infection[f]	42 (21)	6 (3)
Cough	33 (16)	0
Mental status changes[h]	33 (16)	14 (7)
Pyrexia	32 (16)	1 (0.5)
Hyperglycaemia	31 (15)	15 (7)
Dizziness	30 (15)	0
Insomnia	30 (15)	4 (2)
Lymphopenia	30 (15)	20 (10)
Dehydration	28 (14)	7 (3.5)
Hypercreatininaemia[i]	28 (14)	4 (2)

Pneumonia[j]	**26 (13)**	**18 (9)[k]**
Epistaxis	**25 (12)**	**1 (0.5)**
Hypokalaemia	**25 (12)**	**7 (3.5)**
Dysgeusia	**22 (11)**	**0**
Vision blurred	**21 (10)**	**1 (0.5)**
Headache	**20 (10)**	**0**

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

Description of selected adverse events

Infection

In the BOSTON trial of patients with multiple myeloma, 69% of patients in the XPOVIO 100 mg once weekly combined with bortezomib and dexamethasone (SVd, n=195) arm and 59% of patients in bortezomib and dexamethasone arm (Vd, n=204) experience any grade of infection. Grade ≥3 infections were reported in 32% and 18% of the SVd and Vd treated patients, respectively. Fatal infections were reported in 3.1% and 1.5% of SVd- and Vd- treated patients, respectively. The most common reported Grade ≥3 infection was pneumonia (14% SVd and 12% Vd), upper respiratory tract infection (3.6% SVd and 1.5% Vd) and sepsis (4.1% SVd and <1% Vd).

In the STORM trial, infection was the most common non-haematological toxicity; occurring in 53% of patients. Of these, 22% were Grade 3 or 4. Upper respiratory tract infection and pneumonia were the most commonly reported infections (in 15% and 13% of patients, respectively) with 25% of reported infections being serious and fatal infections occurring in 3% of treated patients. Infection led to dose discontinuation in 7% of patients, treatment interruption in 19% patients, and a dose reduction in 1% of patients.

Thrombocytopenia

In the BOSTON trial of patients with multiple myeloma (n=399), thrombocytopenia (all Grades) and severe thrombocytopenia (Grade 3-4) were reported in 92% and 43% of patients in the XPOVIO 100 mg once weekly combined with bortezomib and dexamethasone (SVd, n=195) arm and in 51% and 19% of patients in the bortezomib and dexamethasone arm (Vd, n=204), respectively. The median time to first onset was 22 days for any-grade thrombocytopenia in both the SVd and Vd arms. The median time to first onset for Grade 3 or higher thrombocytopenia was 43 and 32 days for the SVd and Vd arms, respectively. Bleeding/clinically significant bleeding occurred in 16%/4% and 7%/4% of SVd- and Vd-treated patients with

thrombocytopenia, respectively. Fatal hemorrhage occurred in 1% and <1% of patients with thrombocytopenia in the SVd and Vd arm, respectively. Discontinuations due to thrombocytopenia occurred in 2% of SVd- and <1% of Vd-treated patients.

In the STORM trial, thrombocytopenia occurred in 75% of patients and 65% of these AEs were Grade 3 or 4. Thrombocytopenia was serious in 5% of patients. Of the 65% patients with Grade 3 or 4 thrombocytopenia, serious/grade 3 or higher concurrent bleeding events (concurrency defined as ±5 days) were reported in 5% of patients. Thrombocytopenia led to dose discontinuation in 3% of patients, treatment interruption in 22% of patients, and a dose reduction in 32% of patients.

Neutropenia

In the BOSTON trial of patients with multiple myeloma (n=399), neutropenia (all Grades) and severe neutropenia (Grade 3-4) were reported in 48% and 12% of patients in the XPOVIO 100 mg once weekly combined with bortezomib and dexamethasone (SVd, n=192) arm, 19% and 7% of patients in the bortezomib and dexamethasone arm (Vd, n=196). The median time to first onset was 23 and 36 days for any-grade neutropenia in the SVd and Vd arms, respectively. The median time to first onset for Grade 3 or higher neutropenia was 40 and 28 days for the SVd and Vd arms, respectively. Febrile neutropenia occurred in <1% of SVd- and Vd-treated patients. Discontinuations due to neutropenia did not occur in SVd- nor Vd-treated patients.

In the STORM trial, neutropenia occurred in 36% of patients and 25% of these were Grade 3 or 4. Neutropenia was serious in less than 1% of patients. None of the patients had a dose discontinuation due to neutropenia, and neutropenia led to treatment interruption in 2% of patients, and a dose reduction in 6% of patients. Febrile neutropenia occurred in 3% of patients; all were Grade 3 or 4. Febrile neutropenia was reported to be serious in 2% of patients and led to a dose discontinuation, treatment interruption, or a dose reduction in less than 1% of patients (each). Of the 53 patients with grade 3 or higher neutropenia, serious/grade 3 or higher concurrent infections (concurrency defined as ±5 days) were reported in 11 patients. Most commonly reported infections included pneumonia (4), sepsis (3), bacteraemia (2) and lung infection (2).

Anaemia

In the BOSTON trial, anaemia was reported in the most frequent (≥10%) AEs with a 5% greater incidence in the SVd arm compared to the Vd arm. Thirty-six percent of patients were reported as having Any Grade, with 16% as Grade 3.

In the STORM trial, anaemia occurred in 61% of patients and 44% of these were Grade 3 or 4. Anaemia was serious in 3% of patients and led to dose discontinuation in <1% of patients, treatment interruption in 4% of patients, and a dose reduction in 1% of patients.

Gastrointestinal toxicity

Prophylaxis with 5HT3 antagonists and other similar antiemetics should be administered prior to and during XPOVIO treatment. Administer intravenous fluids and replace electrolytes to prevent dehydration in patients at risk. Use additional anti-nausea medications as clinically indicated. Nausea/vomiting can be managed by dose interruption, reduction and/or discontinuation. Diarrhoea can be managed with dose modification or administration of anti-diarrhoea medicinal products. For dose modification guidelines refer to Table 1 and Table 3.

In the BOSTON trial, nausea (all Grades) and ≥Grade 3 nausea were reported in 50% and 8% of patients in the SVd arm and in 10% and 0% of patients in the Vd arm. The median time to onset of the first event was 6 and 73 days in the SVd- and Vd-treated patients, respectively. Discontinuations due to nausea occurred in 3% of SVd-treated patients and none of Vd-treated patients.

Vomiting (all Grades) and ≥Grade 3 vomiting was reported in 21% and 4% of patients in the SVd-treated patients and 4% and 0% in the Vd- treated patients. The median time to onset of the first event was 8 days and 49 days in the SVd- and Vd-treated patients, respectively. Discontinuations due to vomiting occurred in 2% of SVd-treated patients and none of Vd-treated patients.

Diarrhea (all Grades) and ≥Grade 3 diarrhea were reported in 32% and 6% of patients in the SVd arm and 25% and <1% of patients in the Vd arm. The median time to onset of the first event was 50 days in SVd- and 71 days in Vd-treated patients. Discontinuations due to diarrhea occurred in 1% and <1% of SVd- and Vd- treated patients, respectively.

In the STORM trial, nausea/vomiting occurred in 79% of patients and 10% of these were Grade 3 or 4 and they were serious in 3% of patients. When anti-nausea treatment was administered, the median duration of nausea or vomiting improved by 3 days. Nausea/vomiting led to dose discontinuation in 5% of patients, treatment interruption in 8% of patients, and a dose reduction in 5% of patients.

Diarrhoea occurred in 47% of patients and 7% were Grade 3 or 4. Diarrhoea was serious in 2% of patients, and led to dose discontinuation in 1% of patients, treatment interruption in 2% of patients, and a dose reduction in 1% of patients.

Hyponatraemia

Hyponatraemia can be managed with dose interruptions/reductions and with intravenous saline and/or salt tablets, including dietary review. Advise patients that levels of sodium will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first two months of treatment. For additional supportive care information please refer to Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

In the BOSTON trial of patients with multiple myeloma, hyponatremia (all Grades) and Grade 3-4 were reported in 58% and 14% of patients in the XPOVIO 100 mg once weekly combined with bortezomib and dexamethasone (SVd, n=195) arm and in 25% and 3% of patients in the bortezomib and dexamethasone arm (Vd, n=201). The median time to first onset was 21 and 43 days for any-grade hyponatremia in the SVd and Vd arms, respectively. The median time to first onset for Grade 3 or higher hyponatremia was 22 and 14 days for the SVd and Vd arms, respectively. No treatment discontinuation due to hyponatremia occurred.

In the STORM trial, hyponatraemia occurred in 40% of patients and 24% were Grade 3 or 4. Hyponatraemia was serious in 3% of patients. Most cases of hyponatraemia were not associated with any symptoms. There were no reports of concurrent seizures. Hyponatraemia did not lead to any dose discontinuation, and it led to treatment interruption in 6% of patients, and a dose reduction in 1% of patients.

Tumour lysis syndrome

Patients at a high risk for TLS should be monitored closely. Treat TLS promptly in accordance with institutional guidelines (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

In the STORM trial, tumour lysis syndrome (TLS) occurred in one (<1%) patient which was considered Grade 3 and serious.

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

In the BOSTON trial of patients with multiple myeloma, neurological AEs (excluding peripheral neuropathy) including dizziness, syncope, depressed level of consciousness, vertigo, amnesia and mental status changes (including delirium and confusional state) occurred in 26% and 9% of SVd-treated patients (XPOVIO 100 mg once weekly combined with bortezomib and dexamethasone, n=195) and Vd-treated patients (bortezomib and dexamethasone arm, n=204), respectively. Severe events (Grade 3-4) occurred in 3.6% and 1.5% of patients treated with SVd and Vd, respectively. Median time to the first event was 29 days in the SVd arm and 61 days in the Vd arm. Discontinuations due to neurological AEs occurred in 2.1% of SVd-treated patients and 1% of Vd-treated patients.

In the STORM trial, neurological AEs including dizziness, dysgeusia and headache were reported as very common, with syncope a common Grade 3-4 reaction. Other common neurological AEs included peripheral neuropathy, disturbance in attention, ageusia and cognitive disorders. Encephalopathy was considered an uncommon Grade 3-4 reaction.

Anorexia/Weight loss

Monitor patient weight at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Manage anorexia and weight loss with dose modifications, appetite stimulants, and nutritional support.

In the BOSTON trial, anorexia (all Grades) and ≥Grade 3 anorexia was reported in 35% and 4% of patients in the SVd arm and in 5% and 0% of patients in the Vd arm. The median time to onset of the first event was 35 and 63 days in the SVd- and Vd-arms, respectively. Discontinuations due to anorexia occurred in 2% and <1% of SVd and Vd treated patients, respectively.

Weight loss (all Grades) and Grade 3 weight loss was reported in 26% and 2% of patients in the SVd arm and in 12% and 1% of patients in the Vd arm. The median time to onset of the first event was 58 and 110 days in the SVd and Vd arms, respectively. Discontinuations due to weight loss occurred in 1% and <1% of the SVd and Vd-treated patients, respectively.

Cataracts

Manage cataract per standard clinical guidelines.

In the BOSTON study, the incidence of new onset or worsening all Grades cataract requiring clinical intervention was reported in 22% and 6% in the SVd- and Vd-treated patients, respectively. Grade 3/4 cataracts occurred in 9%/0% and 0%/1% of SVd- and Vd-treated patients, respectively. In patients who received XPOVIO, cataract did not result in treatment discontinuation.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose due to accidental excessive ingestion of selinexor has been reported. Please refer to selinexor dosing instructions to avoid dosing errors (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Symptoms

In general, overdoses have been associated with similar side effects to those reported for standard dosing and have generally been reversible within 1 week.

Potential acute symptoms include nausea, vomiting, diarrhoea, 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.

Management

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

In the event of an overdose, monitor the patient for any adverse reactions and appropriate symptomatic treatment should be provided immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Selinexor is a reversible covalent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). XPO1 is a major nuclear export protein that transports cargo proteins and several classes of mRNA from the nucleus to the cytoplasm. XPO1 cargoes include many tumour suppressor proteins (TSPs), growth regulator proteins (GRPs) and mRNAs of growth promoting (oncogenic) proteins. XPO1 inhibition by selinexor leads to

marked accumulation of TSPs and GRPs (such as p53, p21, FOXO and IκB) in the nucleus(their site of action), and reduced expression of several oncoproteins (such as c-Myc, Bcl2 and cyclin D1) and translation/chaperon proteins (Hsp70), resulting in cell cycle arrest and apoptosis of cancer cells. The combination of selinexor and dexamethasone or bortezomib demonstrated synergistic cytostatic and cytotoxic effects in multiple myeloma *in vitro* and *in vivo* models, including those resistant to proteasome inhibitors. Selinexor demonstrated pro apoptotic activity *in vitro* in multiple myeloma and diffuse large B-cell lymphoma cell lines, in murine xenograft models as well as in patient tumour samples.

Cardiac electrophysiology

The effect of multiple doses of selinexor up to 175 mg twice 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.

Clinical trials

Multiple myeloma

In Combination with bortezomib and dexamethasone (SVd), BOSTON Trial

The efficacy of XPOVIO plus dexamethasone was evaluated in BOSTON (KCP-330-023; NCT03110562). BOSTON, a global, randomized, open label, active-controlled Phase 3 study, compared treatment of once weekly XPOVIO 100mg (Days 1, 8, 15, 22, 29) in combination with once-weekly subcutaneous bortezomib 1.3 mg/m2 (Days 1, 8, 15, 22) and twice weekly low-dose dexamethasone 20 mg (Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30) of a repeated 35-day cycle [SVd arm] to treatment with twice-weekly subcutaneous bortezomib 1.3 mg/m2 (Days 1, 4, 8, 11) and low-dose dexamethasone 20 mg (Days 1, 2, 4, 5, 8, 9, 11, 12) of a standard 21-day cycle for the first 8 cycles, followed by weekly subcutaneous bortezomib 1.3 mg/m2 (Days 1, 8, 15, 22), low-dose dexamethasone 20 mg (Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30) of 35-day cycle (Cycle≥9) [Vd arm].

Treatment was continued in both arms until disease progression or unacceptable toxicity. Upon confirmed progressive disease (PD), patients in the control arm (Vd) could cross over to receive XPOVIO-based therapy in the form of weekly SVd (BOSTON regimen) or weekly Sd (XPOVIO 100mg Days 1, 8, 15, 22, 29 and low-dose dexamethasone 20 mg on Days 1, 2, 8, 9, 15, 16, 22, 23, 29, and 30) of each 35-day cycle.

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

A total of 402 patients were randomized: 195 to SVd arm and 207 to Vd arm. Baseline patient and disease characteristics were well balanced and comparable between the two arms as described in Table 8 and Table 9, respectively.

Table 8: Baseline Patient Characteristics (BOSTON) (ITT Population)

Characteristic	SVd (N=195)	Vd (N=207)
Median age, years (range)	66 (40, 87)	67 (38, 90)

Characteristic	SVd (N=195)	Vd (N=207)
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)
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 - <60	53 (27)	60 (29)
≥60	139 (71)	137 (66)

Table 9: Baseline 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)
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)
Prior treatment regimens, mean (range)	1.7 (1, 3)	1.7 (1, 3)
Number of Prior Therapies (%)		
1	51%	48%
2	33%	31%
3	16%	21%
Type of prior therapy, n (%)		
Stem Cell transplantation	76 (39)	63 (30)
Lenalidomide	77 (39)	77 (37)

Parameter	SVd (N=195)	Vd (N=207)
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)
High-risk cytogenetics[a], n (%)	97 (50)	95 (46)

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

The primary endpoint 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). 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).

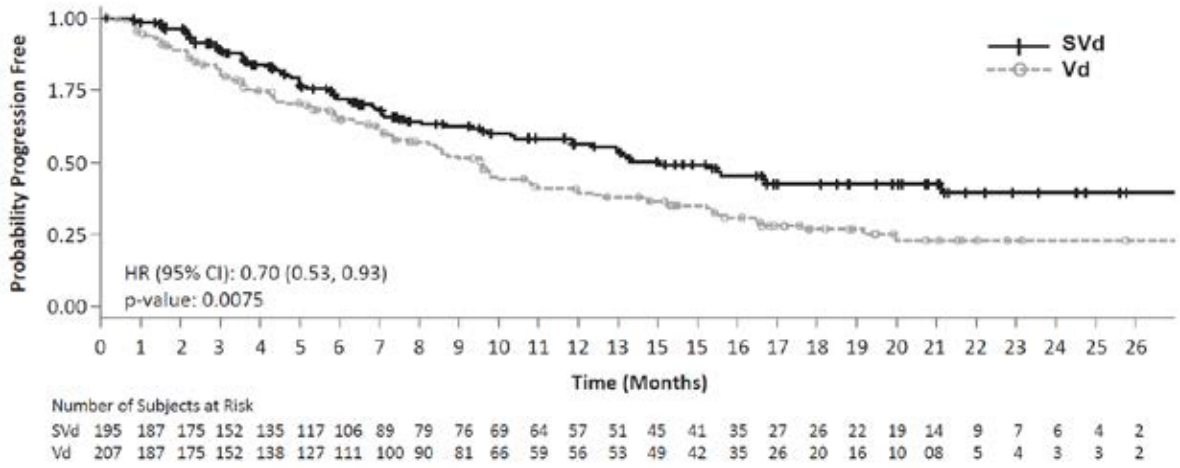
Efficacy results are shown in Table 10 and Figure 1.

Table 10: Progression Free Survival and Response Rate (BOSTON) (ITT Population)

	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	0.0075	
Median PFS in months [95% CI]	13.9 (11.7, Not Reached)	9.5 (8.1, 10.8)
Overall Response Rate (ORR)[b], 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[c], 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.
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: BOSTON Kaplan-Meier Curve of PFS (ITT Population)



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

At the time of the pre-planned OS interim analysis (median follow up of 17.3 and 17.5 months for SVd and Vd arms respectively), a total of 109 OS events have occurred; there were 47 and 62 deaths in the SVd and Vd arms respectively (HR=0.84 [95% CI: 0.58, 1.23]).

In combination with dexamethasone (Sd, STORM trial)

In a phase 2, multi-centre, single-arm, open-label, study, 123 patients with RRMM were treated with 80 mg selinexor in combination with 20 mg dexamethasone on Days 1 and 3 of every week.

Treatment continued until disease progression, death or unacceptable toxicity. The median duration of selinexor treatment was 9 weeks (range: 1 to 76 weeks). The median total dose of selinexor received was 920 mg (range 160 to 6,220 mg), with a median dose of 113.6 mg (range: 22 to 240 mg) received per week.

Table 11 provides patients disease and prior treatment characteristics.

Table 11: Demographics and Disease Characteristics of Patients with Relapsed Refractory Multiple Myeloma treated with 80 mg Selinexor and 20 mg Dexamethasone (N=123)

Characteristics		
Median from diagnosis to start of study treatment, years (range)		6.6 years (1.1, 23.4)
Number of prior treatment regimens, median (range)		7 (3, 18)
Age, median (range)		65 years (40, 86)
Number of patients less than 50 years of age		8 (6.5%)
Males : Females		71 M (58%): 52 F (42%)
	Refractory status to the treatments, n (%)	
Lenalidomide (L)		107 (87.0)

Pomalidomide (P)		121 (98.4)
Bortezomib (B)		100 (81.3)
Carfilzomib (C)		119 (96.7)
Daratumumab (D)		123 (100)
	Refractory status to specific treatment combinations, n (%)	
Triple refractory (CPD)		117 (95.1)
Quad refractory (CLPD)		101 (82.1)
Quad refractory (BCPD)		94 (76.4)
Penta refractory (BCLPD)		83 (67.5)
Daratumumab in any combination		86 (69.9)
Daratumumab in last prior regimen		58 (47.2)
Previous stem cell transplant[1], n (%) ≥2 transplants		102 (83%) 29 (28%)
Intensive combination chemotherapy (eg DT-PACE)		32 (26%)
CAR-T Cell Therapy		2 (2%)
Revised Integrated Staging System at baseline, n (%)		
I		20 (16.3)
II		79 (64.2)
III		23 (18.7)
Unknown		1 (0.8)
Creatinine clearance < 60 mL/min		40 (32.5%)
High-risk cytogenetics (includes any of del(17p)/p53, t(14; 16), t(4; 14), or 1q21)		65 (53)
MM subtype: FLC		35 (29%)
ECOG performance status: 0 to 1		88.5%
Changes in multiple myeloma markers (SPEP, UPEP, or FLC) between screening and first dose		Median: +22% in 12 days

[1]One patient had an allogenic stem cell transplant.

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee based on the International Myeloma Working Group (IMWG) uniform response criteria for multiple myeloma. Responses were assessed monthly and as per IMWG guidelines. Secondary efficacy endpoints included duration of response (DOR), defined as defined the duration from start of response to disease progression, and overall survival (OS), defined as the duration from start of study treatment to death due to any cause. Table 12 provides an overview of the efficacy results.

Table 12: Efficacy Results: Assessed by Independent Review Committee

Efficacy endpoint	**XPOVIO 80 mg + dexamethasone 20 mg N=123**
Overall response rate (ORR), n (%) (includes sCR + VGPR + PR)[1]	32 (26.0)

Efficacy endpoint	**XPOVIO 80 mg + dexamethasone 20 mg N=123**
95% confidence interval	18.5, 34.7
sCR, MRD negative, n (%)	2 (1.6)
VGPR, n (%)	6 (4.9)
PR, n (%)	24 (19.5)
Minimal response (MR), n (%)	16 (13.0)
Stable disease (SD), n (%)	48 (39.0)
Progession disease (PD) /not evaluable (NE), n (%)	27 (22.0)
Median time to first response (weeks) (range: 1 to 14 weeks)	4.1
Median duration of response (DOR) months (95% confidence interval)	4.4 (3.7, 10.8)
Overall survival (OS); months	
Median OS; months (95% CI)	8.6 (6.2, 11.3)
Among patients with ≥PR, n=32	Not Reached
Among patients with ≥MR, n=48	Not Reached
Among patients with SD, n=48	6.3
Among patients with PD or NE, n=27	1.9

[1] sCR= stringent complete response, VGPR= very good partial response, PR= partial response

No difference in ORR was observed based on baseline characteristics. Both patients relapsing from prior CAR-T therapy had a PR on selinexor plus dexamethasone.

5.2 PHARMACOKINETIC PROPERTIES

Following a single-dose administration of XPOVIO 100 mg, the mean (standard deviation) peak plasma concentration (Cmax) was 693 (201) ng/mL and the mean AUC was 6998 (818) ng•h/mL.

Selinexor C_{max} and AUC increased proportionally over doses from 3 mg/m2 to 85 mg/m_2 (0.045 to 1.8 times the approved recommended dose based on 1.7 m2 body surface area). No clinically relevant accumulation at steady state was observed

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) did not have a clinically significant effect on the pharmacokinetics of selinexor.

Distribution

Selinexor is 95% 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 metabolised by CYP3A4, multiple UDP-glucuronosyltransferases (UGTs) and glutathione S-transferases (GSTs).

Excretion

Following a single dose of 80 mg selinexor the mean half-life ($t_{1/2}$) 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

Age, Sex, Race

Age (18 to 94 years of age), body weight (36 to 168 kg) sex, or race had no clinically significant effect on the pharmacokinetics of selinexor.

In the population pharmacokinetic dataset, the median age was 68 years. Although age was identified as a significant covariate for the absorption rate constant (k_a), the estimate was very small. The overall exposure (AUC and C_{max}) was similar between younger (18-64 years of age) and older patients (65 years of age and older).

There was no clinically significant effect of gender; although it was identified as a significant covariate.

Renal Impairment

No clinically significant differences in the pharmacokinetics of selinexor were observed based on age, mild to severe renal impairment (CLCR: 15 to 89 mL/min, estimated by the Cockcroft-Gault equation), and disease type (hematological non-DLBCL, solid tumor, DLBCL). The effect of end-stage renal disease (CLCR <15 mL/min) or hemodialysis on selinexor pharmacokinetics is unknown. Mild renal impairment had no clinically significant effect on the pharmacokinetics of selinexor.

Hepatic Impairment

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. No dose adjustment is needed in patients with mild to moderate hepatic impairment according to the National Cancer Institute – Organ Dysfunction Working Group (NCI-ODWG) criteria.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Carcinogenicity

Carcinogenicity studies have not been conducted with selinexor.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose (PH-101)

Croscarmellose sodium

Povidone

Silicon dioxide

Magnesium stearate

Microcrystalline cellulose (PH-102)

Sodium lauryl sulfate

OPADRY 200 Optimized Performance Coatings 203A190001 Clear

OPADRY II Complete Film Coating System 85F90892 Blue

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

PVC/PCTFE/PVC-aluminium blisters.

Each pack contains an outer carton containing 16, 20, 24 or 32 tablets.

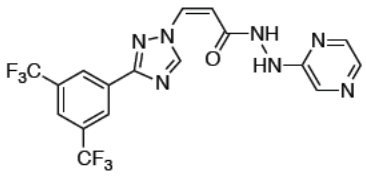
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical structure



Molecular Formula: $C_{17}H_{11}F_6N_7O$

CAS number

1393477-72-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

08 March 2022

10 DATE OF REVISION

08 March 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	New Product Information