XPOVIO (selinexor) 20mg film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

XPOVIO 20 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of selinexor.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

Blue, round, bi-convex, film-coated tablet (4 mm thick and 7 mm in diameter) with "K20" debossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

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 multiple myeloma in adult patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

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

Posology

Selinexor in combination with bortezomib and dexamethasone (SVd)
The recommended selinexor, bortezomib and dexamethasone doses based on a 35-day cycle are as follows:

- Selinexor 100 mg taken orally once weekly on Day 1 of each week. The dose of selinexor should not exceed 70 mg/ m^2 per dose.
- 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 with selinexor combined with bortezomib and dexamethasone should be continued until disease progression or unacceptable toxicity.

Selinexor in combination with dexamethasone (Sd)
The recommended selinexor and dexamethasone starting doses are as follows:

- Selinexor 80 mg taken orally on Days 1 and 3 of each week.
- Dexamethasone 20 mg taken orally on Days 1 and 3 of each week with selinexor.

Treatment with selinexor combined with dexamethasone should be continued until disease progression or unacceptable toxicity.

For information regarding the posology of medicinal products administered with XPOVIO, refer to the Summary of Product Characteristics (SmPC) for these medicinal products.

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

Dose modifications
Recommended XPOVIO dose modifications for adverse reactions are presented in Table 1,2 and Table 3.
For information regarding dosage modification of medicinal products administered with XPOVIO, refer to their corresponding SmPC.

Table 1: Prespecified dose modification steps for adverse reactions

	Selinexor in combination with Bortezomib and Dexamethasone (SVd)	**Selinexor in combination with Dexamethasone (Sd)**
Recommended starting dose	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
Discontinue*		

* If symptoms do not resolve, treatment should be discontinued

Table 2: Dose Modification Guidelines for Haematologic Adverse Reactions in Patients with Multiple Myeloma

Adverse reaction[a]	Occurrence	Action
Haematologic adverse reactions		
Thrombocytopenia		
Platelet count 25,000 to less than 75,000/mcL	Any	• Reduce selinexor by 1 dose level (see **Table 1**).
Platelet count 25,000 to less than 75,000/mcL with concurrent bleeding	Any	• Interrupt selinexor. • Restart selinexor at 1 dose level lower (see **Table 1**), after bleeding has resolved.
Platelet count less than 25,000/mcL	Any	• Interrupt selinexor. • Monitor until platelet count returns to at least 50,000/mcL. • Restart selinexor 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 selinexor by 1 dose level (see **Table 1**).
Absolute neutrophil count less than 0.5 x 10^9/L OR Febrile neutropenia	Any	• Interrupt selinexor. • Monitor until neutrophil counts return to 1.0 x 10^9/L or higher. • Restart selinexor at 1 dose level lower (see **Table 1**).
Anaemia		
Haemoglobin less than 8.0 g/dL	Any	• Reduce selinexor by 1 dose level (see **Table 1**). • Administer blood transfusions and/or other treatments per clinical guidelines.
Life-threatening consequences (urgent intervention indicated)	Any	• Interrupt selinexor. • Monitor haemoglobin until levels return to 8 g/dL or higher. • Restart selinexor at 1 dose level lower (see **Table 1**). • Administer blood transfusions and/or other treatments per clinical guidelines.

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

Table 3: Dose Modification Guidelines for Adverse Reactions

Adverse reaction[a]	Occurrence	Action
Non-haematologic adverse reactions		
Hyponatraemia		
Sodium level 130 mmol/L or less	Any	• Interrupt selinexor and provide appropriate supportive care. • Monitor until sodium levels return to 130 mmol/L or higher. • Restart selinexor at 1 dose level lower (see **Table 1**).
Fatigue		

Adverse reaction[a]	**Occurrence**	**Action**
Grade 2 lasting greater than 7 days OR Grade 3	Any	• Interrupt selinexor. • Monitor until fatigue resolves to Grade 1 or baseline. • Restart selinexor at 1 dose level lower (see **Table 1**).
Nausea and vomiting		
Grade 1 or 2 nausea (oral intake decreased without significant weight loss, dehydration or malnutrition) OR Grade 1 or 2 vomiting (5 or fewer episodes per day)	Any	• Maintain selinexor and initiate additional anti-nausea medicinal products.
Grade 3 nausea (inadequate oral caloric or fluid intake) OR Grade 3 or higher vomiting (6 or more episodes per day)	Any	• Interrupt selinexor. • Monitor until nausea or vomiting has resolved to Grade 2 or lower or baseline. • Initiate additional anti-nausea medicinal products. • Restart selinexor at 1 dose level lower (see **Table 1**).
Diarrhoea		
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	• Maintain selinexor and institute supportive care.
	2nd and subsequent	• Reduce selinexor by 1 dose level (see **Table 1**). • Institute supportive care.
Grade 3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated)	Any	• Interrupt selinexor and institute supportive care. • Monitor until diarrhoea resolves to Grade 2 or lower. • Restart selinexor 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 selinexor and institute supportive care. • Monitor until weight returns to more than 90% of baseline weight. • Restart selinexor at 1 dose level lower (see **Table 1**).
Ocular adverse reactions		
Grade 2, excluding cataract	Any	• Perform ophthalmologic evaluation. • Interrupt selinexor and provide supportive care. • Monitor until ocular symptoms resolve to Grade 1 or baseline. • Restart selinexor at 1 dose level lower (see **Table 1**).
Grade ≥3, excluding cataract	Any	• Permanently discontinue selinexor. • Perform ophthalmologic evaluation.
Other non-haematologic adverse reactions		

Adverse reaction[a]	Occurrence	Action
Grade 3 or 4 (life threatening)	Any	• Interrupt selinexor. • Monitor until resolved to Grade 2 or lower. • Restart selinexor at 1 dose level lower (see **Table 1**).

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

Special populations

Elderly population
No dose adjustment of selinexor is required for patients over 65 years of age (see sections 4.8, 5.1 and 5.2).

Renal impairment
No dose adjustment of selinexor is required for patients with mild, moderate, or severe renal impairment (see section 5.2). There are no data in patients with end-stage renal disease or haemodialysis to support a dose recommendation.

Hepatic impairment
No dose adjustment of selinexor is required for patients with mild hepatic impairment (see section 5.2). There are insufficient data in patients with moderate or severe hepatic impairment to support a dose recommendation.

Paediatric population
The safety and efficacy of XPOVIO in children below the age of 18 years of age have not been established. No data are available (see section 5.1 and 5.2).

There is no relevant use of XPOVIO in children less than 18 years of age in the treatment of multiple myeloma.

Method of administration
XPOVIO is for oral use.

XPOVIO in combination with bortezomib and dexamethasone (SVd) should be taken orally at approximately the same time once weekly on Day 1 of each week.

XPOVIO in combination with dexamethasone (Sd) should be taken at approximately the same time on Days 1 and 3 of each week.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

For medicinal products administered in combination with selinexor, the Summary of Product Characteristics (SmPC) of these medicinal products must be consulted prior to initiation of treatment, including for special warnings and precaution for use and recommended concomitant treatments.

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

Prophylactic concomitant treatment with a 5-HT3 antagonist and/or other anti-nausea agents should be provided prior to and during treatment with XPOVIO (see section 4.8).

Haematology
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.

Thrombocytopenia
Thrombocytopenic events (thrombocytopenia and platelet count decreased) were frequently reported in patients receiving selinexor which can be severe (Grade 3/4). Grade 3/4 thrombocytopenia can sometimes lead to clinically significant bleeding and in rare cases may lead to potentially fatal haemorrhage (see section 4.8).

Thrombocytopenia can be managed with dose interruptions, modifications, platelet transfusions, and/or other treatments as clinically indicated. Patients should be monitored for signs and symptoms of bleeding and evaluated promptly. For dose modification guidelines refer to Table 1, 2 and Table 3 in section 4.2.

Neutropenia
Neutropenia including severe neutropenia (Grade 3/4) has been reported with selinexor. In a few cases concurrent infections occurred in patients with Grade 3/4 neutropenia (see section 4.8).

Patients with neutropenia should be monitored for signs of infection and evaluated promptly. Neutropenia can be managed with dose interruptions, modifications, and colony-stimulating factors as per medical guidelines. For dose modification guidelines refer to Table 1,2 and Table 3 in section 4.2.

Gastrointestinal toxicity
Nausea, vomiting, diarrhoea, which sometimes can be severe and require the use of anti-emetic and anti-diarrhoeal medicinal products (see section 4.8).

Prophylaxis with 5HT3 antagonists and/or other anti-nausea agents should be provided prior to and during treatment with selinexor. Fluids with electrolytes should be administered to prevent dehydration in patients at risk.

Nausea/vomiting can be managed by dose interruptions, modifications, and/or initiation of other antiemetics medicinal products as clinically indicated. Diarrhoea can be managed with dose interruptions, modifications and/or administration of anti-diarrhoea medicinal products. For dose modification guidelines refer to Table 1, 2 and Table 3 in section 4.2.

Weight loss and anorexia
Selinexor can cause weight loss and anorexia. Patients should have their body weight, nutritional status and volume checked at baseline, during treatment, and as clinically indicated. Monitoring should be more frequent during the first two months of treatment. Patients experiencing new or worsening decreased appetite and weight may require dose modification, appetite stimulants, and nutritional consultations. For dose modification guidelines refer to Table 1, 2 and Table 3 in section 4.2.

Confusional state and dizziness
Selinexor can cause 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 heavy machinery until symptoms resolve (see section 4.7).

Hyponatraemia

Selinexor can cause hyponatraemia. Patients should have their sodium levels checked at baseline, during treatment, and as clinically indicated. Monitoring should be more frequent 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 medical guidelines (intravenous sodium chloride solution and/or salt tablets), including dietary review.

Patients may require selinexor dose interruption and/or modification. For dose modification guidelines refer to Table 1, 2 and Table 3 in section 4.2.

Cataract
Selinexor can cause new onset or exacerbation of cataract (see section 4.8). Ophthalmologic evaluation may be performed as clinically indicated. Cataract should be treated as per medical guidelines, including surgery if warranted.

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

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 selinexor and for at least 1 week following the last dose of selinexor.

Women of childbearing potential and male patients of reproductive potential should be advised to use effective contraceptive measures or abstain from sexual activity to prevent pregnancy during treatment with selinexor and for at least 1 week following the last dose of selinexor (see section 4.6).

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per 20 mg tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No dedicated clinical drug interaction studies have been conducted.

Concomitant use of strong CYP3A4 inducer might lead to lower exposure of selinexor.

No clinically significant differences in selinexor pharmacokinetics were observed when co-administered with up to 1000 mg daily dose of paracetamol.

4.6 Fertility, pregnancy and lactation

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 selinexor and for at least 1 week following the last dose of selinexor. A pregnancy test is recommended for women of childbearing potential prior to initiating selinexor treatment.

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

Pregnancy
There are no data from the use of selinexor in pregnant women. Studies in animals have shown

selinexor can cause foetal harm (see section 5.3). Selinexor is not recommended during pregnancy and in women of childbearing potential not using contraception.

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

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

Fertility
Based on findings in animals, selinexor may impair fertility in females and males (see section 5.3).

4.7 Effects on ability to drive and use machines

Selinexor may have major influence on the ability to drive and use machines. Selinexor 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 Undesirable effects

Summary of the safety profile
The safety of selinexor in combination with bortezomib and dexamethasone has been evaluated in 195 patients with multiple myeloma. The most frequent adverse reactions (≥30%) were thrombocytopenia (62%), nausea (50%), fatigue (42%), anaemia (37%), decreased appetite (35%), diarrhoea (33%), and peripheral neuropathy (33%).

The most commonly reported serious adverse reactions (≥3%) were pneumonia (14.9%), cataract (4.6%), sepsis (4.1%), diarrhoea (3.6%), vomiting (3.6%) and anaemia (3.1%).

The safety of selinexor in combination with dexamethasone has been evaluated in 214 patients with multiple myeloma, including 83 patients with penta-refractory disease. The most frequent adverse reactions (≥30%) 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%).

The most commonly reported serious adverse reactions (≥3%) were pneumonia (7.5%), sepsis (6.1%) thrombocytopenia (4.7%), acute kidney injury (3.7%), and anaemia (3.3%).

Tabulated list of adverse reactions
Adverse reactions reported in clinical trials with selinexor in combination with bortezomib and dexamethasone (SVd) are summarised in Table 4.

Adverse reactions reported in clinical trials with selinexor in combination with dexamethasone (Sd) are summarised in Table 5.

These reactions are presented by system organ class (SOC) and by frequency. 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse drug reactions (ADRs) observed in patients with multiple myeloma treated with selinexor in combination with bortezomib and dexamethasone (SVd)

System organ class/ preferred term	All ADRs/frequency	Grade 3-4 ADRs/frequency
Infections and infestations	**Very common** Pneumonia*, upper respiratory tract infection, bronchitis, nasopharyngitis **Common** Sepsis*, lower respiratory tract infection	**Very common** Pneumonia* **Common** Sepsis*, lower respiratory tract infection, bronchitis, upper respiratory tract infection
Blood and lymphatic system disorders	**Very common** Thrombocytopenia, anaemia, neutropenia* **Common** Leukopenia, lymphopenia	**Very common** Thrombocytopenia, anaemia **Common** Neutropenia*, lymphopenia **Uncommon** Leukopenia
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hyponatraemia, dehydration, hypokalaemia, hypocalcaemia, hypophosphataemia, hyperkalaemia, hypomagnesaemia	**Common** Hyponatraemia, dehydration, decreased appetite, hypokalaemia, hypocalcaemia, hypophosphataemia
Psychiatric disorders	**Very common** Insomnia **Common** Confusional state,	**Common** Confusional state, insomnia
Nervous system disorders	**Very common** Peripheral neuropathy, dizziness, headache **Common** Syncope, amnesia*, balance disorder, dysgeusia, ageusia	**Common** Syncope, peripheral neuropathy **Uncommon** Headache, dizziness, amnesia*
Ear and labyrinth disorders	**Common** Vertigo	None

System organ class/ preferred term	All ADRs/frequency	Grade 3-4 ADRs/frequency
Eye disorders	**Very common** Cataract, vision blurred*	**Very common** Cataract **Common** Vision blurred*
Cardiac disorders	**Common** Tachycardia	None
Vascular disorders	**Common** Hypotension	**Common** Hypotension
Respiratory, thoracic and mediastinal disorders	**Very common** Cough **Common** Dyspnoea*, epistaxis	**Common** Epistaxis **Uncommon** Dyspnoea*, cough
Gastrointestinal disorders	**Very common** Nausea, diarrhoea, vomiting, constipation **Common** Abdominal pain, dyspepsia, dry mouth, flatulence	**Common** Nausea, diarrhoea, vomiting
Skin and subcutaneous tissue disorders	**Common** Alopecia, night sweats*, pruritus	**Uncommon** Night sweats*
Musculoskeletal and connective tissue disorders	**Common** Hypercreatinaemia	**Common** 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	**Very common** Fatigue **Common** Pyrexia, asthenia, general physical health deterioration
Investigations	**Very common** Weight decreased **Common** Aspartate aminotransferase increased, alanine aminotransferase increased	**Common** Weight decreased, aspartate aminotransferase increased, alanine aminotransferase increased

System organ class/ preferred term	All ADRs/frequency	Grade 3-4 ADRs/frequency
Injury, poisoning and procedural complications	**Common** Fall, contusion	**Common** Fall

* Grouping of more than one MedDRA preferred term including:
Pneumonia: pneumonia, lung infection, pneumonia pneumococcal, pneumonia influenzal, pneumonia parainfluenzae viral, pneumonia bacterial and pneumonia fungal
- Sepsis: sepsis, septic shock, staphylococcal sepsis and urosepsis
- Neutropenia: neutropenia and febrile neutropenia
- Amnesia: amnesia and memory impairment
- Vision blurred: vision blurred, visual impairment and visual acuity reduced
- Dyspnoea: dyspnoea and exertional dyspnoea
- Night sweats: night sweats and hyperhidrosis

Table 5: Adverse drug reactions (ADRs) observed in patients treated with selinexor in combination with dexamethasone (Sd)

System organ class/ preferred term	All ADRs/frequency	Grade 3-4 ADRs/frequency
Infections and infestations	**Very common** Pneumonia, upper respiratory tract infection **Common** Sepsis, bacteraemia	**Common** Pneumonia, sepsis, bacteraemia **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 **Common** Hypocalcaemia, hypophosphataemia, hyperkalaemia, hypomagnesaemia, hyperamylasaemia, hyperuricaemia, hyperlipasaemia **Uncommon** Tumour lysis syndrome	**Very common** Hyponatraemia **Common** Dehydration, decreased appetite, hypokalaemia, hyperglycaemia, hypocalcaemia, hyperkalaemia, hyperamylasaemia, hypophosphataemia hyperuricaemia, hyperlipasaemia **Uncommon** Tumour lysis syndrome
Psychiatric disorders	**Very common** Confusional state, insomnia **Common** Delirium, hallucination	**Common** Confusional state, insomnia **Uncommon** Delirium, hallucination

System organ class/ preferred term	All ADRs/frequency	Grade 3-4 ADRs/frequency
Nervous system disorders	**Very common** Dizziness, dysgeusia, headache **Common** Peripheral neuropathy, syncope, ageusia, taste disorder, balance disorder, cognitive disorder, disturbance in attention, memory impairment **Uncommon** Encephalopathy	**Common** Syncope, cognitive disorder **Uncommon** Peripheral neuropathy, encephalopathy
Eye disorders	**Very common** Vision blurred **Common** Cataract, visual impairment	**Common** 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, flatulence	**Common** Nausea, diarrhoea, vomiting, constipation **Uncommon** Abdominal pain
Skin and subcutaneous tissue disorders	**Common** Alopecia, night sweats, pruritus	None
Musculoskeletal and connective tissue disorders	**Common** Muscle spasms, hypercreatinaemia	**Uncommon** Muscle spasms, hypercreatinaemia
Renal and urinary disorders	**Common** Acute kidney injury	**Common** Acute kidney injury

System organ class/ preferred term	All ADRs/frequency	Grade 3-4 ADRs/frequency
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, pain **Uncommon** Pyrexia
Investigations	**Very common** Weight decreased **Common** Aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased	**Common** Alanine aminotransferase increased **Uncommon** Weight decreased; aspartate aminotransferase increased
Injury, poisoning and procedural complications	**Common** Fall	**Common** Fall

Description of selected adverse reactions

Infections
Infection was the most common non-haematological toxicity.

In patients who received SVd, infections were reported in 70% of patients and 28% of patients had Grade 3 or 4 infections. Serious infections were reported in 28% of patients with fatal infections occurring in 4% of treated patients. Upper respiratory tract infection and pneumonia were the most commonly reported infections in 21% and 15% of patients, respectively. Infection led to dose discontinuation in 1% of patients, treatment interruption in 48% patients, and a dose reduction in 10% of patients.

In patients who received Sd, infections were reported 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 patients who received SVd, thrombocytopenia occurred in 62% of patients and 41% of patients had Grade 3 or 4 thrombocytopenia. Thrombocytopenia was serious in 2% of patients. Of the 41% patients with Grade 3 or 4 thrombocytopenia, Grade 3 or higher concurrent bleeding events (concurrency defined as ±5 days) were reported in 5% of patients. Fatal haemorrhage occurred in 2% of patients with thrombocytopenia. Thrombocytopenia led to dose discontinuation in 2% of patients, treatment interruption in 35% of patients, and a dose reduction in 33% of patients.

In patients who received Sd, thrombocytopenia occurred in 75% of patients and 65% of these ADRs 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.

Thrombocytopenia can be managed with dose modifications (see section 4.2), supportive care and platelet transfusions. Patients should be monitored for signs and symptoms of bleeding and evaluated promptly (see section 4.4).

Neutropenia
In patients who received SVd, neutropenia occurred in 16% of patients and 10% of patients had Grade 3 or 4 events of neutropenia. Neutropenia was serious in 1% of patients. None of the patients had a dose discontinuation due to neutropenia, and neutropenia led to treatment interruption in 9% of patients, and a dose reduction in 5% of patients.

Febrile neutropenia, reported as serious, occurred in one patient (<1%) who received SVd; and was Grade 4. Febrile neutropenia led to treatment interruption and dose reduction; no dose discontinuation occurred due to febrile neutropenia. Of the 19 patients with Grade 3 or higher neutropenia, serious Grade 3 or higher concurrent infections (concurrency defined as ±5 days) were reported in 3 (16%) patients. Concurrent Grade 3 or higher infections included lower respiratory tract infection, bronchitis and ear infection (1 patient each).

In patients who received Sd, neutropenia occurred in 36% of patients and 25% of these were Grade 3 or 4. Neutropenia was serious in 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 who received Sd; 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 6 (11%) patients. Most commonly reported Grade 3 or higher concurrent infection included urinary tract infection (3 patients), and sepsis (2 patients).

Anaemia
In patients who received SVd, anaemia occurred in 37% of patients and 16% of patients had Grade 3 anaemia, no patients had Grade 4 or 5 anaemia. Anaemia was serious in 3% of patients. Anaemia led to dose discontinuation in 1% of patients, treatment interruption in 6% of patients, and a dose reduction in 3% of patients.

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

Anaemia can be managed with dose modifications (see section 4.2) and with blood transfusions and/or erythropoietin administration as per medical guidelines. For dose modification guidelines refer to Table 2 of section 4.2.

Gastrointestinal toxicity
In patients who received SVd, nausea occurred in 50% of patients and 8% of patients had Grade 3 or 4 nausea. Nausea was serious in 2% of patients. When anti-nausea treatment was administered, the median duration of nausea improved by 10 days. Nausea led to dose discontinuation in 3% of patients, treatment interruption in 7% of patients, and a dose reduction in 7% of patients.

Vomiting occurred in 21% of patients who received SVd, and 4% of patients had Grade 3 vomiting. No patients had Grade 4 vomiting. Vomiting was serious in 4% of patients. Vomiting led to dose discontinuation in 2% of patients, treatment interruption in 3% of patients, and a dose reduction in 3% of patients.

Diarrhoea occurred in 33% of patients who received SVd and 7% of patients had Grade 3 or 4 diarrhoea. Diarrhoea was serious in 4% of patients. Diarrhoea led to dose discontinuation in 1% of patients, treatment interruption in 8% of patients, and a dose reduction in 2% of patients.

In patients who received Sd, nausea/vomiting occurred in 79% of patients and 10% of these were Grade 3 or 4 and was 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 who received Sd and 7% were Grade 3 or 4 and diarrhoea was serious in 2% of patients. Diarrhoea led to dose discontinuation in 1% of patients, treatment interruption in 2% of patients, and a dose reduction in 1% of patients.

Hyponatraemia
In patients who received SVd, hyponatraemia occurred in 8% of patients and 5% of patients had Grade 3 or 4 hyponatremia. Hyponatraemia was serious in <1% 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 <1% of patients, and a dose reduction in 1% of patients.

In patients who received Sd, 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.

Cataract
In patients receiving SVd, the incidence of new onset or worsening cataracts requiring clinical intervention was reported in 24% of patients. The median time to new onset of cataract was 233 days. The median time for worsening of cataract in patients presenting with cataract at start of selinexor therapy was 261 days (SVd). Cataract did not lead to treatment discontinuation, it led to treatment interruption in 4% of patients and a dose reduction in 3 % of patients. Cataract should be treated as per medical guidelines, including surgery if warranted (see sections 4.4 and 4.2).

Tumour lysis syndrome
Tumour lysis syndrome (TLS) occurred in one (<1%) patient (who received Sd) which was considered Grade 3 and serious. Patients at a high risk for TLS should be monitored closely. Treat TLS promptly in accordance with institutional guidelines (see section 4.4).

Elderly population
Among patients with multiple myeloma who received SVd, 56% were 65 years of age and over, while 17% were 75 years of age and over. 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 higher incidence of serious adverse reactions (57% vs 51%).

Among patients with multiple myeloma who received Sd, 47% were 65 years of age and over, while 11% were 75 years of age and over. 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 (52% vs 25%), higher incidence of serious adverse reactions (74% vs 59%), and higher incidence of fatal adverse reactions (22% vs 8%).

Reporting of suspected adverse reactions
Reporting of suspected adverse reactions after authorisation 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 via the national reporting system.

4.9 Overdose

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

Symptoms
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
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

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX66

Mechanism of action
Selinexor is a reversible covalent selective inhibitor of nuclear export (SINE) compound that specifically blocks exportin 1 (XPO1). XPO1 is the major mediator of the nuclear export of many cargo proteins including tumour suppressor proteins (TSPs), growth regulators and mRNAs of growth promoting (oncogenic) proteins. 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 and/or bortezomib demonstrated synergistic cytotoxic effects in multiple myeloma *in vitro* and increased anti-tumour activity in murine xenograft multiple myeloma models *in vivo*, including those resistant to proteasome inhibitors.

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 efficacy and safety

Selinexor in combination with bortezomib and dexamethasone (SVd) for the treatment of patients with multiple myeloma

The efficacy and safety of selinexor in combination with bortezomib and dexamethasone were evaluated in Study KCP-330-023 (BOSTON), a phase 3, global, randomised, open-label, active-controlled study, in patients with multiple myeloma who had received at least one prior therapy. BOSTON required patients to have measurable myeloma per International Myeloma Working Group (IMWG) criteria with documented evidence of progressive disease on or after their most recent treatment regimen, have previously received treatment with one to three prior different regimens for multiple myeloma. Patients who had previously received proteasome inhibitors (alone or as part of a combination treatment) were required to have had at least a partial response to the therapy and at least a 6-month interval since their last proteasome inhibitor therapy, with no history of discontinuation of bortezomib due to Grade 3 or higher toxicity. Patients had to have an ECOG performance score of ≤2, adequate hepatic, renal and haematopoietic function. Patients with systemic light-chain amyloidosis,

active central nervous system myeloma, peripheral neuropathy of Grade 2 or higher, or painful neuropathy of Grade 2, plasma cell leukaemia, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, or skin changes (POEMS) syndrome were excluded from trial participation.

The study compared treatment with once weekly selinexor 100 mg (administered orally on Day 1 of each week) in combination with twice weekly dexamethasone 20 mg (administered orally on Days 1 and 2 of each week) and once-weekly bortezomib 1.3 mg/m^2 (administered subcutaneous on Day 1 of weeks 1-4 with week 5 off) [SVd arm] to treatment with twice-weekly bortezomib 1.3 mg/m^2 (administered subcutaneous on Days 1, 4, 8, 11) with twice weekly low-dose dexamethasone 20 mg (administered orally on Days 1, 2, 4, 5, 8, 9, 11, 12) of a standard 21-day cycle for the first 8 cycles, followed by once weekly subcutaneous bortezomib 1.3 mg/m^2 (administered subcutaneously on Day 1 of weeks 1-4 with week 5 off) with twice weekly low-dose dexamethasone 20 mg (administered orally on Days 1 and 2 of each week) for cycles ≥9 [Vd arm].

Treatment continued in both arms until disease progression, death or unacceptable toxicity. Upon confirmed progressive disease (PD), patients in the control arm (Vd) could cross over to receive selinexor based therapy in the form of weekly SVd (BOSTON regimen) or weekly Sd (selinexor 100mg once weekly (Day 1 of each week) and low-dose dexamethasone 20 mg twice weekly (Days 1 and 2 of each week).

A total of 402 patients were randomised: 195 to SVd arm and 207 to Vd arm.

Baseline patient and disease characteristics are described in Table 6.

Table 6: Demographics and disease characteristics of patients with relapsed refractory multiple myeloma in BOSTON Study (n=402)

Characteristic	**SVd (n=195)**	**Vd (n=207)**
Median from diagnosis to randomization, years (range)	3.81 (0.4, 23.0)	3.59 (0.4, 22.0)
Time since end of last prior therapy, median (range)	48 weeks (1, 1088)	42 weeks (2, 405)
Number of 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%
Age, median (range)	66 years (40, 87)	67 years (38, 90)
Patients <65 years of age, n (%)	86 (44)	75 (36)
Patients 65-74 years of age, n (%)	75 (39)	85 (41)
Patients ≥75 years of age, n (%)	34 (17)	47 (23)
Males : Females, n (%)	115 (59) : 80 (41)	115 (56) : 92 (44)
Type of prior therapy, n (%)		
Stem Cell transplantation	76 (39)	63 (30)
Lenalidomide in any combination	77 (39)	77 (37)
Pomalidomide in any combination	11 (6)	7 (3)
Bortezomib in any combination	134 (69)	145 (70)
Carfilzomib in any combination	20 (10)	21 (10)
Any proteasome inhibitor in any combination	148 (76)	159 (77)
Daratumumab in any combination	11 (6)	6 (3)
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)
High-risk cytogenetics[a], n (%)	97 (50)	95 (46)
ECOG performance status: 0 to 1, n (%)	175 (90)	191 (92)

[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 IMWG Uniform Response Criteria for Multiple Myeloma, as assessed by an Independent Review Committee (IRC).

Based on a pre-planned PFS interim analysis, where the boundary for PFS was crossed (median follow up of 15.1 months); BOSTON showed a statistically significant improvement in PFS in the SVd arm as compared to the Vd arm; hazard ratio (HR)=0.70 (95% CI: 0.53-0.93; p=0.0075), a median PFS of 13.9 months (95% CI: 11.7, not reached) and 9.5 months (95% CI: 8.1, 10.8) in the SVd and Vd arms respectively.

There was a statistically significant improvement in overall response rate (ORR): 76.4% in the SVd arm vs 62.3% in the Vd arm, p=0.0012. The ≥ very good partial response rate (≥VGPR rate includes stringent complete response [sCR], complete response [CR] and VGPR) was 44.6% in the SVd arm compared with 32.4% in the Vd arm.

The median time to response was 1.4 months in the SVd-treated patients and 1.6 months in the Vd treated patients. The median duration of response (DoR), 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 PFS interim analysis, 109 overall survival (OS) events had occurred; there were 47 and 62 deaths in the SVd and Vd arms respectively (HR=0.84 [95% CI: 0.57, 1.23]). Median OS was not reached for the SVd arm and was of 25 months for the Vd arm.

At an updated descriptive analysis with a median follow up of 22.1 months results were consistent with the primary analysis. Efficacy results are shown in Table 7 and Figure 1.

Table 7: Efficacy results assessed by independent review committee in BOSTON study (median follow-up 22.1 months)

	SVd (n=195)	**Vd (n=207)**
Progression Free Survival (PFS)[a]		
Hazard Ratio (95% CI)	0.71 (0.54, 0.93)	
Median PFS in months (95% CI)	13.2 (11.7, 23.4)	9.5 (8.1, 10.8)
Overall Response Rate (ORR)[b], n (%)	150 (76.9)	131 (63.3)
95% CI	(70.4, 82.6)	(56.3, 69.9)
sCR	19 (10)	13 (6)
CR	14 (7)	9 (4)
VGPR	54 (28)	45 (22)
PR	63 (32)	64 (31)
Time to Response, months (95% CI)	1.4 (1.4, 1.5)	1.6 (1.5, 2.1)
Median Duration of Response, months (95% CI)[c]	17.3 (12.6, 26.3)	12.9 (9.3, 15.8)
Overall survival (OS, median follow-up 28.7 months)[a]		
Number of events, n (%)	68 (35)	80 (39)
Median OS, months (95% CI)	36.7 (30.2, Not Reached)	32.8 (27.8, Not Reached)
Hazard Ratio (95% CI)	0.88 (0.63, 1.22)	

SVd=selinexor-bortezomib-dexamethasone, Vd=bortezomib-dexamethasone, sCR= stringent complete response, CR= complete response, VGPR= very good partial response, PR= partial response

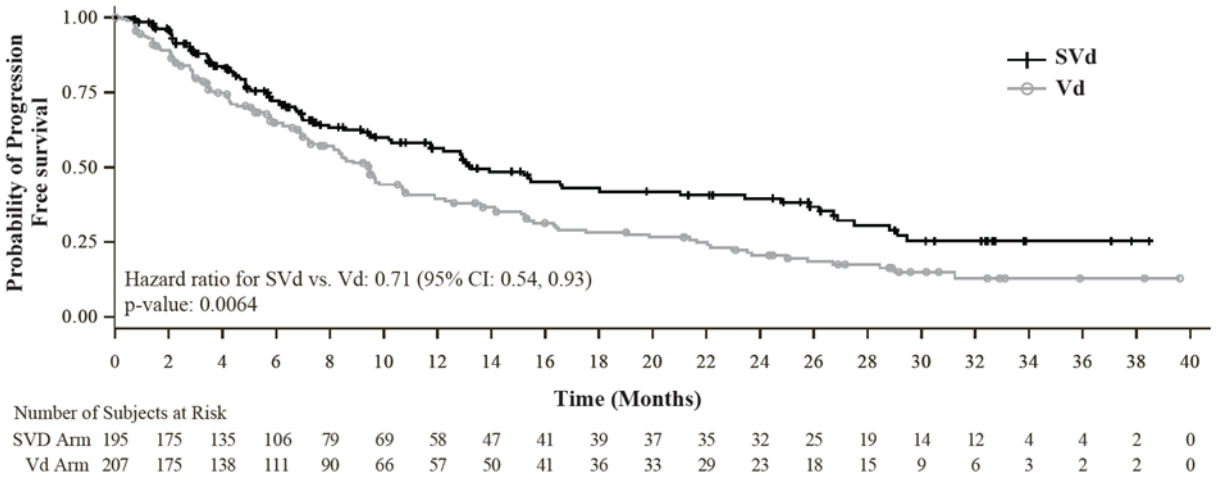
*Efficacy results reported correspond to a descriptive analysis based on the 15 Feb 2021 data cut off.

[a] Hazard ratio is based on stratified Cox's proportional hazard regression modelling, p-value based on stratified log-rank test.

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

[c] Includes responding patients who achieved a PR or better

Figure 1: Kaplan-Meier Curve of PFS in BOSTON study (median follow-up 22.1 months)



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.

Selinexor in combination with dexamethasone (Sd) for the treatment of patients with relapsed/refractory multiple myeloma

Study KCP-330-012 (STORM), a phase 2, multi-centre, single-arm, open-label, study, enrolled patients with relapsed and/or refractory multiple myeloma (RRMM). STORM Part 2 required patients to have measurable disease per IMWG criteria, have previously received three or more antimyeloma treatment regimens including an alkylating agent, glucocorticoids, bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody; and whose myeloma was documented to be refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory agent, an anti-CD38 monoclonal antibody, and to the last line of therapy. Patients had to have an ECOG performance status score ≤2, adequate hepatic, renal and haematopoietic function. Systemic light chain amyloidosis, active central nervous system myeloma, peripheral neuropathy of Grade 3 or higher, or painful neuropathy of Grade 2 or higher were exclusion criteria.

Patients 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.

Among patients enrolled in STORM Part 2 (n=123), eighty-three (83) patients had RRMM that was refractory to two proteasome inhibitors (bortezomib, carfilzomib), two immunomodulators (lenalidomide, pomalidomide) and an anti-CD38 monoclonal antibody (daratumumab). The median duration of selinexor treatment in these 83 patients was 9 weeks (range: 1 to 61 weeks). The median total dose of selinexor received was 880 mg (range 160 to 6,220 mg), with a median dose of 105 mg (range: 22 to 180 mg) received per week.

The data presented below is from the 83 patients whose disease was refractory to bortezomib (B), carfilzomib (C), lenalidomide (L), pomalidomide (P), and daratumumab (D) (penta-refractory).

Table 8 provides patients disease and prior treatment characteristics.

Table 8: Demographics and disease characteristics of patients with relapsed refractory multiple myeloma treated with twice weekly 80 mg selinexor and 20 mg dexamethasone (n=83)

Characteristics	
Median from diagnosis to start of study treatment, years (range)	7 years (1, 23)
Number of prior treatment regimens, median (range)	8 (4, 18)
Age, median (range)	65 years (40, 86)
Patients < 65 years of age, n (%)	40 (48)
Patients 65-74 years of age, n (%)	31 (37)
Patients ≥ 75 years of age, n (%)	12 (15)
Males : Females, n (%)	51 M (61) : 32 F (39)
Refractory status to specific treatment combinations, n (%)	
Penta refractory (BCLPD)	83 (100)
Daratumumab in any combination	57 (69)
Daratumumab as single agent	26 (31)
Previous stem cell transplant[1], n (%) ≥2 transplants	67 (81) 23 (28)
Previous CAR-T Cell Therapy, n (%)	2 (2.4)
Revised Integrated Staging System at baseline, n (%)	
I	10 (12)
II	56 (68)
III	17 (21)
High-risk cytogenetics, n (%) (includes any of del(17p)/p53, t(14; 16), t(4; 14), or 1q21)	47 (57)
ECOG performance status: 0 to 1, n (%)	74 (89)

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

The primary efficacy endpoint was overall response rate (ORR) as assessed by an Independent Review Committee based on the IMWG uniform response criteria for multiple myeloma. Responses were assessed monthly and as per IMWG guidelines. Table 11 provides an overview of the efficacy results.

Table 9: Efficacy results: assessed by Independent Review Committee (STORM, patients with relapsed refractory multiple myeloma treated with twice weekly 80 mg selinexor and 20 mg dexamethasone)

Efficacy endpoint	**XPOVIO 80 mg + dexamethasone 20 mg n=83**
Overall response rate (ORR), n (%) (includes sCR + VGPR + PR)[1]	21 (25.3)
95% confidence interval	16.4, 36
sCR, MRD negative, n (%)	1 (1.2)
CR, n (%)	0 (0)
VGPR, n (%)	4 (4.8)
PR, n (%)	16 (19.3)
Minimal response (MR), n (%)	10 (12.0)
Stable disease (SD), n (%)	32 (38.6)
Progressive disease (PD) /not evaluable (NE), n (%)	20 (24.1)
Median time to first response (weeks) (range: 1 to 10 weeks)	3.9
Median duration of response (DOR) months (95% confidence interval)	3.8 (2.3, 10.8)

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

5.2 Pharmacokinetic properties

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 95.0% 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.

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

Elimination
Following a single dose of 80 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.

Specific populations

Age, sex and race
Age (18 to 94 years of age), sex, or race had no clinically significant effect on the pharmacokinetics of selinexor.

In the population PK dataset, age and race were not identified as a significant covariate, gender was identified as a significant covariate.

Renal impairment
The degree of renal impairment was determined by creatinine clearance as estimated by the Cockcroft-Gault equation. Results from population PK analyses of patients with normal (n=283, CL_{cr}: ≥90 mL/min), mild (n=309, CL_{cr}: 60 to 89 mL/min), moderate (n=185, CL_{cr}: 30 to 59 mL/min) or severe (n=13, CL_{cr}: 15 to 29 mL/min) renal dysfunction indicated that creatinine clearance had no impact on the PK of NEXPOVIO. 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.

Hepatic impairment
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. Similar finding was observed 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).

5.3 Preclinical safety data

Repeated-dose Toxicity
Findings in the repeat dose 13-week rat study were decrements in body weight gain and food consumption, and haematopoietic/lymphoid hypoplasia, and male/female reproductive organ effects. In the 13-week monkey study, the treatment-related effects observed included body weight loss, gastrointestinal effects, and lymphoid/haematologic depletion. 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.

Genotoxicity
Selinexor was not mutagenic in a bacterial reverse mutation assay. Selinexor was not clastogenic in either the *in vitro* cytogenetic assay in human lymphocytes or in the *in vivo* rat micronucleus assay.

Carcinogenicity
Carcinogenicity studies have not been conducted with selinexor.

Toxicity to Reproduction and Development
Fertility studies in animals have not been conducted with selinexor. In repeat-dose oral toxicity studies, selinexor was administered for up to 13 weeks in rats and monkeys. Reduced sperm, spermatids, and germ cells in epididymides and testes were observed in rats, decreased ovarian follicles were also observed in rats, and single cell necrosis of testes was observed in monkeys. These findings were observed at systemic exposures approximately 0.11, 0.28, and 0.53 times, respectively, the exposure (AUC_{last}) in humans at the recommended human dose of 80 mg. Developmental effects were seen with daily exposure in pregnant rats at systemic exposures below the exposure (AUC_{last}) in humans at the recommended human dose of 80 mg.

Other Toxicities
A guinea pig sensitisation assay showed that selinexor at 25% induced a mild Grade II dermal contact hypersensitivity response at 24 and 48 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (pH-101) (E460i)
Croscarmellose sodium (E468)

Povidone K30 (E1201)
Colloidal silicon dioxide (E551)
Magnesium stearate (E470b)
Microcrystalline cellulose (PH-102) (E460i)
Sodium lauryl sulphate (E514i)

Tablet coating
Talc (E553b)
Poly(vinyl alcohol) partially hydrolysed (E1203)
Glyceryl monostearate (E471)
Polysorbate 80 (E433)
Titanium dioxide (E171)
Macrogol (E1521)
Indigo carmine aluminium lake (E132)
Brilliant blue FCF aluminium lake (E133)

6.2 Storage conditions

Store at or below 30 deg C.

6.3 Nature and contents of container

PVC/PCTFE/PVC-aluminium blisters containing 4, 5, 6 or 8 film-coated tablets.
Cartons contain a total of 16, 20, 24 or 32 film-coated tablets. Not all pack-sizes may be marketed.

7. MARKETING AUTHORISATION HOLDER

DKSH (Thailand) Limited
Bangkok, Thailand

8. MARKETING AUTHORISATION NUMBER(S)

1C 32/67 (NC)

9. DATE OF FIRST AUTHORISATION

18 September 2024

10. DATE OF REVISION OF THE TEXT

June 2024