Summary Report of Benefit-Risk Assessment

XPOVIO FILM COATED TABLET 20MG

NEW DRUG APPLICATION

Active Ingredient(s)	Selinexor
Product Registrant	Antengene Singapore Pte Ltd
Product Registration Number	SIN16434P
Application Route	Abridged evaluation
Date of Approval	01 March 2022

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A INTRODUCTION

Xpovio is indicated for the following indications:

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

Xpovio in combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma (RR MM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

Xpovio is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy who are not eligible for haematopoietic cell transplant.

The active substance, selinexor, is a selective inhibitor of nuclear export (SINE) that specifically blocks exportin 1 in a slowly reversible manner. The antineoplastic activity of SINE is mediated through nuclear retention of tumour suppressor proteins (TSPs) and suppression of the translation of oncoproteins. SINE induces nuclear accumulation and activation of multiple TSPs and other growth modulators, leading to G1/G2 cell cycle arrest and eventually apoptosis of malignant cells. SINE also reduces the levels of oncoproteins including c-myc, cyclin D, Bcl-X_L, Bcl2 and Bcl6.

Xpovio is available as a film-coated tablet containing 20mg of selinexor. Other ingredients in the tablet core are microcrystalline cellulose, croscarmellose sodium, povidone K30, colloidal silicon dioxide, magnesium stearate, and sodium lauryl sulfate. Ingredients in the film coating include talc, polyvinyl alcohol-part hydrolysed, glyceryl monostearate, polysorbate 80, titanium dioxide, polyethylene glycol (macrogol), FD&C Blue #2/Indigo carmine aluminium and FD&C Blue #1/Brillant blue FCF aluminium.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, selinexor, is manufactured at Novasep Classe sur Rhone site, France. The drug product Xpovio Film-coated Tablets 20mg, is manufactured at Catalent CTS LLC, Kansas, USA.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH

guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented for Novasep Classe sur Rhone site was adequate to support the approved storage condition and re-test period. The packaging is LDPE bag inside a heat-sealed foil pouch inside a heat-density polyethylene HDPE drum. The drug substance is approved for storage at 25°C / 60% RH with a re-test period of 48 months.

Drug product:

The tablet is manufactured using a dry granulation/compression approach, followed by film-coating. The process is considered a standard process.

The manufacturing site is compliant with Good Manufacturing Practice. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30 ºC. The container closure system is PVC/PCTFE/PVC with aluminium foil blister containing 16, 20, 24 or 32 tablets.

C ASSESSMENT OF CLINICAL EFFICACY

Multiple Myeloma who had received at least 1 prior anti-MM therapy

The clinical efficacy of selinexor in the treatment of MM patients who have received at least 1 prior anti-MM therapy was based on the pivotal study, BOSTON. This was a Phase 3, double-blind, randomised, multicentre trial comparing selinexor in combination with bortezomib and dexamethasone (once weekly) versus bortezomib and dexamethasone (twice weekly) in patients who had received 1-3 prior anti-MM therapies and had progressed on or after their most recent regimen.

Patients in the study were randomised in a 1:1 ratio to receive oral selinexor 100mg taken once weekly or placebo in combination with subcutaneous bortezomib 1.3 mg/m^2 and dexamethasone 20mg (Vd) twice weekly. Patients received treatment until progressive disease, unacceptable toxicity, withdrawal of consent or study termination. Dose reductions were allowed for unacceptable toxicity. The choice of Vd as the standard therapy and the dosing regimens used were acceptable and consistent with the recommended standard of care.

The primary efficacy endpoint was progression-free survival (PFS) defined as the time from the date of randomisation until the first date of Independent Review Committee (IRC)-confirmed progressive disease (PD), determined according to International Myeloma Working Group (IMWG) response criteria or death due to any cause, whichever occurred first. The key

secondary efficacy endpoint, objective response rate (ORR), was defined as patients who experienced partial response (PR), very good partial response (VGPR), complete response (CR), or stringent CR (sCR) according to the IMWG response criteria. Other secondary endpoints included overall survival (OS) and duration of response (DOR). Recruited patients underwent MM evaluations every 3 weeks from baseline MM evaluations on first day of cycle 1 (regardless of drug holidays or interruptions) through the first day of Week 37 to identify patients who progressed quickly, then every 5 weeks for the remainder of the study regardless of the cycle length.

A total of 402 patients were randomised in the study and 399 patients received at least 1 dose of study treatment, comprising 195 in the selinexor plus Vd (SVd) arm and 204 in the Vd arm. As of the data cut-off (18 Feb 2020), the median follow up was 17.3 months in SVd arm and 17.5 months in the Vd arm. There was a slightly higher rate of discontinuation in Vd arm (82.4%) compared to SVd arm (81.0%), which was largely due to progressive disease (Vd, 52.5% vs SVd, 34.4%).

The demographics and baseline disease characteristics in the intention-to-treat (ITT) population were balanced between the treatment arms except the number of patients who had 3 prior anti-MM regimen which was higher in the Vd arm (difference of 5.4%), and those who had prior stem cell transplant which was higher in the SVd arm (difference of 8.6%). The majority of the patients were 65 years of age or older (SVd, 55.9% vs Vd, 63.8%) and White (SVd, 82.6% vs Vd, 79.7%). The proportions of Asians were 12.8% in the SVd arm and 12.1% in the Vd arm. The median number of prior anti-MM drugs was 5.0 (range 1 to 9) for both arms with most receiving 1 prior anti-MM therapy (SVd, 50.8% vs Vd, 47.8%), followed by 2 anti-MM therapies (SVd, 33.3% vs Vd, 30.3%). Most patients were treated with prior proteosome inhibitor (PI) therapy (SVd, 75.9%% vs Vd, 76.8%), predominantly bortezomib (SVd, 68.7% vs Vd, 70.0%) or carfilzomib (SVd, 10.3% vs Vd, 10.1%).

In the ITT population, the primary endpoint of PFS demonstrated a statistically significant improvement in the SVd arm compared to Vd arm (HR=0.70, p=0.0075). The median duration of PFS was 13.93 months in the SVd arm compared to 9.46 months in the Vd arm. The improvement in PFS in the SVd arm was maintained during all the different sensitivity analyses.

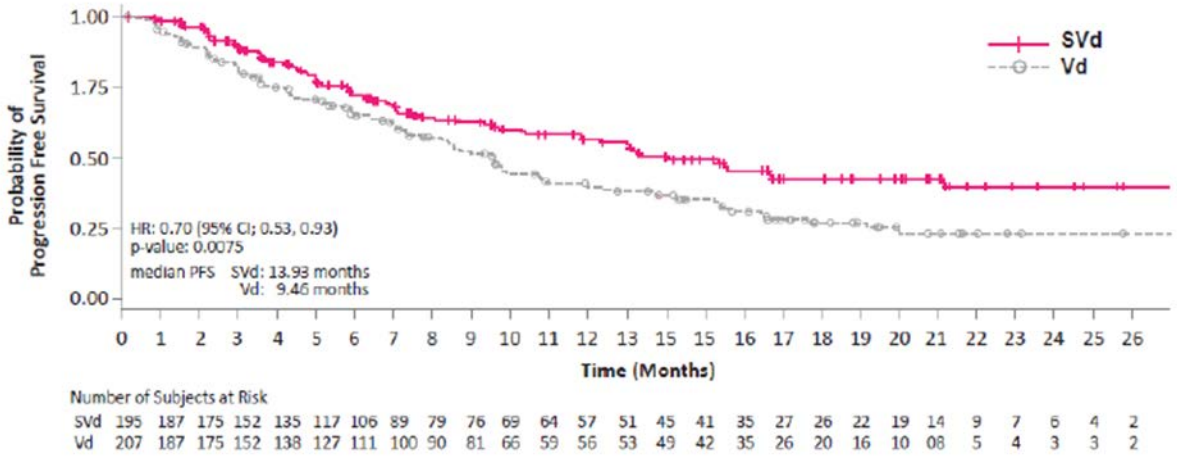
Statistically significant improvement in the key secondary endpoint ORR (odds ratio 1.96) was also observed. No statistically significant differences were demonstrated for the other secondary endpoints in terms of median OS and DOR, though OS data was immature while DOR results numerically favoured selinexor.

Summary of Key Efficacy Results (BOSTON) (ITT Population)

	SVd arm (N=195)		**Vd arm (N=207)**
Primary endpoint			
Median PFS, months (95% CI)	13.93 (11.73, NE)		9.46 (8.11, 10.78)
One sided p-value		p=0.0075; HR=0.70	
Sensitivity Analysis			
Patients with PD or death after 2 or more missed visits were censored	15.21 (11.76, NE)		9.46 (8.11, 10.78)
Stratified log-rank p-value		0.0042	
Initiation of non-study antineoplastic therapy counted as an event	13.24 (10.28, NE)		9.43 (7.62, 10.71)

Stratified log-rank p-value		0.0097	
Secondary endpoints			
ORR, n(%)	149 (76.4%)		129 (62.3%)
(95% CI)	(69.8, 82.2)		(55.3, 68.9)
One sided p-value		p=0.0012	
odds ratio		1.9626 (95% CI; 1.2641, 3.0471)	
Median OS, months	NE		24.97
(95% CI)	(NE, NE)		(23.49, NE)
One sided p-value		p=0.1852	
DOR, months	20.3		12.9
(95% CI)	(12.55, NE)		(9.26, 15.77)
One sided p-value		p=0.1364	

Figure 2: Kaplan-Meier Curve of Progression-Free Survival Based on IRC Assessments by Treatment Arm (Intent-to-Treat Population)



Overall, the efficacy of selinexor in the treatment of MM patients who have received at least 1 prior anti-MM therapy was adequately demonstrated in terms of a statistically significant improvements in PFS and ORR compared to standard of care (Vd).

Multiple Myeloma who had received at least 4 prior anti-MM therapies

The clinical efficacy of selinexor in combination with dexamethasone (Sd) for the treatment of RR MM patients who have received at least 4 prior therapies and whose disease is refractory to at least 2 PIs, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody was based on the pivotal study, STORM.

This was a Phase 2b, multicentre, single-arm, open-label, 2-part study of selinexor and dexamethasone. The efficacy was based on Part 2 of the study with patients who had MM that relapsed after prior treatments which include alkylating agent, immunomodulating agents (lenalidomide and/or pomalidomide), PIs (bortezomib and/or carfilzomib), anti-CD38 monoclonal antibody (daratumumab) and a glucocorticoid (dexamethasone). Based on the results of dose finding in Part 1 of the study, patients received selinexor dosed at 80mg in combination with low-dose dexamethasone at 20mg (Sd) twice-weekly on Days 1 and 3 of each week until progressive disease, death or unacceptable toxicity in part 2 of the study. Dose reductions were allowed for unacceptable toxicity. The primary efficacy endpoint was ORR based on IMWG response criteria and the secondary efficacy endpoints included DOR, OS and PFS.

The efficacy analysis comprised 122 patients from the modified intention to treat (mITT) population, which included all patients with penta-exposed, triple-class-refractory MM who met all eligibility criteria and had received at least 1 dose of Sd. The median age of the patients was 65.2 years (range 40 to 86 years). The majority of patients were White (69.7%) followed by Black/African American (17.2%) with a small number of Asian (1.6%). The median number of prior treatment regimens was 7.0 (range 3 to 18). All patients had prior exposure to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab, and were documented to be refractory to immunomodulatory drugs, PIs therapy and daratumumab. Of the 122 patients treated, 35 patients (28.5%) completed 1 year of survival follow-up. All the patients had discontinued treatment as of 7 Sep 2019 with disease progression (56.9%) and adverse events (31.7%) being the most common reasons for discontinuation.

In the mITT population, the treatment with Sd demonstrated an ORR of 26.2% according to IRC, which included 2 patients (1.6%) with stringent CR/CR, 6 patients (4.9%) with a VGPR, and 24 patients (19.7%) with a PR; 16 patients (13.1%) had MR, 48 patients (39.3%) had stable disease (SD), and 26 patients (21.3%) had progressive disease/ not evaluable (PD/NE). The observed ORR was consistent across the subgroups of prior anti-MM therapy history analysed, including patients who were documented refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab.

For the secondary endpoints, the median DOR per IRC was 4.4 months (range 3.7 to 10.8 months), median PFS was 3.7 months (range 2.8 to 4.7 months), and median OS was 8.4 months (range 6.2 to 11.2 months).

Summary of Key Efficacy Results (STORM) (mITT Population)

			Sd arm (N=123)	
Primary endpoint				
ORR, n(%)			32 (26.2%)	
(95% CI)			(18.7, 35.0)	
Best Response (sCR/CR)				
Complete Response (CR)			2 (1.6%)	
Very Good Partial Response (VGPR)			6 (4.9%)	
Partial Response (PR)			24 (19.7%)	
Minimal Response (MR)			16 (13.1%)	
Stable Disease (SD)			48 (39.3%)	
Progressive Disease/Not Evaluable (PD/NE)			26 (21.3%)	
Secondary endpoints				
Duration of Response (months)			4.4	
(95% CI)			(3.7, 10.8)	
PFS (months)			3.7	
(95% CI)			(2.8, 4.7)	
OS (months)			8.4	
(95% CI)			(6.2, 11.2)	
Refractory status	**BCLPD-Ref[a]**	**CLPD-Ref[b]**	**BCPD-Ref[c]**	**CPD-Ref[d]**
N	83	101	94	117
ORR, n (%)	21 (25.3%)	26 (25.7%)	25 (26.6%)	31 (26.5%)
(95% CI)	(16.4, 36.0)	(17.6, 35.4)	(18.0, 36.7)	(18.8, 35.5)
Median DOR (months)	3.8	3.8	4.4	4.4
(95% CI)	(3.7, 10.8)	(2.8, 10.8)	(3.7, 10.8)	(3.7, 10.8)

[a] patients in mITT population who are refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide and daratumumab

[b] patients in mITT population who are refractory to carfilzomib, lenalidomide, pomalidomide and daratumumab

[c] patients in mITT population who are refractory to bortezomib, carfilzomib, pomalidomide and daratumumab
[d] patients in mITT population who are refractory to carfilzomib, pomalidomide and daratumumab

Taking into consideration the limited treatment options in the later-line setting, the efficacy data based on a surrogate endpoint ORR in the single-arm non-comparative study could be considered acceptable in the intended patient population who received at least 4 prior anti-MM therapies.

Relapsed or Refractory Diffuse-Large B-cell Lymphoma

The clinical efficacy of selinexor in the treatment of relapsed or refractory DLBCL was based on one pivotal study, SADAL. This was a Phase 2b, multicentre, single-arm, open-label study that evaluated the safety and efficacy of selinexor in patients who had received 2-5 systemic regimens for the treatment of their de novo or transformed DLBCL. Eligible patients were not suitable or had progressed on autologous haematopoietic cell transplant therapy (ASCT). Patients received selinexor 60mg twice a week on day 1 and 3 until disease progression as confirmed by the central imaging laboratory or they discontinued study treatment.

The primary efficacy endpoint was the ORR defined as either a PR or CR as assessed by the IRC according to the 2014 Lugano classification. The secondary efficacy endpoints included DOR and disease control rate. OS and PFS were included as exploratory endpoints.

A total of 175 patients received selinexor 60mg and the mITT population consisted of 127 patients who received at least 1 dose of selinexor 60mg. The median age was 67.0 years (range 35 to 87 years) with majority of the patients being White (78.7%). There was a small population of Asians (7.9%) recruited. Approximately three-quarters of patients (74.0%) were diagnosed with de novo DLBCL and one-quarter (24.4%) were diagnosed with DLBCL that had transformed from indolent NHL. The median number of prior regimens was 2 (range 2.0-5.0) with more than half of patients (59.1%) who had received 2 prior regimens. There were 29.9% of patients who had prior ASCT and a large proportion (71.7%) were refractory to the most recent systemic treatment regimen.

The ORR in the mITT population based on assessments by the central imaging laboratory was 28.3%, which included CR in 15 patients (11.8%) and PR in 21 patients (16.5%). The subgroup analyses of ORR generally showed consistent ORR across the subgroups analysed, including in patients who had prior ASCT and more than 2 prior systemic regimens for DLBCL. With respect to the secondary endpoints, the DOR was 9.3 months and disease control rate was 37.0%. Exploratory endpoint of PFS was 2.6 months and OS 9.1 months.

Summary of Key Efficacy Results (SADAL) (mITT Population)

	Selinexor arm (N=127)
Primary endpoint	
Overall response rate (ORR), n(%)	36 (28.3%)
Complete Response (CR)	15 (11.8%)
Partial Response (PR)	21 (16.5%)
Stable Disease (SD)	11 (8.7%)
Progressive Disease (PD)	47 (37.0%)
Non-Evaluable (NE)	33 (26.0%)
Secondary endpoints	
Disease Control rate (DCR), n (%)	47 (37.0%)
Exact 95%	28.6, 46.0

Duration of Response (DOR), (months)			9.3	
(95% CI)			4.8, 23.0	
Progression Free Survival (PFS), (months)			2.6	
(95% CI)			1.9, 4.0	
Overall Survivial (OS), (months)			9.1	
(95% CI)			6.6, 15.1	
Subgroups	**Prior ASCT**	**>2 prior regimens**	**2 prior regimens**	**≥70 years**
N	38	52	75	57
ORR, n(%)	16 (42.1)	16 (30.8)	20 (26.7)	14 (24.6)

The ORR of 28.3% met the statistical pre-specified minimal accepted level of 15%. The overall evidence on efficacy as demonstrated by ORR and supported by secondary endpoints (DOR, PFS and OS) was deemed reasonable in a population who had received 2-5 prior treatments and who were not suitable or progressed on ASCT.

D ASSESSMENT OF CLINICAL SAFETY

Multiple Myeloma who had received at least 1 prior anti-MM therapy

The safety evaluation of selinexor given in combination with Vd was based primarily on the safety data derived from the pivotal Phase 3 study, BOSTON, comprising a total of 399 patients who received at least 1 dose of study treatment: 195 patients in the selinexor arm (SVd) and 204 patients in the Vd arm. The median duration of exposure was shorter in the SVd arm (30 weeks) compared to the Vd arm (32 weeks).

Overview of Safety profile for BOSTON (Safety Population)

Parameter	**SVd Arm**	**Vd Arm**	**Total**
n	195	204	399
Treatment emergent adverse events (TEAE)	194 (99.5)	198 (97.1)	392 (98.2)
Grade 3/4 TEAE	154 (79.0)	114 (55.9)	268 (67.2)
Grade 4 TEAE	34 (17.4)	22 (10.8)	56 (14.0)
Serious Adverse events (SAE)	101 (51.8)	77 (37.7)	178 (44.6)
TEAE Leading to Dose modification in Study Treatment	173 (88.7)	156 (76.5)	329 (82.5)
TEAE Leading to Dose reduction in Study Treatment	141 (72.3)	104 (51.0)	245 (61.4)
TEAE Leading to Dose interruption in Study Treatment	167 (85.6)	139 (68.1)	306 (76.7)
TEAE Leading to Study Treatment discontinuation	41 (21.0)	32 (15.7)	73 (18.3)
TEAE leading to death	12 (6.2)	11 (5.4)	23 (5.8)

The proportion of patients experiencing a treatment-emergent adverse event (TEAE) was comparable between the SVd arm (99.5%) and the Vd arm (97.1%). The commonly reported TEAE (frequency ≥10%) with higher incidences in the SVd arm compared to the Vd arm were thrombocytopaenia (SVd, 60.0% vs Vd, 27.0%), nausea (SVd, 50.3% vs Vd, 9.8%), fatigue (SVd, 42.1% vs Vd, 18.1%), anaemia (SVd, 36.4% vs Vd, 23.0%), decreased appetite (SVd, 35.4% vs Vd, 5.4%), weight decrease (SVd, 26.2% vs Vd, 12.3%), asthenia (SVd, 24.6% vs Vd, 13.2%), cataract (SVd, 21.5% vs Vd, 6.4%) and vomiting (SVd, 20.5% vs Vd, 4.4%). Peripheral neuropathy occurred more frequently in the Vd arm (Vd, 47.1% vs SVd, 32.3%).

The majority of these events were manageable with standard measures such as dose modifications and supportive care.

The incidences of serious AEs (SAEs) were observed to be higher in the SVd arm (51.8%) compared to the Vd arm (37.7%). The most common reported SAEs in SVd arm were pneumonia (SVd, 14.4% vs Vd, 12.7%) and sepsis (SVd, 4.1% vs Vd, 1.0%).

Patients with TEAEs leading to death were generally comparable between the 2 arms with 12 patients (6.2%) in the SVd arm and 11 patients (5.4%) in the Vd arm. TEAEs leading to death that occurred in more than 1 patient were pneumonia (SVd, 1.0% vs Vd, 1.5%) and septic shock (SVd, 1.5%). There were 2 deaths related to SVd.

Overall, the safety profile of selinexor in combination with Vd was considered acceptable in the target population of patients with MM who had received 1-3 prior anti-MM regimens. The main safety risks, including haematological AEs and gastrointestinal AEs, had been adequately described in the package insert and can be managed with monitoring, dose modifications and supportive care.

Multiple Myeloma who had received at least 4 prior anti-MM therapies

The clinical safety of selinexor given in combination with dexamethasone was based primarily on safety data derived from the pivotal Phase 2 study, STORM, comprising a total of 202 patients who received at least 1 dose of study treatment: 79 patients in Part 1 and 123 patients in Part 2 of the study. The median duration of exposure was shorter in the Part 1 (8 weeks, range 1 to 58 weeks) compared to the Part 2 (9.0 weeks, range 1 to 76 weeks).

Overview of Safety profile for STORM (Safety Population)

	Part 1	**Part 2**	**Total**
n	79	123	202
Treatment Related TEAE	78 (98.7%)	121 (98.4%)	199 (98.5%)
Grade 3 or 4 TEAE	69 (87.3%)	110 (89.4%)	179 (88.6%)
Treatment Emergent SAE (TESAE)	21 (26.6%)	38 (30.9%)	59 (29.2%)
TEAE leading to dose modification	54 (68.4%)	88 (71.5%)	142 (70.3%)
TEAE leading to dose hold	37 (46.8%)	64 (52.0%)	101 (50.0%)
TEAE leading to dose reduction	32 (40.5%)	70 (56.9%)	102 (50.5%)
TEAE leading to treatment discontinuation	13 (16.5%)	24 (19.5%)	37 (18.3%)
TEAE with an outcome of death	1 (1.3%)	3 (2.4%)	4 (2.0%)

Nearly all patients (98.5%) treated on study had a TEAE assessed as related to treatment. The most common haematological TEAEs assessed to be related to Sd were thrombocytopaenia (68.8%) and anaemia (45.5%). The most common non-haematological TEAEs among MM patients were nausea (71.8%), fatigue (59.4%), decreased appetite (53.5%) and weight decreased (46.0%).

Infectious events were the most common treatment-emergent serious adverse events (TESAEs) (occurring in >2.5% of patients), which included pneumonia (7.9%) and sepsis (6.4%). The common haematologic TESAEs included thrombocytopaenia (4.0%) and anaemia (3.0%). Fatal TEAEs considered related to treatment occurred in 4 patients (2.0%) and included 2 patients with sepsis (1.0%), and 1 patient (0.5%) each with subdural haematoma

and pneumonia. Of these, 3 fatal events were assessed by investigators as related to Sd: subdural haematoma, pneumonia, and sepsis.

Safety findings in STORM were consistent with those observed in other selinexor studies and were representative of an older, very heavily pre-treated patient population with advanced MM and multiple comorbidities. The AEs were adequately described in the proposed package insert and were considered to be manageable in the clinical setting.

Relapsed or Refractory Diffuse-Large B-cell Lymphoma

The clinical safety of selinexor as monotherapy for RR DLBCL was based primarily on safety data derived from the pivotal Phase 2b study, SADAL, comprising a total of 127 patients who received at least 1 dose of study treatment. The median duration of exposure was 9 weeks (range 1 to 193 weeks).

Overview of Safety profile for SADAL

	mITT
N	127
Treatment Related TEAE	125 (98.4%)
Grade 3 or 4 TEAE	102 (80.3%)
TESAE	61 (48.0%)
TEAE leading to dose modification	89 (70.1%)
TEAE leading to dose reduction	43 (33.9%)
TEAE leading to dose interruption	77 (60.6%)
TEAE leading to treatment discontinuation	22 (17.3%)[a]
TEAE with an outcome of death	5 (3.9%)

[a] Includes 1 patient (ID 0940-004) who had PD (malignant neoplasm progression) that was erroneously reported as a TEAE leading to discontinuation.

Almost all patients (98.4%) reported at least 1 TEAE. The most common haematological TEAEs were thrombocytopaenia (61.4%), anaemia (42.5%) and neutropaenia (29.9%). The most common non-haematological TEAEs were nausea (58.3%), fatigue (47.2%), decreased appetite (37.0%), diarrhoea (35.4%), constipation (30.7%), weight decreased (29.9%), vomiting (29.1%), pyrexia (22.0%) and asthenia (21.3%).

There were 48.0% of patients experienced at least 1 TESAE. The most common serious TEAEs were pyrexia (7.1%), pneumonia (4.7%), sepsis (includes septic shock, sepsis, and pulmonary sepsis) (4.7%), fatigue (3.9%), anaemia, cardiac failure, febrile neutropaenia (all 3.1%), asthenia, hypotension, lower respiratory tract infection, neutropaenia, and urinary tract infection (all 2.4%). Of the 25 patients who died within 30 days of the last dose, 5 patients died due to TEAEs. The TEAEs leading to a fatal outcome included acute respiratory distress syndrome, cerebrovascular accident, pulmonary sepsis, sepsis, and septic shock (1 patient each).

Similar to the studies conducted in MM patients, the safety profile of selinexor in RR DLBCL patients was mainly characterised by high incidences of non-haematological (nausea and fatigue) and haematological AEs (neutropaenia and anaemia). The AEs of special interest had been adequately described as warnings and precautions in the proposed package insert.

The adverse events observed in the RR DLBCL population was generally consistent with MM population, with a predominance of haematological TEAEs such as thrombocytopaenia,

neutropaenia and anaemia. This was considered acceptable for the intended patient population who have advanced on multiple lines of therapies.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Multiple Myeloma who had received at least 1 prior anti-MM therapy

For MM patients whose disease have progressed on at least 1 prior therapy, available treatment options include combination treatments such as bortezomib with dexamethasone. Despite the available regimens, MM remains a largely fatal disease as relapse rates are high and new therapeutic options are required to overcome resistance.

In the pivotal study BOSTON, selinexor in combination with Vd demonstrated a statistically significant improvements in the median PFS (SVd, 13.93 months vs Vd, 9.46 months) as well as the key secondary endpoint of ORR (SVd, 76.4% vs Vd, 62.3%). The OS benefit has not been demonstrated as the data was immature and required longer follow-up.

The incidence of AEs reported for selinexor in combination with Vd was higher compared to Vd, which was not unexpected for a triplet combination. Haematological AEs such as thrombocytopaenia and anaemia, non-haematological AEs such as fatigue, nausea and decreased appetite were noted to be higher in the SVd arm. Similarly, the AEs of special interest such as neutropaenia, sepsis, nausea and vomiting, decreased appetite and cataracts were higher in the SVd arm compared with Vd arm. Relevant warnings and precautions have been included in the package insert to highlight the risks and the mitigation measures for toxicities, including dose adjustment recommendations and supportive care.

Overall, the median PFS demonstrated a statistically significant improvement compared to standard of care (Vd). While the treatment was associated with notable AEs, they were manageable and the clinical benefits of selinexor were considered to outweigh the risks in the treatment of MM patients who had received at least 1 prior regimen.

Multiple Myeloma who had received at least 4 prior anti-MM therapies

There is no registered treatment available for RR MM patients whose disease have progressed on at least 4 prior anti-MM therapies. Survival outcomes are generally poor in patients who are refractory to 2 PIs, 2 immunomodulatory drugs and an anti-CD38 monoclonal antibody (median OS of 5.6 months) and there is an unmet medical need in this patient population.

The efficacy of selinexor and dexamethasone in treatment with patients who had relapsed on at least 4 anti-MM therapies was demonstrated in terms of an ORR of 26.2% in study STORM. The ORR in the subgroup analysis by prior treatment therapies was generally consistent, regardless of prior treatment therapies and prognostic risk. The median DOR, PFS and OS was 4.4 months, 3.7 months and 8.4 months respectively.

The absence of a comparator arm was a limitation of the single-arm study, which did not allow any meaningful conclusion to be drawn on the magnitude of clinical benefit in terms of time-to-event endpoints such as PFS and OS. The consistent ORR regardless of prior anti-MM treatment was preliminarily meaningful in the heavily pre-treated target population with no currently registered therapies. The median OS (8.4 months) could be considered clinically relevant in the penta-refractory patient population.

The safety profile was considered acceptable in the intended patient population who have limited treatment options. The main safety risks included nausea (71.8%), thrombocytopaenia (68.8%), fatigue (59.4%), decreased appetite (53.5%), weight decreased (46.0%) and anaemia (45.5%). These AEs have been adequately described in the package insert, including recommendations for monitoring and dose modifications.

Taking into the account the response rate in a heavily pre-treated RR MM patients whose disease have progressed on at least 4 prior anti-MM therapies, the benefits of selinexor for the treatment of these patients were considered to outweigh the risks associated with the treatment.

Relapsed or Refractory Diffuse-Large B-cell Lymphoma

Patients with RR DLBCL who have progressed after at least 2 lines of systemic therapy are recommended a variety of parental chemotherapy regimens depending on patient characteristics. These regimens are associated with poor survival outcomes (OS less than 6 months) and significant haematological AEs. There is currently no registered oral therapy for treatment of RR DLBCL.

The efficacy of selinexor in RR DLBCL patients was demonstrated in study SADAL based on ORR of 28.3%, together with a median OS of 9.1 months and DOR of 9.3 months. While the single arm design limited the interpretation of the study results, the results were considered clinically meaningful for these patients who were not suitable or have relapsed on prior transplant given the poor prognosis of these patients.

The safety profile of selinexor for RR DLBCL was similar to that reported for MM. The most notable safety concerns were haematological TEAEs (thrombocytopaenia and anaemia) and non-haematological TEAEs (nausea and fatigue). The high rate of haematological AEs reported for RR DLBCL was not unexpected in the heavily pre-treated patient population with low bone marrow reserves. Adequate information with regard to monitoring and dose modifications to mitigate the safety risks have been included in the proposed package insert.

Overall, the median DOR and OS observed with selinexor was considered clinically relevant to the patient population and the safety profile was acceptable. Taken together, the benefits of selinexor for the treatment of adult patients with RR DLBCL after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant were deemed to outweigh the risks associated with the treatment.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of selinexor was considered favourable for the following indications:

- In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy;
- In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody;

- For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant.

Approval of the product registration was granted on 1 March 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

XPOVIO (selinexor) Film Coated Tablet 20mg

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

- XPOVIO in combination with bortezomib and dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- XPOVIO in combination with dexamethasone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

1.2 Diffuse Large B-Cell Lymphoma

XPOVIO is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant [see Clinical Studies (14.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Multiple Myeloma

In Combination with Bortezomib and Dexamethasone (SVd)

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

- Bortezomib 1.3 mg/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.

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

In Combination with Dexamethasone (Sd)

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

For additional information regarding the administration of dexamethasone, refer to its prescribing information.

2.2 Recommended Dosage for Diffuse Large B-Cell Lymphoma

The recommended dosage of XPOVIO is 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.

2.3 Recommended Monitoring for Safety

Monitor complete blood count (CBC) with differential, standard blood chemistries, body weight, nutritional status, and volume status at baseline and during treatment as clinically indicated. Monitor more frequently during the first three months of treatment *[see Warning and Precautions (5.1, 5.2, 5.3, and 5.4)]*. Assess the need for dosage modifications of XPOVIO for adverse reactions *[see Dosage and Administration (2.5)]*.

2.4 Recommended Concomitant Treatments

Advise patients to maintain adequate fluid and caloric intake throughout treatment. Consider intravenous hydration for patients at risk of dehydration *[see Warnings and Precautions (5.3, 5.4)]*.

Provide prophylactic antiemetics. Administer a 5-HT3 receptor antagonist and other anti-nausea agents prior to and during treatment with XPOVIO *[see Warnings and Precautions (5.3)]*.

2.5 Dosage Modification for Adverse Reactions

Recommended XPOVIO dosage reduction steps are presented in Table 1.

Table 1: XPOVIO Dosage Reduction Steps for Adverse Reactions

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

Recommended dosage modifications for hematologic adverse reactions in patients with multiple myeloma and DLBCL are presented in Table 2 and Table 3, respectively. Recommended dosage modifications for non-hematologic adverse reactions are presented in Table 4.

Table 2: XPOVIO Dosage Modification Guidelines for Hematologic Adverse Reactions in Patients with Multiple Myeloma

Adverse Reaction	**Occurrence**	**Action**
Thrombocytopenia *[see Warning and Precautions (5.1)]*		
Platelet count 25,000 to less than 75,000/mcL	Any	• Reduce XPOVIO by 1 dose level (see Table 1).
Platelet count 25,000 to less than 75,000/mcL *with* concurrent bleeding	Any	• Interrupt XPOVIO. • Restart XPOVIO at 1 dose level lower (see Table 1) after bleeding has resolved. • Administer platelet transfusions per clinical guidelines.
Platelet count less than 25,000/mcL	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Restart XPOVIO at 1 dose level lower (see Table 1).

Adverse Reaction	Occurrence	Action
Neutropenia *[see Warning and Precautions (5.2)]*		
Absolute neutrophil count of 0.5 to 1 x 10^9/L without fever	Any	• Reduce XPOVIO by 1 dose level (see Table 1).
Absolute neutrophil count less than 0.5 x 10^9/L *OR* febrile neutropenia	Any	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1 x 10^9/L or higher. • Restart XPOVIO at 1 dose level lower (see Table 1).
Anemia		
Hemoglobin less than 8 g/dL	Any	• Reduce XPOVIO by 1 dose level (see Table 1). • Administer blood transfusions per clinical guidelines.
Life-threatening consequences	Any	• Interrupt XPOVIO. • Monitor hemoglobin until levels return to 8 g/dL or higher. • Restart XPOVIO at 1 dose level lower (see Table 1). • Administer blood transfusions per clinical guidelines.

Table 3: XPOVIO Dosage Modification Guidelines for Hematologic Adverse Reactions in Patients with Diffuse Large B-Cell Lymphoma

Adverse Reaction	Occurrence	Action
Thrombocytopenia *[see Warning and Precautions (5.1)]*		
Platelet count 50,000 to less than 75,000/mcL	Any	• Interrupt one dose of XPOVIO. • Restart XPOVIO at the same dose level.
Platelet count 25,000 to less than 50,000/mcL *without* bleeding	1st	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Reduce XPOVIO by 1 dose level (see Table 1).
Platelet count 25,000 to less than 50,000/mcL *with* concurrent bleeding	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Restart XPOVIO at 1 dose level lower (see Table 1), after bleeding has resolved. • Administer platelet transfusions per clinical guidelines.
Platelet count less than 25,000/mcL	Any	• Interrupt XPOVIO. • Monitor until platelet count returns to at least 50,000/mcL. • Restart XPOVIO at 1 dose level lower (see Table 1). • Administer platelet transfusions per clinical guidelines.
Neutropenia *[see Warning and Precautions (5.2)]*		
Absolute neutrophil count of 0.5 to less than 1 x 10^9/L without fever	1st occurrence	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1 x 10^9/L or higher. • Restart XPOVIO at the same dose level.
	Recurrence	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1 x 10^9/L or higher. • Administer growth factors per clinical guidelines. • Restart XPOVIO at 1 dose level lower (see Table 1).
Absolute neutrophil count less than 0.5 x 10^9/L *OR* Febrile neutropenia	Any	• Interrupt XPOVIO. • Monitor until neutrophil counts return to 1 x 10^9/L or higher. • Administer growth factors per clinical guidelines. • Restart XPOVIO at 1 dose level lower (see Table 1).

Adverse Reaction	Occurrence	Action
Anemia		
Hemoglobin less than 8 g/dL	Any	• Reduce XPOVIO by 1 dose level (see Table 1). • Administer blood transfusions per clinical guidelines.
Life-threatening consequences	Any	• Interrupt XPOVIO. • Monitor hemoglobin until levels return to 8 g/dL or higher. • Restart XPOVIO at 1 dose level lower (see Table 1). • Administer blood transfusions per clinical guidelines.

Table 4: XPOVIO Dosage Modification Guidelines for Non-Hematologic Adverse Reactions

Adverse Reaction	Occurrence	Action
Nausea and Vomiting *[see Warning and Precautions (5.3)]*		
Grade 1 or 2 nausea (oral intake decreased without significant weight loss, dehydration or malnutrition) *OR* Grade 1 or 2 vomiting (5 or fewer episodes per day)	Any	• Maintain XPOVIO and initiate additional anti-nausea medications.
Grade 3 nausea (inadequate oral caloric or fluid intake) *OR* Grade 3 or higher vomiting (6 or more episodes per day)	Any	• Interrupt XPOVIO. • Monitor until nausea or vomiting has resolved to Grade 2 or lower or baseline. • Initiate additional anti-nausea medications. • Restart XPOVIO at 1 dose level lower (see Table 1).
Diarrhea *[see Warning and Precautions (5.3)]*		
Grade 2 (increase of 4 to 6 stools per day over baseline)	1st	• Maintain XPOVIO and institute supportive care.
	2nd and subsequent	• Reduce XPOVIO by 1 dose level (see Table 1). • Institute supportive care.
Grade 3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated)	Any	• Interrupt XPOVIO and institute supportive care. • Monitor until diarrhea resolves to Grade 2 or lower. • Restart XPOVIO at 1 dose level lower (see Table 1).
Weight Loss and Anorexia *[see Warning and Precautions (5.3)]*		
Weight loss of 10% to less than 20% *OR* Anorexia associated with significant weight loss or malnutrition	Any	• Interrupt XPOVIO and institute supportive care. • Monitor until weight returns to more than 90% of baseline weight. • Restart XPOVIO at 1 dose level lower (see Table 1).
Hyponatremia *[see Warning and Precautions (5.4)]*		
Sodium level 130 mmol/L or less	Any	• Interrupt XPOVIO, evaluate, and provide supportive care. • Monitor until sodium levels return to greater than 130 mmol/L. • Restart XPOVIO at 1 dose level lower (see Table 1).
Fatigue		
Grade 2 lasting greater than 7 days *OR* Grade 3	Any	• Interrupt XPOVIO. • Monitor until fatigue resolves to Grade 1 or baseline. • Restart XPOVIO at 1 dose level lower (see Table 1).

Adverse Reaction	Occurrence	Action
Ocular Toxicity *[see Warning and Precautions (5.8)]*		
Grade 2, excluding cataract	Any	• Perform ophthalmologic evaluation. • Interrupt XPOVIO and provide supportive care. • Monitor until ocular symptoms resolve to Grade 1 or baseline. • Restart XPOVIO at 1 dose level lower (see Table 1).
Grade ≥3, excluding cataract	Any	• Permanently discontinue XPOVIO. • Perform ophthalmologic evaluation.
Other Non-Hematologic Adverse Reactions *[see Warning and Precautions (5.6)]*		
Grade 3 or 4	Any	• Interrupt XPOVIO. • Monitor until resolved to Grade 2 or lower; restart XPOVIO at 1 dose level lower (see Table 1).

2.6 Administration

Each XPOVIO dose should be taken at approximately the same time of day and each tablet should be swallowed whole with water. Do not break, chew, crush, or divide the tablets.

If a dose of XPOVIO is missed or delayed, instruct patients to take their next dose at the next regularly scheduled time.

If a patient vomits a dose of XPOVIO, the patient should not repeat the dose and the patient should take the next dose on the next regularly scheduled day.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 20 mg, blue, round, bi-convex, film-coated tablets with “K20” debossed on one side and nothing on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombocytopenia

XPOVIO can cause life-threatening thrombocytopenia, potentially leading to hemorrhage. Thrombocytopenia is the leading cause of dosage modifications *[see Adverse Reactions (6.1)]*.

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

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), thrombocytopenia was reported as an adverse reaction in 74% of patients and severe (Grade 3-4) thrombocytopenia was reported in 61% of patients. The median time to onset of the first event was 22 days. Bleeding occurred in 23% of patients with thrombocytopenia, clinically significant bleeding occurred in 5% of patients with thrombocytopenia, and fatal hemorrhage occurred in <1% of patients.

In patients with DLBCL who received XPOVIO 60 mg twice weekly (SADAL, n=134), thrombocytopenia developed or worsened in 86% of patients, including Grade 3-4 thrombocytopenia in 49% of patients (Grade 4, 18%). The median time to first onset was 28 days for any grade thrombocytopenia and 33 days for Grade 3 or 4 thrombocytopenia.

Monitor platelet counts at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt, reduce dose, or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)].*

5.2 Neutropenia

XPOVIO can cause life-threatening neutropenia, potentially increasing the risk of infection *[see Adverse Reactions (6.1)]*.

In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, n=195), neutropenia was reported in 48% of patients and severe neutropenia (Grade 3-4) was reported in 12% of patients. The median time to onset of the first event was 23 days for any grade neutropenia and 40 days for Grade 3-4 neutropenia. Febrile neutropenia was reported in <1% of patients.

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), neutropenia was reported as an adverse reaction in 34% of patients and severe (Grade 3-4) neutropenia was reported in 21% of patients. The median time to onset of the first event was 25 days. Febrile neutropenia was reported in 3% of patients.

In patients with DLBCL (SADAL, n=134), Grade 3 neutropenia developed in 21% of patients and Grade 4 neutropenia developed in 9% of patients. The median time to first onset of Grade 3 or 4 neutropenia was 32 days. Febrile neutropenia was reported in 3% of patients.

Obtain white blood cell counts with differential at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures, including antimicrobials and growth factors (e.g., G-CSF). Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)].*

5.3 Gastrointestinal Toxicity

XPOVIO can cause severe gastrointestinal toxicities *[see Adverse Reactions (6.1)]*. In patients with DLBCL (n=134), gastrointestinal toxicity occurred in 80% of patients with Grade 3 or 4 in 13%.

Nausea/Vomiting

In patients with multiple myeloma who received XPOVIO once weekly (BOSTON, n=195) with use of antiemetic prophylaxis (88% of patients), nausea was reported in 50% of patients and Grade 3 nausea was reported in 8% of patients. The median time to onset of the first event was 6 days. Vomiting was reported in 21% of patients and Grade 3 vomiting was reported in 4.1% of patients. The median time to onset of the first event was 8
days. Permanent discontinuation due to nausea occurred in 3.1% of patients and due to vomiting occurred in 2.1% of patients.

In patients with multiple myeloma receiving XPOVIO 80 mg twice weekly (STORM, n=202) with use of antiemetic prophylaxis, nausea was reported as an adverse reaction in 72% of patients and Grade 3 nausea

occurred in 9%. The median time to first onset of nausea was 3 days. Vomiting was reported in 41% of patients and Grade 3 vomiting occurred in 4% of patients. The median time to first onset of vomiting was 5 days.

In patients with DLBCL (SADAL, n=134) with use of antiemetic prophylaxis, nausea occurred in 57% of patients and Grade 3 nausea occurred in 6% of patients. Vomiting occurred in 28% of patients and Grade 3 vomiting occurred in 1.5% of patients. The median time to first onset was 3 days for nausea and 7 days for vomiting.

Provide prophylactic antiemetics. Administer 5-HT3 receptor antagonists and other anti-nausea agents prior to and during treatment with XPOVIO. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)]*. Administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Diarrhea

In patients with multiple myeloma who received XPOVIO once weekly (BOSTON, n=195), diarrhea was reported in 32% of patients and Grade 3 diarrhea was reported in 6% of patients. The median time to onset of the first event was 50 days. Permanent discontinuation due to diarrhea occurred in 1% of patients.

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), diarrhea was reported as an adverse reaction in 44% of patients and Grade 3 diarrhea occurred in 6% of patients. The median time to onset of diarrhea was 15 days.

In patients with DLBCL (SADAL, n=134), diarrhea occurred in 37% of patients and Grade 3 diarrhea occurred in 3% of patients treated with XPOVIO. The median time to onset of the first event was 12 days.

Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)]*. Provide standard anti-diarrheal agents, administer intravenous fluids to prevent dehydration and replace electrolytes as clinically indicated.

Anorexia/Weight Loss

In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, n=195), anorexia was reported in 35% of patients and Grade 3 anorexia was reported in 3.6% of patients. The median time to onset of the first event was 35 days. Permanent discontinuations due to anorexia occurred in 2.1% of patients.
Weight loss was reported in 26% of patients and Grade 3 weight loss was reported in 2.1% of patients. The median time to onset of the first event was 58 days. Permanent discontinuation due to weight loss occurred in 1% of patients.

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM n=202), anorexia was reported as an adverse reaction in 53% of patients and Grade 3 anorexia occurred in 5% of patients. The median time to onset of anorexia was 8 days. Weight loss was reported as an adverse reaction in 47% of patients, and Grade 3 weight loss occurred in 1% of patients treated with XPOVIO. The median time to onset of weight loss was 15 days.

In patients with DLBCL (SADAL, n=134), anorexia was reported as an adverse reaction in 37% of patients and Grade 3 anorexia occurred in 3.7% of patients treated with XPOVIO. Weight loss (Grade 1-2) was reported as an adverse reaction in 30% of patients.

Monitor weight, nutritional status, and volume status at baseline and throughout treatment. Monitor more frequently during the first three months of treatment. Interrupt, reduce dose or permanently discontinue based on severity of adverse reaction *[see Dosage and Administration (2.5)].* Provide nutritional support, fluids, and electrolyte repletion as clinically indicated.

5.4 Hyponatremia

XPOVIO can cause severe or life-threatening hyponatremia *[see Adverse Reactions (6.1)]*.

In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, n=195), hyponatremia was reported in 58% of patients and Grade 3-4 hyponatremia was reported in 14% of patients. The median time to first onset was 21 days for any grade hyponatremia and the median time to first onset for Grade 3 or 4 hyponatremia was 22 days.

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), hyponatremia was reported as an adverse reaction in 39% of patients and Grade 3 or 4 hyponatremia was reported in 22% of patients. The median time to onset of the first event was 8 days.

In patients with DLBCL (SADAL, n=134), hyponatremia developed in 62% of patients and Grade 3 hyponatremia developed in 16% of patients treated with XPOVIO. In approximately 63% of cases, hyponatremia occurred in the context of gastrointestinal toxicity such as nausea, vomiting, diarrhea, dehydration, and anorexia.

Monitor sodium level at baseline and throughout treatment. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Assess hydration status and manage hyponatremia per clinical guidelines, including intravenous saline and/or salt tablets as appropriate and dietary review. Interrupt, reduce dose or permanently discontinue based on severity of the adverse reaction *[see Dosage and Administration (2.5)].*

5.5 Serious Infection

XPOVIO can cause serious and fatal infections. Most of these infections were not associated with Grade 3 or higher neutropenia *[see Adverse Reactions (6.1)].*

In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, n=195), 69% of patients experienced any grade of infection. Grade ≥3 infections were reported in 32% of patients, and deaths from infections occurred in 3.1% of patients. The most frequently reported Grade ≥3 infection was pneumonia in 14% of patients, followed by sepsis in 4.1% and upper respiratory tract infection in 3.6% of patients.

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), 52% of patients experienced any grade of infection. Grade ≥3 infections were reported in 25% of patients, and deaths from infections occurred in 4% of patients within 30 days of last treatment. Upper respiratory tract infection of any grade occurred in 21%, pneumonia in 13%, and sepsis in 6% of patients. The most frequently reported Grade
≥3 infections were pneumonia in 9% of patients, followed by sepsis in 6%. The median time to onset was 54 days for pneumonia and 42 days for sepsis.

In patients with DLBCL (SADAL, n=134), 25% of patients experienced Grade 3 or higher infection and 21% had an infection-related serious adverse reaction; 49% developed an infection of any grade, most frequently involving the upper or lower respiratory tract. The most frequently reported Grade ≥3 infections were lower respiratory tract infections in 9% of patients (including pneumonia in 6%), followed by sepsis (6%). The median time to onset of Grade ≥3 infection was 42 days.

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

Monitor for signs and symptoms of infection, evaluate and treat promptly.

5.6 Neurological Toxicity

XPOVIO can cause life-threatening neurological toxicities *[see Adverse Reactions (6.1)]*.

In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, n=195), neurological adverse reactions (excluding peripheral neuropathy) including dizziness, syncope, depressed level of consciousness, vertigo, amnesia and mental status changes (including delirium and confusional state) occurred in 26% of patients and severe events (Grade 3-4) occurred in 3.6% of patients. The median time to the first event was 29 days. Permanent discontinuation due to neurological adverse reactions occurred in 2.1% of patients.

In patients with multiple myeloma who received XPOVIO 80 mg twice weekly (STORM, n=202), neurological adverse reactions, including dizziness, syncope, depressed level of consciousness, and mental status changes (including delirium and confusional state) occurred in 30% of patients and severe events (Grade 3-4) occurred in 9% of patients. The median time to the first event was 15 days.

In patients with DLBCL (SADAL, n=134), neurological adverse reactions occurred in 25% of patients and severe events (Grade 3-4) occurred in 6% of patients treated with XPOVIO. The most frequent manifestations were dizziness (16%) and mental status changes (11%), including confusion, cognitive disorders, somnolence, hallucination, delirium, and depressed level of consciousness. Syncope occurred in 2.2% of patients. The median time to the first event was 28 days. Among patients with such neurological adverse reactions, 68% recovered with a median time to recovery of 14 days.

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

Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, until the neurological toxicity fully resolves. Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes. Institute fall precautions as appropriate.

5.7 Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. Selinexor administration to pregnant animals during organogenesis resulted in structural abnormalities and alterations to growth at exposures below those occurring clinically at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

5.8 Cataract

New onset or exacerbation of cataract has occurred during treatment with XPOVIO *[see Adverse Reactions (6.1)]*. In patients with multiple myeloma who received XPOVIO 100 mg once weekly (BOSTON, n=195), the incidence of new onset or worsening cataracts requiring clinical intervention was reported in 22% of patients. The median time to new onset of cataract was 228 days and was 237 days for worsening of cataract in patients presenting with cataract at start of XPOVIO therapy. Treatment of cataracts usually requires surgical removal of the cataract.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described in detail in other labeling sections:

- Thrombocytopenia *[see Warnings and Precautions (5.1)]*.
- Neutropenia *[see Warnings and Precautions (5.2)]*.
- Gastrointestinal Toxicity *[see Warnings and Precautions (5.3)]*.
- Hyponatremia *[see Warnings and Precautions (5.4)]*.
- Serious Infection *[see Warnings and Precautions (5.5)]*.
- Neurological Toxicity *[see Warnings and Precautions (5.6)]*.
- Cataract *[see Warnings and Precautions (5.8)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Multiple Myeloma

XPOVIO in Combination with Bortezomib and Dexamethasone (SVd)

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

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

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

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

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

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

The most common adverse reactions (≥20% with a difference between arms of >5% compared to Vd) were

fatigue, nausea, decreased appetite, diarrhea, peripheral neuropathy, upper respiratory tract infection, weight decrease, cataract, and vomiting. Grade 3-4 laboratory abnormalities (≥10%) were thrombocytopenia, lymphopenia, hypophosphatemia, anemia, hyponatremia and neutropenia.

Table 5 summarizes the adverse reactions in BOSTON.

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

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

Key: S=selinexor, Vd=bortezomib-dexamethasone

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

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

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

Table 6 summarizes selected laboratory abnormalities in BOSTON.

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

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

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

XPOVIO in Combination with Dexamethasone (Sd)

The safety of XPOVIO in combination with dexamethasone was evaluated in STORM *[see Clinical Studies (14.1)].* Patients received XPOVIO 80 mg orally with dexamethasone 20 mg on Days 1 and 3 of every week (n=202). The median duration of XPOVIO treatment was 8 weeks (range: 1 to 60 weeks). The median dose was 115 mg (range: 36 to 200 mg) per week.

Fatal adverse reactions occurred in 9% of XPOVIO treated patients. Serious adverse reactions occurred in 58% of patients.

The treatment discontinuation rate due to adverse reactions was 27%; 53% of patients had a reduction in the XPOVIO dose, and 65% had the dose of XPOVIO interrupted. Thrombocytopenia was the leading cause of dose modification, resulting in dose reduction and/or interruption in >25% of patients. The most frequent adverse reactions requiring permanent discontinuation in 4% or greater of patients who received XPOVIO included fatigue, nausea, and thrombocytopenia.

Table 7 summarizes the adverse reactions in STORM.

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

Adverse Reaction	XPOVIO 80 mg twice weekly + Dexamethasone (n=202)	
	All Grades ≥3	Grades ≥3 (%)
Thrombocytopenia[a]	74	61
Fatigue[b]	73	22
Nausea	72	9
Anemia[c]	59	40
Decreased appetite	53	4.5
Weight decreased	47	0.5
Diarrhea	44	6
Vomiting	41	3.5
Hyponatremia	39	22
Neutropenia[d]	34	21
Leukopenia	28	11
Constipation	25	1.5
Dyspnea[e]	24	3.5[k]
Upper respiratory tract infection[f]	21	3
Cough[g]	16	0
Mental status changes[h]	16	7
Pyrexia	16	0.5
Hyperglycemia	15	7
Dizziness	15	0
Insomnia	15	2
Lymphopenia	15	10
Dehydration	14	3.5
Hypercreatininemia[i]	14	2
Pneumonia[j]	13	9[k]
Epistaxis	12	0.5
Hypokalemia	12	3.5
Dysgeusia	11	0
Vision blurred	10	0.5
Headache	10	0

a. Thrombocytopenia includes thrombocytopenia and platelet count decreased.
b. Fatigue includes fatigue and asthenia.
c. Anemia includes anemia and hematocrit decreased.
d. Neutropenia includes neutropenia and neutrophil count decreased.
e. Dyspnea includes dyspnea, dyspnea exertional, and dyspnea at rest.
f. Upper respiratory tract infection includes upper respiratory tract infection, respiratory tract infection, pharyngitis, nasopharyngitis, bronchitis, bronchiolitis, respiratory syncytial virus infection, parainfluenza virus infection, rhinitis, rhinovirus infection, and adenovirus infection.

g. Cough includes cough, productive cough, and upper-airway cough syndrome.
h. Mental status changes includes mental status changes, confusional state, and delirium.
i. Hypercreatininemia includes hypercreatininemia and hypercreatinemia.
j. Pneumonia includes pneumonia, atypical pneumonia, lung infection, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia aspiration, pneumonia influenzal, and pneumonia viral.
k. Includes fatal event.

Diffuse Large B-Cell Lymphoma

The safety of XPOVIO was evaluated in SADAL *[see Clinical Studies (14.2)].* Patients received XPOVIO 60 mg orally on Days 1 and 3 of every week (n=134). The study required an absolute neutrophil count ≥1000/µL, platelet count ≥75,000/µL, hepatic transaminases ≤2.5 times upper limit of normal (ULN) unless abnormal from lymphoma, and bilirubin ≤2 times ULN. The study permitted a maximum of 5 prior systemic regimens for
DLBCL. Antiemetic prophylaxis with a 5HT-3 receptor antagonist was required. The median duration of XPOVIO treatment was 2.1 months (range: 1 week to 3.7 years) with 38% receiving at least 3 months and 22% receiving at least 6 months of treatment. The median exposure was 100 mg per week.

Fatal adverse reactions occurred in 3.7% of patients within 30 days and 5% of patients within 60 days of last treatment; the most frequent fatal adverse reaction was infection (4.5% of patients). Serious adverse reactions occurred in 46% of patients who received XPOVIO; the most frequent serious adverse reaction was infection (21% of patients).

Discontinuation due to adverse reactions occurred in 17% of patients who received XPOVIO. Adverse reactions which results in discontinuation in ≥2% of patients included: infection, fatigue, thrombocytopenia, and nausea.

Adverse reactions led to XPOVIO dose interruption in 61% of patients and dose reduction in 49%, with 17% of all patients having 2 or more dose reductions. The median time to first dose modification (reduction or interruption) was 4 weeks, with the leading causes being thrombocytopenia (40% of all patients), neutropenia (16%), fatigue (16%), nausea (10%), and anemia (10%). The median time to first dose reduction was 6 weeks, with 83% of first dose reductions occurring within the first 3 months.

The most common adverse reactions, excluding laboratory abnormalities, in ≥20% of patients were fatigue, nausea, diarrhea, appetite decrease, weight decrease, constipation, vomiting, and pyrexia. Table 8 summarizes selected adverse reactions in SADAL.

Table 8: Adverse Reactions (≥10%), Excluding Laboratory Terms, in Patients with DLBCL Who Received XPOVIO in SADAL

	XPOVIO 60 mg twice weekly (n=134)	
Adverse Reaction	**All Grades (%)**	**Grade 3 or 4 (%)**
General Conditions		
Fatigue[a]	63	15
Pyrexia	22	4.5
Edema[b]	17	2.2
Gastrointestinal		
Nausea	57	6
Diarrhea[c]	37	3.0
Constipation	29	0
Vomiting	28	1.5
Abdominal pain[d]	10	0

Adverse Reaction	XPOVIO 60 mg twice weekly (n=134)	
	All Grades (%)	Grade 3 or 4 (%)
Metabolism and Nutrition		
Appetite decrease[e]	37	3.7
Weight decrease	30	0
Respiratory		
Cough[f]	18	0
Dyspnea[g]	10	1.5
Infections		
Upper respiratory tract infection[h]	17	1.5
Pneumonia	10	6
Urinary tract infection[i]	10	3
Nervous System		
Dizziness[j]	16	0.7
Taste disorder[k]	13	0
Mental status changes[l]	11	3.7
Peripheral neuropathy, sensory[m]	10	0
Musculoskeletal		
Musculoskeletal pain[n]	15	2.2
Vascular		
Hypotension	13	3.0
Hemorrhage[o]	10	0.7
Eye Disorders		
Vision blurred[p]	11	0.7

a. Fatigue includes fatigue and asthenia.
b. Edema includes edema, swelling, swelling face, edema peripheral, peripheral swelling, acute pulmonary edema.
c. Diarrhea includes diarrhea, post-procedural diarrhea, gastroenteritis.
d. Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, epigastric discomfort.
e. Appetite decrease includes decreased appetite and hypophagia.
f. Cough includes cough and productive cough.
g. Dyspnea includes dyspnea and dyspnea exertional.
h. Upper respiratory tract infection includes upper respiratory tract infection, sinusitis, nasopharyngitis, pharyngitis, rhinitis, viral upper respiratory infection.
i. Urinary tract infection includes urinary tract infection and specific types of urinary tract infection.
j. Dizziness includes dizziness and vertigo.
k. Taste disorder includes taste disorder, dysgeusia, ageusia.
l. Mental status changes include confusional state, amnesia, cognitive disorder, hallucination, delirium, somnolence, depressed level of consciousness, memory impairment.
m. Peripheral neuropathy includes peripheral neuropathy, peripheral sensory neuropathy, sensory disturbance, paresthesia, neuralgia.
n. Musculoskeletal pain includes musculoskeletal pain, back pain, musculoskeletal chest pain, neck pain, pain in extremity, bone pain.
o. Hemorrhage includes hemorrhage, hematoma, hematuria, epistaxis, rectal hemorrhage, injection site hematoma, subdural hematoma, upper gastrointestinal hemorrhage, corneal bleeding.
p. Vision blurred includes vision blurred, visual acuity reduced, visual impairment.

Clinically relevant adverse reactions in <10% of patients who received XPOVIO included:

- **Injury:** fall (8%)
- **Metabolic and nutrition disorders**: dehydration (7%)

- **Neurologic disorders:** headache (4.5%), syncope (2.2%)
- **Infection:** sepsis (6%), herpesvirus infection (3%)
- **Eye disorders:** cataract (3.7%)
- **Blood and lymphatic disorders**: febrile neutropenia (3%)
- **Cardiac disorders:** cardiac failure (3%)

Table 9 summarizes selected new or worsening laboratory abnormalities in SADAL. Grade 3-4 laboratory abnormalities in ≥15% included thrombocytopenia, lymphopenia, neutropenia, anemia, and hyponatremia. Grade 4 laboratory abnormalities in ≥5% were thrombocytopenia (18%), lymphopenia (5%), and neutropenia (9%).

Table 9: Select Laboratory Abnormalities (≥15%) Worsening from Baseline in Patients with DLBCL Who Received XPOVIO in SADAL

	XPOVIO 60 mg twice weekly	
Laboratory Abnormality	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematologic		
Platelet count decrease	86	49
Hemoglobin decrease	82	25
Lymphocyte count decrease	63	37
Neutrophil count decrease	58	31
Chemistry		
Sodium decrease	62	16
Glucose increase	57[a]	5
Creatinine increase	47	3.9
Phosphate decrease	34	11
Magnesium decrease	30	2.6
Calcium decrease	30	0.9
Potassium increase	26	3.9
Potassium decrease	23	7
CK increase[b]	21	1.9
Hepatic		
ALT increase	29	0.8
Albumin decrease	25	0
AST increase	24	3.1
Bilirubin increase	16	1.6

The denominator used to calculate the rate varied from 107 to 128 based on the number of patients with at least one post-treatment value.
a. Not fasting.
b. CK increase was not associated with reports of myopathy or myalgia.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies and its mechanism of action *[see Clinical Pharmacology (12.1)]*, XPOVIO can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of Selinexor to pregnant rats during organogenesis resulted in structural abnormalities and alterations to growth at exposures

that were below those occurring clinically at the recommended dose *(see Data)*. Advise pregnant women of the risks to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal data

In an embryo-fetal development study in pregnant rats, daily oral administration of selinexor at 0, 0.25, 0.75, or 2 mg/kg throughout organogenesis caused incomplete or delayed ossification, skeletal variations, and reduced fetal weight compared with controls at a dose of 0.75 mg/kg (approximately 0.08-fold of human area under the curve [AUC] at the recommended dose). Malformations were observed at 2 mg/kg, including microphthalmia, fetal edema, malpositioned kidney, and persistent truncus arteriosus.

8.2 Lactation

Risk Summary

There is no information regarding the presence of selinexor or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with XPOVIO and for 1 week after the last dose.

8.3 Females and Males of Reproductive Potential

XPOVIO can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating XPOVIO *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Males

Advise males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

Infertility

Females and Males

Based on findings in animals, XPOVIO may impair fertility in females and males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

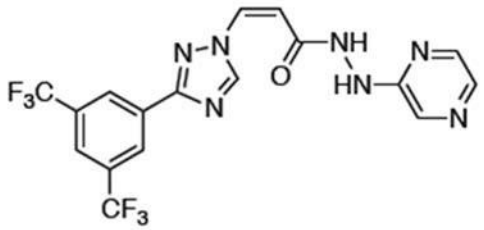
In BOSTON, of the 195 patients with multiple myeloma who received XPOVIO in combination with bortezomib and dexamethasone, 56% were 65 years of age and older, while 17% were 75 years of age and older. No overall differences in effectiveness were observed between these patients and younger patients. When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

In STORM, of the 202 patients with multiple myeloma who received XPOVIO, 49% were 65 years of age and older, while 11% were 75 years of age and older. No overall difference in effectiveness was observed in patients over 65 years of age, including patients over 75 years of age, when compared with younger patients. When comparing patients 75 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (44% vs 27%), higher incidence of serious adverse reactions (70% vs 58%), and higher incidence of fatal adverse reactions (17% vs 9%).

Among 134 patients with DLBCL who received XPOVIO in SADAL, 61% were 65 years of age and older, while 25% were 75 years of age and older. Clinical studies of XPOVIO in patients with relapsed or refractory DLBCL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

11 DESCRIPTION

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



Each XPOVIO (selinexor) tablet contains 20 mg of selinexor as the active ingredient. XPOVIO tablets are blue, round, bi-convex, film-coated tablets with “K20” debossed on one side and nothing on the other side. The inactive ingredients are colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry 200 clear, Opadry II blue, povidone K30, and sodium lauryl sulfate, OPADRY II Blue contains FD&C Blue#1/Brilliant Blue FCF Aluminum Lake,FD&C Blue#2/Indigo Carmine Aluminum Lake, PolyethyleneGlycol (Macrogol, Polyvinyl Alcohol-Part. Hydrolyzed, Talc, Titanium Dioxide. Opadry 200 clear contains Glyceryl Monostearate, Polysorbate 80, Polyvinyl Alcohol-Part. Hydrolyzed, Talc

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In nonclinical studies, selinexor reversibly inhibits nuclear export of tumor suppressor proteins (TSPs), growth regulators, and mRNAs of oncogenic proteins by blocking exportin 1 (XPO1). XPO1 inhibition by selinexor leads to accumulation of TSPs in the nucleus and reductions in several oncoproteins, such as c-myc and cyclin D1, cell cycle arrest, and apoptosis of cancer cells. Selinexor demonstrated pro-apoptotic activity in vitro in multiple myeloma cells and showed anti-tumor activity in murine xenograft models of multiple myeloma and

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

12.2 Pharmacodynamics

An increase in selinexor exposure was associated with an increase in the probability of dose modification and some adverse reactions.

Cardiac Electrophysiology

The effect of multiple doses of XPOVIO, up to 175 mg per dose (1.75 times the maximum approved recommended dose), on the QTc interval was evaluated in patients with heavily pretreated hematologic malignancies. XPOVIO had no large effect (i.e. no greater than 20 ms) on QTc interval at the therapeutic dose level.

12.3 Pharmacokinetics

Selinexor C_{max} and AUC increased proportionally over a dose range from 3 mg/m^2 to 85 mg/m^2 (0.05 to 1.44) times the maximum approved recommended dose, based on 1.7 m^2 body surface area). No clinically relevant accumulation at steady state was observed. Selinexor C_{max} and $AUC_{0\text{-}INF}$ after administration of a single dose of XPOVIO in patients with hematologic malignancies are presented in Table 10.

Table 10: Selinexor C_{max} and AUC After Administration of a Single Dose of XPOVIO

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

Absorption

The C_{max} is reached within 4 hours following oral administration of XPOVIO.

Effect of Food

Concomitant administration of a high-fat meal (800 to 1,000 calories with approximately 50% of total caloric content of the meal from fat) did not affect the pharmacokinetics of selinexor to a clinically significant extent.

Distribution

The apparent volume of distribution of selinexor is 133 L in patients with cancer. The protein binding of selinexor is 95%.

Elimination

Following a single dose of XPOVIO, the mean half-life is 6 to 8 hours. The apparent total clearance of selinexor is 18.6 L/h in patients with cancer.

Metabolism

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

Specific Populations

No clinically significant differences in the pharmacokinetics of selinexor were observed based on age (18 to 94 years old), sex, body weight (36 to 168 kg), ethnicity, mild to severe renal impairment (CL_{CR}: 15 to 89 mL/min, estimated by the Cockcroft-Gault equation), and disease type (hematological non-DLBCL, solid tumor, DLBCL). The effect of end-stage renal disease (CL_{CR} <15 mL/min) or hemodialysis on selinexor pharmacokinetics is unknown. Mild hepatic impairment had no clinically significant effect on the pharmacokinetics of selinexor. The effect of moderate and severe hepatic impairment on selinexor pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

Acetaminophen: No clinically significant differences in selinexor pharmacokinetics were observed when co-administered with acetaminophen (up to 1,000 mg daily dose of acetaminophen).

In vitro Studies

CYP Enzymes: Selinexor does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5. Selinexor is not a CYP3A4, CYP1A2, or CYP2B6 inducer.

Non-CYP Enzyme Systems: Selinexor is a substrate of UGTs and GSTs.

Transporter Systems: Selinexor inhibits OATP1B3 but does not inhibit other solute carrier (SLC) transporters. Selinexor is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2-K.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with selinexor.

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

Fertility studies in animals have not been conducted with selinexor. In repeat-dose oral toxicity studies, selinexor was administered for up to 13 weeks in rats and monkeys. Reduced sperm, spermatids, and germ cells in epididymides and testes were observed in rats at ≥1 mg/kg, decreased ovarian follicles were observed in rats at ≥2 mg/kg, and single cell necrosis of testes was observed in monkeys at ≥1.5 mg/kg. These dose levels resulted in systemic exposures approximately 0.11, 0.28, and 0.53 times, respectively, the exposure (AUC_{last}) in humans at the recommended human dose of 80 mg.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory Multiple Myeloma

XPOVIO Combination with Bortezomib and Dexamethasone (SVd)

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

Patients were randomized to receive one of the following:

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

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

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

Table 11: Baseline Demographics (BOSTON)

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

Table 12: Disease Characteristics (BOSTON)

Parameter	SVd (n=195)	Vd (n=207)
Median years from diagnosis to randomization (range)	3.81 (0.4,23.0)	3.59 (0.4, 22.0)
ECOG performance status score, n (%)		
0-1	175 (90)	191 (92)
≥2	20 (10)	16 (8)
Creatinine Clearance, n (%), mL per minute		
<30	3 (1.5)	10 (5)
30 to 59	53 (27)	60 (29)
≥60	139 (71)	137 (66)
Revised International Staging System at Baseline, n (%)		
I	56 (29)	52 (25)
II	117 (60)	125 (60)
III	12 (6)	16 (8)
Unknown	10 (5)	14 (7)
Number of Prior Therapies, n (%)		
1	99 (51)	99 (48)
2	65 (33)	64 (31)
3	31 (16)	44 (21)
Type of known prior therapy, n (%)		
Stem Cell transplantation	76 (39)	63 (30)
Lenalidomide	77 (39)	77 (37)
Pomalidomide	11 (6)	7 (3)
Bortezomib	134 (69)	145 (70)
Carfilzomib	20 (10)	21 (10)
Daratumumab	11 (6)	6 (3)
Median weeks since end of last prior therapy, (range)	48 (1, 1088)	42 (2, 405)
Known high-risk cytogenetics[a], n (%)	97 (50)	95 (46)

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

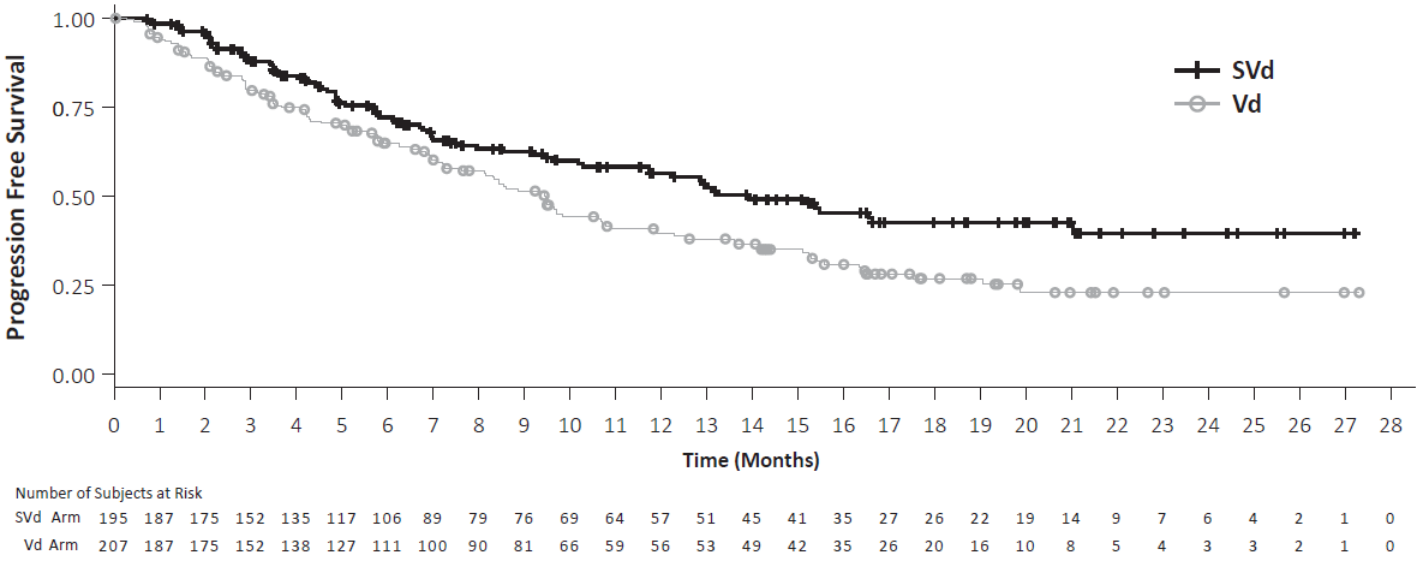
Efficacy was based on progression free survival (PFS) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma, as assessed by an Independent Review Committee (IRC). Efficacy results based on a preplanned PFS interim analysis, are shown in Table 13 and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

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

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

a. Hazard ratio is based on stratified Cox's proportional hazard regression modeling, p-value based on stratified log-rank test. Median follow up of 15.1 months at the time of the analysis.
b. The pre-planned PFS interim analysis boundary of statistical significance was defined as a p-value <0.0103.
c. Includes sCR + CR + VGPR + PR, p value based on Cochran-Mantel-Haenszel test.
d. Includes sCR + CR + VGPR, p value based on Cochran-Mantel-Haenszel test.

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



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

XPOVIO Combination with Dexamethasone (Sd)

The efficacy of XPOVIO plus dexamethasone was evaluated in STORM (KCP-330-012; NCT02336815). STORM was a multicenter, single-arm, open-label study of adults with relapsed or refractory multiple myeloma (RRMM). STORM Part 2 included 122 patients with RRMM who had previously received three or more anti-myeloma treatment regimens including an alkylating agent, glucocorticoids, bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody; and whose myeloma was documented to be refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory agent, an anti-CD38 monoclonal antibody, and to the last line of therapy.

In STORM Part 2, a total of 122 patients received XPOVIO 80 mg orally in combination with dexamethasone 20 mg orally on Days 1 and 3 of every week. Treatment continued until disease progression or unacceptable toxicity. Eighty-three patients had RRMM that was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab. Baseline patient demographics and disease characteristics of these 83 patients are summarized in Table 14 and Table 15, respectively.

Efficacy was based on overall response rate (ORR), as assessed by an Independent Review Committee (IRC) based on the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma. The approval of XPOVIO was based upon the efficacy and safety in a prespecified subgroup analysis of the 83 patients whose disease was refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and
daratumumab, as the benefit-risk ratio appeared to be greater in this more heavily pretreated population than in the overall trial population. Overall response rate results are presented in Table 16. The median time to first response was 4 weeks (range: 1 to 10 weeks). The median duration of response was 3.8 months (95% CI: 2.3, not estimable).

Table 14: Baseline Demographics (STORM)

Demographic	**STORM (n=83)**
Median age, years (range)	65 (40, 86)
Age category, n (%)	
<65 years	40 (48)
65 – 74 years	31 (37)
≥75 years	12 (15)
Sex, n (%)	
Male	51 (61)
Female	32 (39)
Race, n (%)	
White	58 (70)
Black or African American	13 (16)
Asian	2 (2)
Native Hawaiian or other Pacific Islander	1 (1)
Other	6 (7)
Missing	3 (4)

Table 15: Disease Characteristics (STORM)

Parameter	STORM (n=83)
Median years from diagnosis to start of study treatment (range)	7 (1, 23)
Prior treatment regimens, median (range)	8 (4, 18)
Documented refractory status, n (%)	
Lenalidomide	83 (100)
Pomalidomide	83 (100)
Bortezomib	83 (100)
Carfilzomib	83 (100)
Daratumumab	83 (100)
Documented refractory status to specific combinations, n (%)	
Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab	83 (100)
Daratumumab in any combination	57 (69)
Daratumumab as single agent (+/- dexamethasone)	26 (31)
Previous stem cell transplant, n (%)	67 (81)
Revised International Staging System at Baseline, n (%)	
I	10 (12)
II	56 (68)
III	17 (21)
Unknown	0
High-risk cytogenetics[a], n (%)	47 (57)

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

Table 16: Efficacy Results per IRC in Relapsed or Refractory Multiple Myeloma (STORM)

Response	STORM (n=83)
Overall Response Rate (ORR)[a], n (%)	21 (25.3)
95% CI	16.4, 36
Stringent Complete Response (sCR)	1 (1)
Complete Response (CR)	0
Very Good Partial Response (VGPR)	4 (5)
Partial Response (PR)	16 (19)

a. Includes sCR + CR + VGPR + PR.

14.2 Relapsed or Refractory Diffuse Large B-Cell Lymphoma

The efficacy of XPOVIO monotherapy was evaluated in SADAL (KCP-330-009; NCT02227251). SADAL was a multicenter, single-arm, open-label study of adults with relapsed or refractory DLBCL, not otherwise specified (NOS), after 2 to 5 systemic regimens. Eligible patients were not candidates for autologous hematopoietic stem cell transplantation (HSCT). The study required a minimum of 60 days since last systemic therapy, with a minimum of 98 days in patients with refractory disease (defined as less than partial response) to last systemic therapy.

Patients received XPOVIO 60 mg orally on Days 1 and 3 of each week. Treatment continued until disease progression or unacceptable toxicity.

Of 134 patients evaluated, the median age was 67 years (range: 35-91), 59% were male, 79% were White, and 7% were Asian. Most patients (88%) had an ECOG performance status of 0 or 1. The diagnosis was de novo DLBCL not otherwise specified (NOS) in 75% and transformed DLBCL in 23%. The median number of prior systemic therapies was 2 (range: 1-5), with 63% of patients receiving 2 prior systemic therapies, 24% receiving 3 prior therapies, and 10% receiving 4 or 5 prior therapies. Twenty-eight percent had documented refractory

disease to the most recent therapy; 30% had prior autologous HSCT. The median time from last systemic therapy to the start of XPOVIO was 5.4 months overall and 3.6 months in the patients with refractory disease.

Efficacy was based on overall response rate (ORR) and duration of response as assessed by an Independent Review Committee (IRC) using Lugano 2014 criteria (Table 17). The median time to first response was 8.1 weeks (range: 6.7-16.4 weeks).

Table 17: Efficacy Results per IRC in Relapsed or Refractory DLBCL (SADAL)

Parameter	XPOVIO 60 mg twice weekly (n=134)
ORR per Lugano criteria, n (%)	39 (29)
95% CI, %	22, 38
Complete Response	18 (13)
Partial Response	21 (16)
Duration of Response	
Patients maintaining response at 3 months, n/N (%)	22/39 (56)
Patients maintaining response at 6 months, n/N (%)	15/39 (38)
Patients maintaining response at 12 months, n/N (%)	6/39 (15)

16 HOW SUPPLIED/STORAGE AND HANDLING

XPOVIO (selinexor) are blue, round, bi-convex, and film-coated 20 mg tablets with "K20" debossed on one side and nothing on the other side. Tablets are packaged in a blister pack of polyvinyl chloride (PVC) /Polychlorotrifluoroethylene(PCTFE) / PVC with aluminum foil

Pack sizes: 32's (8 tablets x 4 blisters), 24's (6 tablets x 4 blisters, 20's (5 tablets x 4 blisters) and 16's (4 tablets x 4 blisters) .

Not all presentations may be available locally.

Store at or below 30°C (86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the patient labeling (Medication Guide).

Dosing Instructions *[see Dosage and Administration (2)]:*

- Instruct patients to take XPOVIO exactly as prescribed.
- Advise patients to swallow the tablet whole with water. The tablet should not be broken, chewed, crushed, or divided.
- If a patient misses a dose, advise them to take their next dose at its regularly scheduled time. If a patient vomits or misses a dose of XPOVIO, advise them to take the next dose on the next regularly scheduled day.
- Advise patients that XPOVIO comes in a child-resistant blister pack.
- Advise patients to take their prescribed dexamethasone (if applicable) and prophylactic anti-nausea medications as directed *[see Dosage and Administration (2.1, 2.3)]*.
- Advise patients that blood tests and body weight will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first three months of treatment *[see Dosage and Administration (2.3)]*.
- Advise patients to maintain appropriate fluid and caloric intake throughout their treatment *[see Dosage and Administration (2.4)]*.

Hematologic Adverse Reactions

Thrombocytopenia

Advise patients that they may develop low platelet counts (thrombocytopenia). Symptoms of thrombocytopenia may include bleeding and easy bruising. Advise patients that platelet counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment. Advise patients to report signs of bleeding right away *[see Warnings and Precautions (5.1)]*.

Anemia

Advise patients that they may develop anemia. Symptoms of anemia may include fatigue and shortness of breath. Advise patients to report signs or symptoms of anemia *[see Adverse Reactions (6.1)]*.

Neutropenia

Advise patients that they may develop low neutrophil counts which may increase their susceptibility to infection *[see Warnings and Precautions (5.2)].* Advise patients that neutrophil counts will be monitored at baseline, during treatment, and as clinically indicated, with more frequent monitoring during the first 3 months of treatment.

Gastrointestinal Adverse Reactions

Advise patients they may experience nausea/vomiting or diarrhea and to contact their physician if these adverse reactions occur or persist *[see Warnings and Precautions (5.3)]*.

Advise patients that they may experience weight loss or decreased appetite. Advise patients to report decreased appetite and weight loss *[see Warnings and Precautions (5.3)]*.

Hyponatremia

Advise patients that they may develop low sodium levels (hyponatremia). Most cases of hyponatremia were not associated with specific symptoms. Advise patients that levels of sodium will be monitored at baseline and during treatment as clinically indicated, with more frequent monitoring during the first two months of treatment *[see Warnings and Precautions (5.4)].*

Serious Infection

Advise patients of the possibility of serious infections. Instruct patients to immediately report infection-related signs or symptoms (e.g., chills, fever) *[see Warnings and Precautions (5.5)]*.

Neurotoxicity

Advise patients that they may experience confusion and dizziness. Advise patients to report symptoms of neurological toxicity right away. Advise patients not to drive or operate hazardous machinery until the neurological toxicity fully resolves. Advise patients to use fall prevention measures as warranted *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to contact their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the final dose *[see Use in Specific Populations (8.3)]*.

Cataract

Advise patients of the potential risk of worsening or new onset of cataract, that may require surgery. Advise

patients to readily inform their healthcare professionals of changes in vision (i.e. blurred vision) and that ophthalmologic evaluation may be performed as clinically indicated *[see Warnings and Precautions (5.8)]*.

Fatigue

Advise patients that they may experience fatigue *[see Adverse Reactions (6.1)].*

Lactation

Advise women not to breastfeed during treatment with XPOVIO and for 1 week after the final dose *[see Use in Specific Populations (8.2)]*.

Concomitant Medications

Advise patients to take 5-HT3 antagonist prophylactic treatment and other anti-nausea agents prior to and during treatment with XPOVIO *[see Dosage and Administration (2.4)]*.

Advise patients to speak with their physician about other medications they are currently taking and before starting any new medication.

Manufactured by: Catalent CTS LLC, 10245 Hickman Mills Drive, Kansas City, Missouri 64137, USA
Name and details of product owner: Karyopharm Therapeutics Inc.
85 Wells Avenue, Suite 210, Newton, Massachusetts 02459, UNITED STATES

Date of revision: Jan 2022

MEDICATION GUIDE

XPOVIO® (x-PO-Vee-O)

(selinexor)

tablets

What is the most important information I should know about XPOVIO?

XPOVIO can cause serious side effects, including:

- **Low platelet counts**. Low platelet counts are common with XPOVIO and can lead to bleeding which can be severe and can sometimes cause death. Your healthcare provider may prescribe platelet transfusions or other treatments for your low platelet counts.

  Tell your healthcare provider right away if you have any bleeding or easy bruising during treatment with XPOVIO.
- **Low white blood cell counts.** Low white blood cell counts are common with XPOVIO and can sometimes be severe. You may have an increased risk of getting bacterial infections during treatment with XPOVIO. Your healthcare provider may prescribe antibiotics if you have signs or symptoms of infection, or certain medicines to help increase your white blood cell count, if needed.

Your healthcare provider will do blood tests before you start taking XPOVIO, and often during the first 3 months of treatment, and then as needed during treatment to monitor you for side effects.

Your healthcare provider may change your dose of XPOVIO, stop your treatment for a period of time, or completely stop your treatment if you have certain side effects during treatment with XPOVIO.

See "What are the possible side effects of XPOVIO?" for more information about side effects.

What is XPOVIO?

XPOVIO is a prescription medicine used:

- in combination with the medicines VELCADE® (bortezomib) and dexamethasone to treat adults with multiple myeloma (MM) who have received at least one prior treatment for their disease.
- in combination with dexamethasone to treat adults with multiple myeloma (MM) that has come back (relapsed) or that did not respond to previous treatment (refractory), and
  - who have received at least 4 prior therapies, **and**
  - whose disease did not respond to (refractory) to at least 2 proteasome inhibitor medicines, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody medicine.

to treat adults with certain types of diffuse large B-cell lymphoma (DLBCL) that has come back (relapsed) or that did not respond to previous treatment (refractory) and who have received at at least 2 lines of systemic therapy who are not eligible for haematopoietic cell transplant.It is not known if XPOVIO is safe and effective in children less than 18 years of age.

What should I tell my healthcare provider before taking XPOVIO?

Before taking XPOVIO, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had a recent or active infection
- have or have had bleeding problems
- are pregnant or plan to become pregnant. XPOVIO can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider will check to see if you are pregnant before you start taking XPOVIO.
  - You should use effective birth control (contraception) during treatment with XPOVIO and for 1 week after your last dose.
  - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with XPOVIO.

  Males with female partners who are able to become pregnant:
  - You should use effective birth control during treatment with XPOVIO and for 1 week after your last dose.
- are breastfeeding or plan to breastfeed. It is not known if XPOVIO passes into your breast milk.
  - Do not breastfeed during treatment with XPOVIO and for 1 week after your last dose of XPOVIO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Talk with your healthcare provider before taking any new medicines.

How should I take XPOVIO?

- Take XPOVIO exactly as prescribed by your healthcare provider.
- If you have multiple myeloma, your healthcare provider will prescribe dexamethasone with your XPOVIO treatment. Take dexamethasone exactly as prescribed.
- Your healthcare provider will tell you how much XPOVIO to take and when to take it. Do not change your dose or stop taking XPOVIO without talking to your healthcare provider first.
- Swallow XPOVIO tablets whole with water. **Do not break, chew, crush, or divide the tablets.**

- Be sure to take any medicines prescribed by your healthcare provider before and during treatment with XPOVIO to help prevent nausea and vomiting. Tell your healthcare provider if the prescribed medicine does not control your nausea and vomiting.
- It is important for you to drink enough fluids to help prevent dehydration and to eat enough calories to help prevent weight loss during treatment with XPOVIO. Talk to your healthcare provider if this is a problem for you. **See "What are the possible side effects of XPOVIO?"**
- If you miss a dose of XPOVIO, take your next dose at your next regularly scheduled day and time.
- If you vomit after taking a dose of XPOVIO, do not take an extra dose. Take your next dose at your next regularly scheduled day and time.
- If you take too much XPOVIO, call your healthcare provider right away.

What should I avoid while taking XPOVIO?

XPOVIO can cause neurologic side effects.

- **See "What are the possible side effects of XPOVIO?" below.**
- If you have any neurologic side effects with XPOVIO, **do not drive or operate heavy or dangerous machinery until your neurologic side effects go away.**
- **Avoid falling.** Use care as needed to avoid falling due to neurologic side effects.

What are the possible side effects of XPOVIO?

XPOVIO can cause serious side effects, including:

- **See "What is the most important information I should know about XPOVIO?"**
- **Nausea and vomiting**. Nausea and vomiting are common with XPOVIO and can sometimes be severe. Nausea and vomiting may affect your ability to eat and drink well. You can lose too much body fluid and body salts (electrolytes) and may be at risk for becoming dehydrated. You may need to receive intravenous (IV) fluids or other treatments to help prevent dehydration. Your healthcare provider will prescribe anti-nausea medicines for you to take before you start and during treatment with XPOVIO. **See "How should I take XPOVIO?"**
- **Diarrhea.** Diarrhea is common with XPOVIO and can sometimes be severe. You can lose too much body fluid and body salts (electrolytes) and may be at risk for becoming dehydrated. You may need to receive IV fluids or other treatments to help prevent dehydration. Your healthcare provider will prescribe anti-diarrhea medicine for you as needed.
- **Loss of appetite and weight loss**. Loss of appetite and weight loss are common with XPOVIO and can sometimes be severe. Tell your healthcare provider if you have a decrease or loss of appetite and if you notice that you are losing weight at any time during treatment. Your healthcare provider may prescribe medicines that can help increase your appetite or prescribe other kinds of nutritional support. Your healthcare provider will monitor your appetite and weight before you start XPOVIO and often during the first 3 months, then as needed during treatment.
- **Decreased sodium levels in your blood**. Decreased sodium levels in your blood is common with XPOVIO but can also sometimes be severe. Low sodium levels in your blood can happen if you have nausea, vomiting, or diarrhea, you become dehydrated, or if you have loss of appetite with XPOVIO. You may not have any symptoms of a low sodium level. Your healthcare provider may talk with you about your diet and prescribe IV fluids for you based on the sodium levels in your blood. Your healthcare provider will do blood tests before you start taking XPOVIO, and often during the first 2 months of treatment, and then as needed during treatment to monitor the sodium levels in your blood.
- **Serious infections.** Infections are common with XPOVIO and can be serious and can sometimes cause death. XPOVIO can cause infections including upper or lower respiratory tract infections, such as pneumonia, and an infection throughout your body (sepsis). **Tell your healthcare provider right away if you have any signs or symptoms of an infection such as cough, chills or fever, during treatment with XPOVIO.**
- **Neurologic side effects.** XPOVIO can cause neurologic side effects that can sometimes be severe and life-threatening.
  - XPOVIO can cause dizziness, fainting, decreased alertness, and changes in your mental status including confusion and decreased awareness of things around you (delirium).
  - In some people, XPOVIO may also cause problems with thinking (cognitive problems), seeing or hearing things that are not really there (hallucinations), and may become very sleepy or drowsy.
  - Taking other medicines that can cause dizziness or mental status changes during treatment with XPOVIO may increase your risk of neurologic side effects.

  Tell your healthcare provider right away if you get any of these signs or symptoms.
- **New or worsening cataract, a cloudy or loss of transparency of the lens in the eye**. New or worsening cataract are common with XPOVIO. If a cataract forms, your vision may decrease, and you may need eye surgery to remove the cataract and restore your vision. **Tell your healthcare provider right away if you have symptoms of a cataract such as double vision, blurred vision, sensitivity to light or glare.**

Your healthcare provider may change your dose of XPOVIO, stop your treatment for a period of time, or completely stop your treatment if you have certain side effects during treatment with XPOVIO.

Common side effects of XPOVIO include:

- tiredness
- low red blood cell count (anemia). Symptoms may include tiredness and shortness of breath.
- constipation
- shortness of breath
- increased blood sugar
- changes in body salt and mineral levels in your blood
- changes in kidney and liver function blood tests

XPOVIO may cause fertility problems in males and females, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of XPOVIO.

Call your doctor for medical advice about side effects. You may report side effects to Singapore Health Sciences Authority(HSA) at hsa_productsafety@hsa.gov.sg.

How should I store XPOVIO?

- Store XPOVIO at or below 86°F (30°C).
- XPOVIO comes in blister pack.

Keep XPOVIO and all medicines out of the reach of children.

General information about the safe and effective use of XPOVIO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XPOVIO for a condition for which it was not prescribed. Do not give XPOVIO to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about XPOVIO that is written for health professionals.

What are the ingredients in XPOVIO?

Active ingredient: selinexor

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry 200 clear, Opadry II blue, povidone K30, and sodium lauryl sulfate.OPADRY II Blue contains FD&C Blue#1/Brilliant Blue FCF Aluminum Lake,FD&C Blue#2/Indigo Carmine Aluminum Lake, PolyethyleneGlycol (Macrogol, Polyvinyl Alcohol-Part. Hydrolyzed, Talc, Titanium Dioxide. Opadry 200 clear contains Glyceryl Monostearate, Polysorbate 80, Polyvinyl Alcohol-Part. Hydrolyzed, Talc