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XPOVIO PI APAC-Hong Kong

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1. NAME OF THE MEDICINAL PRODUCT

XPOVIO Tablets 20mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20mg 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 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

XPOVIO in combination with dexamethasone (Xd)
The recommended XPOVIO and dexamethasone starting doses are as follows:

- XPOVIO 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 XPOVIO.

Treatment with XPOVIO 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 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.

Dose modifications
Recommended XPOVIO dose modifications for adverse reactions are presented in Table 1 and Table 2. 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

	XPOVIO in combination with Dexamethasone (Xd)
Recommended starting dose	80 mg Days 1 and 3 of each week (160 mg total per week)
First reduction	100 mg once weekly
Second reduction	80 mg once weekly
Third reduction	60 mg once weekly
Discontinue*	

* If symptoms do not resolve, treatment should be discontinued

Table 2: Dose modification guidelines for adverse reactions

Adverse reaction[a]	**Occurrence**	**Action**
Haematologic adverse reactions		
Thrombocytopenia		
Platelet count 25,000 to less than 75,000/mcL	Any	• Reduce XPOVIO by 1 dose level (see **Table 1**).
Platelet count 25,000 to less than 75,000/mcL with concurrent bleeding	Any	• Interrupt XPOVIO. • Restart XPOVIO at 1 dose level lower (see **Table 1**), after bleeding has resolved.
Platelet count less than 25,000/mcL	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Restart XPOVIO at 1 dose level lower (see **Table 1**).
Neutropenia		
Absolute neutrophil count of 0.5 to 1.0 x 10^9/L without fever	Any	• Reduce XPOVIO by 1 dose level (see **Table 1**).
Absolute neutrophil count less than 0.5 x 10^9/L OR Febrile neutropenia	Any	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1.0 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**). • 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.
Non-haematologic adverse reactions		
Hyponatraemia		
Sodium level 130 mmol/L or less	Any	• Interrupt XPOVIO and provide appropriate supportive care. • Monitor until sodium levels return to 130 mmol/L or higher. • Restart XPOVIO at 1 dose level lower (see **Table 1**).
Fatigue		
Grade 2 lasting greater than 7 days OR Grade 3	Any	• Interrupt XPOVIO. • Monitor until fatigue resolves to Grade 1 or baseline. • Restart XPOVIO at 1 dose level lower (see **Table 1**).
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 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 XPOVIO • Monitor until nausea or vomiting has resolved to Grade 2 or lower or baseline. • Initiate additional anti-nausea medicinal products. • Restart XPOVIO at 1 dose level lower (see **Table 1**).
Diarrhoea		
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	• Maintain XPOVIO and institute supportive care.
	2nd and subsequent	• Reduce XPOVIO by 1 dose level (see **Table 1**). • Institute supportive care.
Grade 3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated)	Any	• Interrupt XPOVIO and institute supportive care. • Monitor until diarrhoea resolves to Grade 2 or lower. • Restart XPOVIO at 1 dose level lower (see **Table 1**).
Weight loss and anorexia		
Weight loss of 10% to less than 20% OR Anorexia associated with significant weight loss or malnutrition	Any	• Interrupt XPOVIO and institute supportive care. • Monitor until weight returns to more than 90% of baseline weight. • Restart XPOVIO at 1 dose level lower (see **Table 1**).
Ocular adverse reactions		
Grade 2, excluding cataract	Any	• Perform ophthalmologic evaluation. • Interrupt XPOVIO and provide supportive care. • Monitor until ocular symptoms resolve to Grade 1 or baseline. • Restart XPOVIO at 1 dose level lower (see **Table 1**).
Grade ≥3, excluding cataract	Any	• Permanently discontinue XPOVIO. • Perform ophthalmologic evaluation.
Other non-haematologic adverse reactions		
Grade 3 or 4 (life threatening)	Any	• Interrupt XPOVIO. • Monitor until resolved to Grade 2 or lower. • Restart XPOVIO 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 XPOVIO is required for patients over 65 years of age (see sections 4.8, 5.1 and 5.2).

Renal impairment
No dose adjustment of XPOVIO 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 XPOVIO 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 dexamethasone (Xd) 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 XPOVIO, 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 XPOVIO 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 and Table 2 in section 4.2.

Neutropenia
Neutropenia including severe neutropenia (Grade 3/4) has been reported with XPOVIO. 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 and Table 2 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 XPOVIO. 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 and Table 2 in section 4.2.

Weight loss and anorexia
XPOVIO 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 and Table 2 in section 4.2.

Confusional state and dizziness
XPOVIO 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
XPOVIO 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 XPOVIO dose interruption and/or modification. For dose modification guidelines refer to Table 1 and Table 2 in section 4.2.

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

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

No clinically significant differences in XPOVIO 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 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.

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

Pregnancy
There are no data from the use of XPOVIO in pregnant women. Studies in animals have shown XPOVIO can cause foetal harm (see section 5.3). XPOVIO is not recommended during pregnancy and in women of childbearing potential not using contraception.

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

Breast-feeding
It is unknown whether XPOVIO 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 XPOVIO and for 1 week after the last dose.

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

4.7 Effects on ability to drive and use machines

XPOVIO may have 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 Undesirable effects

Summary of the safety profile
The safety of XPOVIO 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 XPOVIO in combination with dexamethasone (Xd) are summarised in Table 3.

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 3 Adverse drug reactions (ADRs) observed in patients treated with XPOVIO in combination with dexamethasone (Xd)

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
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

Package leaflet: Information for the patient

XPOVIO Tablets 20mg
selinexor

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What XPOVIO is and what it is used for

XPOVIO contains the active substance selinexor. XPOVIO is a cancer medicine known as an XPO1 inhibitor. It blocks the action of a substance called XPO1 that transports proteins from the cell nucleus into the cell cytoplasm. Some cell proteins must be in the nucleus in order to function properly.

By blocking XPO1 function, XPOVIO prevents the exit of certain proteins out of the nucleus, and interfering with the continued growth of cancer cells, and leading to the death of cancer cells.

What XPOVIO is used for

XPOVIO is used to treat adult patients with multiple myeloma that has come back after treatment. XPOVIO is used
- together with dexamethasone in patients who have received at least four previous types of myeloma treatment and whose disease cannot be controlled with prior medicines used to treat multiple myeloma.

Multiple myeloma is a cancer which affects a type of blood cell called the plasma cell. A plasma cell normally produces proteins to fight infections. People with multiple myeloma have cancerous plasma cells, also called myeloma cells, which can damage bones and kidneys and increase the risk of infection. Treatment with XPOVIO kills myeloma cells and reduces symptoms of the disease.

2. What you need to know before you take XPOVIO

Do not take XPOVIO
If you are allergic to selinexor or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking XPOVIO and during treatment if you:
- have or have had bleeding problems.
- have had a recent infection or get an infection.
- have nausea, vomiting or diarrhoea.
- lose your appetite or lose weight.
- have confusion and dizziness.
- have a decrease in your blood sodium levels (hyponatraemia).
- have a new onset or worsening cataract.

Your doctor will examine you and you will be monitored closely during treatment. Before starting XPOVIO and during treatment, you will have blood tests to check that you have enough blood cells.

Children and adolescents
XPOVIO should not be given to children and adolescents under 18 years.

Other medicines and XPOVIO
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy
A pregnancy test is recommended before XPOVIO treatment for women able to have children.
Do not use XPOVIO during pregnancy as it can harm the unborn child. Women who become pregnant while taking XPOVIO must immediately stop treatment and inform the doctor.

Breast-feeding
Do not breast-feed during treatment with XPOVIO or 1 week after the last dose, as it is unknown whether XPOVIO or its metabolites are excreted in human milk and cause harm to the breast-fed children.

Fertility
XPOVIO may impair fertility in females and males.

Contraception
Women who can become pregnant must use effective contraception during treatment and for at least 1 week after the last dose.

Men are recommended to use effective contraceptive measures or avoid sexual intercourse with women able to have children during treatment and for at least 1 week after the last dose.

Driving and using machines
XPOVIO can cause fatigue, confusion and dizziness. Do not drive or use machines if you get such a reaction while being treated with this medicine.

XPOVIO contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 20 mg tablet, that is to say essentially 'sodium-free'.

3. How to take XPOVIO

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is:

- when used with dexamethasone: 80 mg (4 tablets) once daily, on days 1 and 3 of each week, or as directed by your doctor.

Your doctor may alter your dose if side effects occur.
It is important to take this medicine exactly as your doctor has told you to avoid dosing errors.

Method of use
Swallow XPOVIO tablets whole with a glassful of water, either with food or between meals. Do not chew, crush, divide or break the tablets in order to prevent risk of skin irritation from the active substance.

Duration of use
Your doctor will let you know the duration of treatment based on how you are responding to treatment and side effects.

If you take more XPOVIO than you should
Call your doctor or go to the nearest hospital emergency room right away. Take your box of XPOVIO tablets with you.

If you forget to take XPOVIO
Do not take a double dose to make up for a forgotten dose. Also, do not take an extra dose if you vomit after taking XPOVIO. Take your next dose when scheduled.

If you stop taking XPOVIO
Do not stop taking or change your dose of XPOVIO without your doctor's approval. However, if you become pregnant while taking XPOVIO, you must immediately stop treatment and inform your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse immediately if you notice any of the following side effects.

XPOVIO may cause the following **serious side effects:**

Very common (may affect more than 1 in 10 people)
- **reduced number of blood platelets**
  Your doctor will carry out blood tests before you start taking XPOVIO, and as needed during and after treatment. These tests will be more frequent during the first two months of treatment to monitor your blood platelet counts. Your doctor may stop treatment or adjust the dose based on your platelet counts. Tell your doctor immediately if you have signs of reduced number of blood platelets such as:
  - easy or excessive bruising
  - skin changes that appear as a rash of pinpoint-sized reddish-purple spots
  - prolonged bleeding from cuts
  - bleeding from your gums or nose
  - blood in your urine or stools
- **reduced number of red and white blood cells**, including neutrophils and lymphocytes.
  Your doctor will carry out blood tests to monitor your red and white blood cell counts before you start taking XPOVIO and as needed during and after treatment. These tests will be more frequent during the first two months of treatment. Your doctor may stop treatment or adjust the dose based on your blood cell counts or may treat you with other medicines to increase cell counts. Tell your doctor immediately if you have signs of reduced neutrophils such as a fever.
- **fatigue**
  Inform your doctor if you experience new or worsening fatigue. Your doctor may adjust the dose in case of persistent or worsening fatigue.
- **nausea, vomiting, diarrhoea**
  Inform your doctor immediately if you develop nausea, vomiting or diarrhoea. Your doctor may adjust the dose or stop treatment based on the severity of your symptoms. In addition, your doctor may prescribe you medicines to take before or during XPOVIO treatment to prevent and treat nausea and/or vomiting and/or diarrhoea.
- **decreased appetite and/or weight**
  Your doctor will weigh you before you start taking XPOVIO and as needed during and after treatment. This will be more frequent during the first two months of treatment. Tell your doctor if you lose your appetite and if you lose weight. Your doctor may adjust the dose in case of reduced appetite and weight and/or prescribe medicines to increase your appetite. Maintain adequate fluid and caloric intake throughout your treatment.
- **reduced sodium level**
  Your doctor will carry out blood tests to check your sodium level before you start taking XPOVIO, and as necessary during and after treatment. These tests will be more frequent during the first two months of treatment. Your doctor may adjust the dose and/or prescribe salt tablets or fluids based on your sodium level.
- **confusional state and dizziness**
  Inform your doctor if you experience confusion. Avoid situations where dizziness or confusional state may be a problem and do not take other medications that may cause dizziness or confusional state without talking to your doctor. Do not drive or operate machines if you experience any confusion or dizziness until it resolves. Your doctor may adjust the dose to reduce these symptoms.
- **cataract**
  Inform your doctor if you experience symptoms of cataract such as double vision, sensitivity to light or glare. If you notice changes with your vision, your doctor may request an eye examination by an eye specialist (an ophthalmologist) and you may need eye surgery to remove the cataract and restore your vision.

Tell your doctor or nurse immediately if you notice any of the other following side effects as listed below.

Other possible side effects are:

Very common (may affect more than 1 in 10 people):
- Pneumonia
- Upper respiratory tract infection
- Bronchitis
- Viral infection of the nose and throat (Nasopharyngitis)
- Damage to nerves in the hands and feet that can cause tingling and numbness (peripheral neuropathy)
- Bleeding from nose
- Headache
- Dehydration
- Increased blood sugar level
- Decreased potassium level
- Loss of sleep (insomnia)
- Impaired sense of taste
- Blurred vision
- Shortness of breath
- Cough
- Abdominal pain
- Constipation
- Loss of energy
- Fever

Common (may affect more than 1 in 100 people)
- Bacterial infection in the blood
- The body normally releases chemicals into the blood stream to fight an infection, when the body's response to these chemicals is out of balance, triggering changes that can damage multiple organ systems (sepsis)
- Reduced number of neutrophils with fever
- Decreased phosphate level
- Increase potassium level
- Decreased calcium level
- Decreased magnesium level
- Mental confusion (hallucination)
- Increased amylase and lipase level
- Increased uric acid level
- Confusing thinking (delirium)
- Fainting (syncope)
- Increase in heart rate (tachycardia)
- Low vision
- Loss of taste
- Taste disorder
- Balance disorder
- Cognitive disorder
- Disturbance in attention
- Memory impairment
- Low blood pressure (hypotension)
- Spinning sensation (vertigo)
- Indigestion, dry mouth, abdominal discomfort
- Flatulence or bloating
- Skin itchiness
- Muscle spasm
- Kidney problems
- General physical health deterioration, gait disturbance, malaise, chills
- Increased levels of liver enzymes (alanine aminotransferase, aspartate amino transferase, and alkaline phosphatase)
- Fall
- Memory impairment, including amnesia
- Increase in muscle enzyme called creatine
- Loss of hair
- Night sweats including excessive sweating
- Lower respiratory tract infection
- Bruise

Uncommon (may affect up to 1 in 100 people):
- rapid break down of tumour cells that could be potentially life-threatening and cause the symptoms as muscle cramping, muscle weakness, confusion, visual loss or disturbances and shortness of breath (tumour lysis syndrome)
- inflammation of brain that could cause confusion, headache, seizures (encephalopathy)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via local reporting mechanism. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store XPOVIO

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the blister pack and the outer carton after "EXP." The expiry date refers to the last day of that month.

This medicine should be stored at or below 30°C

Do not use this medicine if you notice any damage or signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What XPOVIO contains
- The active substance is selinexor. Each film-coated tablet contains 20 mg selinexor.
- The other ingredients are microcrystalline cellulose, croscarmellose sodium, povidone K30, sodium lauryl sulphate, colloidal silicon dioxide, magnesium stearate. For the tablet coating the ingredients are talc, polyvinyl alcohol) partially hydrolysed, glyceryl monostearate, polysorbate 80, titanium dioxide, macrogol, indigo carmine aluminium lake and brilliant blue FCF aluminium lake. See section 2 "XPOVIO contains sodium".

What XPOVIO looks like and contents of the pack
XPOVIO tablets are blue, round, with "K20" debossed on one side.

Each carton contains four blisters with 3, 4, 5, 6 or 8 tablets, providing a total of 12, 16, 20, 24 or 32 tablets.

This leaflet was last revised on 18 April 2023.

System organ class/ preferred term	All ADRs/frequency	Grade 3-4 ADRs/frequency
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
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 Xd, 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 Xd, 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 Xd, 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 Xd; 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 Xd, 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 Xd, 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 Xd 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 Xd, 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
Tumour lysis syndrome (TLS) occurred in one (<1%) patient (who received Xd) 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 Xd, 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 **local reporting mechanism.**

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

Clinical efficacy and safety
XPOVIO in combination with dexamethasone (Xd) for the treatment of patients with relapsed/refractory multiple myeloma

Study KPC-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 XPOVIO 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 XPOVIO treatment in these 83 patients was 9 weeks (range: 1 to 61 weeks). The median total dose of XPOVIO 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 4 provides patients disease and prior treatment characteristics.

Table 4: Demographics and disease characteristics of patients with relapsed refractory multiple myeloma treated with twice weekly 80 mg XPOVIO 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 5 provides an overview of the efficacy results.

Table 5: Efficacy results: assessed by Independent Review Committee (STORM, patients with relapsed refractory multiple myeloma treated with twice weekly 80 mg XPOVIO 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 XPOVIO peak plasma concentration, Cmax 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 XPOVIO.

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

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

Elimination
Following a single dose of 80 mg XPOVIO the mean half-life (t1/2) is 6 to 8 hours. In a population PK analysis, the apparent total clearance (CL/F) of XPOVIO 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 XPOVIO.

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 XPOVIO. Therefore, mild, moderate, or severe renal impairment is not expected to alter XPOVIO PK, and no adjustments in the dose of XPOVIO 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 XPOVIO. 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
XPOVIO was not mutagenic in a bacterial reverse mutation assay. XPOVIO 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 XPOVIO.

Toxicity to Reproduction and Development
Fertility studies in animals have not been conducted with XPOVIO. In repeat-dose oral toxicity studies, XPOVIO 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 (AUClast) 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 (AUClast) in humans at the recommended human dose of 80 mg.

Other Toxicities
A guinea pig sensitisation assay showed that XPOVIO 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 (E514)

Tablet coating
Talc (E553b)
Polyvinyl 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 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30°C

6.5 Nature and contents of container

PVC/PCTFE/PVC-aluminium blisters containing 3, 4, 5, 6 or 8 film-coated tablets.
Each carton contains a total of 12, 16, 20, 24 or 32 film-coated tablets. Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

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