PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

^{Pr}Kyprolis™

carfilzomib for injection

60 mg per vial

Antineoplastic Agent

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PrKyprolis™

carfilzomib for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Powder for Injection / 60 mg carfilzomib per vial	Not applicable *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

KYPROLIS (carfilzomib) in combination with lenalidomide and dexamethasone is indicated for the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy.

> The clinical effectiveness of KYPROLIS when combined with lenalidomide and dexamethasone (KRd) has not been established in patients with renal impairment (creatinine clearance [CrCL] < 50 mL/min) or in patients who progressed during prior bortezomib therapy (see **WARNINGS AND PRECAUTIONS** and **CLINICAL TRIALS**).

Geriatrics (≥ 65 years of age):

No overall differences in effectiveness of KYPROLIS in combination with lenalidomide and dexamethasone were observed between younger (< 65 years of age) and older (≥ 65 years of age) patients. Overall, the patient incidence of certain adverse events (including cardiac failure) in clinical trials was higher for patients who were ≥ 65 years of age compared to patients who were < 65 years of age (see **WARNINGS AND PRECAUTIONS**).

Pediatrics (< 18 years of age):

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

CONTRAINDICATIONS

Patients who are hypersensitive to KYPROLIS or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

KYPROLIS should be administered under the supervision of a physician experienced in the use of anticancer agents.

The following are clinically significant adverse events:

- Cardiac toxicities (see Cardiovascular below)
- Pulmonary toxicities (see Respiratory below)
- Hepatic failure (see Hepatic below)
- Thrombotic Microangiopathy (see Hematologic below)
- Posterior reversible encephalopathy syndrome (PRES, see Neurologic below)
- Hemorrhage (see Hematologic below)
- Venous Thrombosis (see Cardiovascular below)

General

KYPROLIS as a monotherapy did not show a benefit over an active comparator (corticosteroids and cyclophosphamide) in a phase 3 trial in patients with relapsed and refractory multiple myeloma. There were no differences in overall survival (HR = 1.09 [0.84, 1.41]) or progression-free survival (HR = 0.98[95% CI: 0.76-1.25]) between the two arms. KYPROLIS is not indicated as a monotherapy for the treatment of relapsed and refractory multiple myeloma.

The safety and efficacy of KYPROLIS when combined with lenalidomide and dexamethasone (KRd) have not been established in patients with renal impairment (creatinine clearance [CrCL] < 50 mL/min) or in patients who progressed during prior bortezomib therapy. Patients who progressed during prior bortezomib therapy were excluded from the ASPIRE study, which is the pivotal phase 3 combination study comparing KRd to lenalidomide plus dexamethasone (Rd) alone. Limited data are available in KRd-treated patients with renal impairment at baseline (< 5% of patients were enrolled into ASPIRE with a CrCL = 30-50 mL/min and no patients had CrCL < 30 mL/min).

Infusion Reactions

Infusion reactions, including life-threatening reactions, have been reported in patients who received KYPROLIS. In a pooled KYPROLIS safety population (n = 2044), 43.2% of patients reported an adverse event potentially associated with an infusion reaction within a day of any dose of KYPROLIS and 6.7% of subjects reported an event within a day of the first dose of KYPROLIS. Following the introduction of management strategies (see below and DOSAGE AND ADMINISTRATION), most adverse events that were potentially associated with an infusion reaction in phase 3 trials were low grade and non-serious.

Symptoms have included fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS.

Ensure patients are appropriately hydrated and are administered dexamethasone prior to KYPROLIS to reduce the incidence and severity of reactions (see DOSAGE AND ADMINISTRATION).

Tumour Lysis Syndrome

Cases of tumour lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received KYPROLIS. The incidence of TLS events was 0.8% vs none in patients receiving KRd compared to Rd, respectively, in the ASPIRE study.

Patients with a high tumor burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of KYPROLIS in Cycle 1, and in subsequent cycles as needed. Uric acid lowering drugs should be considered in patients at high risk for TLS (see **DOSAGE AND ADMINISTRATION**). Monitor for evidence of TLS during treatment including regular measurement of serum electrolytes, and manage promptly. Interrupt KYPROLIS until TLS is resolved (see **DOSAGE AND ADMINISTRATION**).

Cardiovascular

Cardiac Disorders

New or worsening cardiac failure (e.g., congestive cardiac failure, pulmonary edema, decreased ejection fraction) and myocardial ischemia and infarction have occurred following administration of KYPROLIS. Death due to cardiac arrest has occurred within a day of KYPROLIS administration and fatal outcomes have been reported with cardiac failure and myocardial infarction. In the ASPIRE study, the incidence of cardiac failure events in the KRd and Rd arms were 6.4% and 4.1%, respectively, and the incidence of myocardial infarction events was 3.3% vs 1.3%, respectively.

While adequate hydration is required prior to dosing in Cycle 1, all patients should be monitored for evidence of volume overload, especially patients at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in patients with baseline cardiac failure or who are at high risk for cardiac failure (see **DOSAGE AND ADMINISTRATION**).

Withhold KYPROLIS until Grade 3 or 4 cardiac events resolve. Carefully consider the benefit and risks when deciding if treatment with KYPROLIS should be re-initiated and, if so, resume at a 1 dose level reduction (see **DOSAGE AND ADMINISTRATION**).

The risk of cardiac failure is increased in elderly patients (≥ 75 years). Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina or arrhythmias uncontrolled by medications were not eligible for enrollment in KYPROLIS clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (particularly, blood pressure optimization and fluid management) prior to starting treatment with KYPROLIS and remain under close follow up.

Electrophysiology

There have been cases of QT interval prolongation reported in patients receiving KYPROLIS in clinical studies. An effect of KYPROLIS on QT interval cannot be excluded (see **ACTION AND CLINICAL PHARMACOLOGY**).

Venous Thrombosis

Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received KYPROLIS. In the ASPIRE study, the incidence of venous thromboembolic events was 15.3% in the KRd arm versus 9.0% in the control arm (Rd). The ASPIRE study protocol required thromboprophylaxis (including aspirin) during therapy with KRd and Rd.

Thromboprophylaxis is recommended in patients being treated with KYPROLIS in combination with lenalidomide and dexamethasone, and the choice of antithrombotic agent should be based on an assessment of the patient's underlying risks and clinical status. Monitor for signs and symptoms of venous thromboembolic events and pulmonary embolism.

Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of hypertension events in the KRd arm and Rd arm were 15.8% and 8.2%, respectively, and the incidence of hypertensive crisis/emergency events was 0.5% vs 0.3%, respectively.

Hypertension should be well-controlled prior to initiation of treatment with KYPROLIS and all patients should be routinely evaluated for hypertension and treated as needed. Withhold KYPROLIS until events of hypertensive crisis and hypertensive emergency resolve or hypertension is under control. Consider a dose reduction when resuming KYPROLIS and carefully consider the benefits and risks when deciding if treatment with KYPROLIS should be re-initiated following hypertensive crisis and hypertensive emergency (see **DOSAGE AND ADMINISTRATION**).

Hematologic

Hemorrhage

Cases of hemorrhage (e.g. gastrointestinal, intracranial and pulmonary hemorrhage) have been reported in patients treated with KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of hemorrhage events in the KRd and Rd arms were 17.3% and 15.9%, respectively (the incidence of Grade ≥ 3 events was 1.3% vs 2.3%, respectively; the incidence of fatal events was 0.5% and none, respectively).

Thrombocytopenia

KYPROLIS causes thrombocytopenia with platelet nadirs observed on Day 8 or Day 15 of each 28-day cycle, which usually recovers to baseline platelet counts by the start of the next cycle (see **ADVERSE REACTIONS**). In the ASPIRE study, the incidence of thrombocytopenia events in the KRd and Rd arms were 32.4% and 25.2%, respectively (the incidence of Grade ≥ 3 events was 19.9% vs 14.4%, respectively).

Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or withhold therapy as appropriate (see **DOSAGE AND ADMINISTRATION**).

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), have been reported in patients who received KYPROLIS. Some of these events have been fatal.

Monitor for signs and symptoms of TTP/HUS. Withhold KYPROLIS if TTP/HUS is suspected and evaluate. If TTP/HUS is confirmed, discontinue KYPROLIS.

Hepatic/Biliary/Pancreatic

Hepatic Toxicity

Cases of hepatic failure, including fatal cases, have been reported in patients who received KYPROLIS. In a pooled KYPROLIS safety population (n=2044), hepatic failure events were reported in 0.2% of patients.

KYPROLIS can cause elevations of serum transaminases (ALT and AST) and bilirubin (see **ADVERSE REACTIONS**). Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold therapy as appropriate (see **DOSAGE AND ADMINISTRATION)**.

Neurologic

Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES), also termed reversible posterior leukoencephalopathy syndrome (RPLS), have been reported in patients receiving KYPROLIS. These patients presented with seizure, headache, lethargy, confusion, blindness, altered consciousness, and/or other visual and neurological disturbances, along with hypertension. Withhold KYPROLIS if PRES is suspected and evaluate by neuro-radiological imaging (eg, MRI). If PRES is confirmed, discontinue KYPROLIS.

Renal

Acute Renal Failure

Cases of acute renal failure have been reported in patients who received KYPROLIS. In clinical studies of KYPROLIS that included patients with renal impairment, this risk was increased in patients with a decrease in estimated CrCL at baseline, calculated using Cockcroft and Gault equation. Limited data are available in KRd treated patients with renal impairment (CrCL < 50 mL/min) at baseline (< 5 % of patients were enrolled into the ASPIRE study [see **CLINICAL TRIALS]**). In the ASPIRE study, the incidence of acute renal failure events in the KRd and Rd arms were 8.4% and 7.2%, respectively (the incidence of Grade ≥3 events was 3.3% vs 3.1%, respectively; the incidence of serious adverse events were 1.5% and 1.0%, respectively). The systemic concentrations of a major carfilzomib metabolite increases with the extent of renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY**).

Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce, withhold or discontinue KYPROLIS as appropriate (see **DOSAGE AND ADMINISTRATION**).

Respiratory

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease, such as pneumonitis and interstitial lung disease have been reported in patients receiving KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of ARDS events in the KRd and Rd arms were 2.0% and 2.1%, respectively, and the incidence of interstitial lung disease events was 1.8% vs 1.3%, respectively.

KYPROLIS should be withheld until these events resolve. Carefully consider the benefits and risks when deciding if treatment with KYPROLIS should be re-initiated (see **DOSAGE AND ADMINISTRATION**).

Pulmonary Hypertension

Pulmonary hypertension has been reported in patients treated with KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of pulmonary hypertension events in the KRd and Rd arms were 0.8% and 0.3%, respectively. Evaluate as appropriate. Withhold KYPROLIS until pulmonary hypertension resolves or returns to baseline. Carefully consider the benefits and risks when deciding if treatment with KYPROLIS should be re-initiated (see **DOSAGE AND ADMINISTRATION**).

Dyspnea

Dyspnea was commonly reported in patients treated with KYPROLIS. In the ASPIRE study, the incidence of dyspnea events in the KRd and Rd arm were 22.7% and 18.0%, respectively (the incidence of Grade ≥3 events was 3.1% vs 2.1%, respectively). Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Withhold KYPROLIS until Grade 3 and 4 dyspnea resolves or returns to baseline. Carefully consider the benefits and risks when deciding if treatment with KYPROLIS should be re-initiated (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**).

Special Populations

Pregnant Women

There are no data on the use of KYPROLIS in pregnant woman. Carfilzomib was clastogenic in *in vitro* tests. In animals, carfilzomib caused embryo-fetal toxicity and although it was not teratogenic during the period of organogenesis, exposure levels were lower in the animals than in patients receiving recommended clinical doses of KYPROLIS (see **TOXICOLOGY**). Based on these findings and its mechanism of action, KYPROLIS can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus.

Female patients of child bearing potential and/or their male partners should use effective contraception methods or abstain from sexual activity during therapy and for 30 days after treatment with KYPROLIS.

Male patients and/or their female partners (if of childbearing potential) should use effective contraceptive methods or abstain from sexual activity while treated with KYPROLIS and for 90 days after treatment.

KYPROLIS is associated with an increased risk of venous thrombosis (see **Venous Thrombosis** above) and it is not known if carfilzomib will reduce the efficacy of oral contraceptives as a result of drug-drug interactions (see **DRUG INTERACTIONS).** Therefore, the concomitant use of oral contraceptives or hormonal methods of contraception associated with a risk of thrombosis should be carefully considered and be based on an individual benefit-risk assessment in patients receiving KYPROLIS.

Nursing Women

It is not known whether carfilzomib is present in human breast milk. KYPROLIS should not be administered to women who are breastfeeding. Due to the potential for adverse effects in nursing infants from KYPROLIS, a decision should be made whether to discontinue nursing or to discontinue KYPROLIS, taking into account the potential benefit of KYPROLIS to the mother.

Pediatrics (< 18 years of age)

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

Geriatrics (≥ 65 years of age)

A total of 392 patients were treated with KYPROLIS in combination with lenalidomide and dexamethasone (KRd); the median age was 64 years. Of these, 185 patients (47%) were ≥ 65 years of age and 43 patients (11%) were ≥ 75 years of age. The incidence of serious adverse events was 50% in patients < 65 years of age, 70% in patients 65 to 74 years of age, and 74% in patients ≥ 75 years of age (see **Cardiovascular** above).

Hepatic Impairment

The safety, efficacy and pharmacokinetics of KYPROLIS in patients with hepatic impairment (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN) have not been systematically evaluated (see **Hepatic/Biliary/Pancreatic** above and **ACTION AND CLINICAL PHARMACOLOGY**).

Renal Impairment

There are limited safety data for KYPROLIS in combination with lenalidomide and dexamethasone in patients with CrCL <50 mL/min. However, patients with renal impairment were enrolled in a Phase 3 clinical study of advanced relapsed refractory multiple myeloma, which demonstrated an increased incidence of acute renal failure adverse events with the extent of renal impairment at baseline in patients treated with KYPROLIS. Carefully monitor renal function in patients and make appropriate dosing modifications (see **DOSAGE and ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**).

Since dialysis clearance of carfilzomib concentrations has not been studied, the drug should be administered after the dialysis procedure. Refer also to the REVLIMID Product Monograph for appropriate dosing modifications of lenalidomide in patients with impaired renal function.

Cardiac Impairment

Patients with New York Heart Association Class III and IV heart failure were not eligible for the clinical trials. Safety and efficacy in this population have not been established.

Monitoring and Laboratory Tests

Blood pressure, complete blood cell count (CBC) including white blood cell count with differential, hemoglobin, platelets, blood chemistries including AST, ALT, total bilirubin, creatinine [or creatinine clearance (CrCL)], and electrolytes (including potassium) should be monitored at baseline and throughout treatment with KYPROLIS.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Safety data for KYPROLIS are available from clinical trials of a pooled patient population (n = 2044). The most common adverse reactions (> 20%) from this pooled safety set were: anemia, thrombocytopenia, diarrhea, nausea, fatigue, pyrexia, peripheral edema, respiratory tract infection, dyspnea, and cough. The most common serious adverse reactions (≥ 2%) from this pooled safety set that occurred during KYPROLIS treatment include: pneumonia (9.6%), pyrexia (3.0%), acute renal failure (3.8%), cardiac failure (2.6%), dyspnea (2.3%), and respiratory tract infection (2.1%). The most common adverse events leading to discontinuation of any study drug in either study arm included thrombocytopenia, disease progression, pneumonia, and acute renal failure, however the patient incidences were < 2% for each of these events.

In the ASPIRE study (Study PX-171-009), which included 392 patients in the KRd arm, the most common adverse reactions (> 20% in the KRd arm) include anemia, diarrhea, neutropenia, fatigue, thrombocytopenia, cough, pyrexia, upper respiratory tract infection, hypokalemia, muscle spasms, peripheral edema, nasopharyngitis and constipation (Table 1). The most common serious adverse reactions reported in the KRd arm as compared with the Rd arm were pneumonia (5.6 vs. 4.4%), pulmonary embolism (2.6% vs. 1.8%), deep vein thrombosis (2.3% vs 1.5%), and febrile neutropenia (2.0% vs. 0.8%). The most common adverse events leading to discontinuation of KYPROLIS included pneumonia (1%), myocardial infarction (0.8%) and upper respiratory tract infection (0.8%).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The safety of KYPROLIS has been evaluated in the ASPIRE study (Study PX-171-009); an open-label randomized Phase 3 pivotal study of patients with relapsed multiple myeloma receiving KYPROLIS in combination with lenalidomide and dexamethasone (N = 392) vs. lenalidomide and dexamethasone (N = 389) (see **CLINICAL TRIALS**). The median overall duration of treatment with any study drug in the KRd and Rd arms were 87.1 and 56.1 weeks, respectively; each treatment cycle was 4 weeks (28 days). In the KRd arm, the median number of cycles of KYPROLIS initiated were 18.0 (the maximum number of cycles allowed per protocol in that study after which patients in that arm continued on treatment with Rd). Adverse reactions that occurred in ≥ 5% of patients can be found in Table 1.

Table 1. Adverse Reactions that Occurred in ≥ 5% of Patients in the ASPIRE Study (Safety Population)

System Organ Class / Preferred Term	KRd (N=392)		Rd (N=389)	
	All Grades	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Anaemia	169 (43.1%)	70 (17.9%)	155 (39.8%)	69 (17.7%)
Neutropenia	148 (37.8%)	116 (29.6%)	131 (33.7%)	103 (26.5%)
Thrombocytopenia	115 (29.3%)	66 (16.8%)	89 (22.9%)	48 (12.3%)
Leukopenia	31 (7.9%)	12 (3.1%)	22 (5.7%)	16 (4.1%)
EYE DISORDERS				
Cataract	34 (8.7%)	15 (3.8%)	27 (6.9%)	11 (2.8%)
Vision Blurred	22 (5.6%)	0	15 (3.9%)	1 (0.3%)
GASTROINTESTINAL DISORDERS				
Diarrhoea	166 (42.3%)	15 (3.8%)	131 (33.7%)	16 (4.1%)
Constipation	79 (20.2%)	1 (0.3%)	67 (17.2%)	2 (0.5%)
Nausea	78 (19.9%)	2 (0.5%)	55 (14.1%)	4 (1.0%)
Vomiting	47 (12.0%)	0	32 (8.2%)	2 (0.5%)
Abdominal Pain	34 (8.7%)	7 (1.8%)	27 (6.9%)	4 (1.0%)
Abdominal Pain Upper	25 (6.4%)	0	11 (2.8%)	1 (0.3%)
Dyspepsia	23 (5.9%)	0	20 (5.1%)	1 (0.3%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Infusion reactions	166 (42.3%)	14 (3.6%)	-*	-*
Fatigue	129 (32.9%)	30 (7.7%)	120 (30.8%)	25 (6.4%)
Pyrexia	112 (28.6%)	7 (1.8%)	81 (20.8%)	2 (0.5%)
Oedema Peripheral	85 (21.7%)	5 (1.3%)	75 (19.3%)	2 (0.5%)
Asthenia	73 (18.6%)	14 (3.6%)	56 (14.4%)	8 (2.1%)
Chills	25 (6.4%)	0	9 (2.3%)	0
INFECTIONS AND INFESTATIONS				
Upper Respiratory Tract Infection	112 (28.6%)	7 (1.8%)	76 (19.5%)	4 (1.0%)
Nasopharyngitis	84 (21.4%)	1 (0.3%)	63 (16.2%)	0
Bronchitis	74 (18.9%)	7 (1.8%)	54 (13.9%)	7 (1.8%)
Pneumonia	68 (17.3%)	49 (12.5%)	56 (14.4%)	41 (10.5%)
Respiratory Tract Infection	43 (11.0%)	16 (4.1%)	39 (10.0%)	8 (2.1%)
Urinary Tract Infection	34 (8.7%)	4 (1.0%)	21 (5.4%)	1 (0.3%)
Influenza	26 (6.6%)	2 (0.5%)	12 (3.1%)	2 (0.5%)
Viral Infection	24 (6.1%)	0	10 (2.6%)	0

Table 1. Adverse Reactions that Occurred in ≥ 5% of Patients in the ASPIRE Study (Safety Population)

System Organ Class / Preferred Term	KRd (N=392)		Rd (N=389)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
INVESTIGATIONS				
Blood Creatinine Increased	26 (6.6%)	4 (1.0%)	18 (4.6%)	1 (0.3%)
Alanine Aminotransferase Increased	20 (5.1%)	9 (2.3%)	15 (3.9%)	3 (0.8%)
METABOLISM AND NUTRITION DISORDERS				
Hypokalaemia	108 (27.6%)	37 (9.4%)	52 (13.4%)	19 (4.9%)
Hypocalcaemia	63 (16.1%)	13 (3.3%)	46 (11.8%)	7 (1.8%)
Hypophosphataemia	52 (13.3%)	33 (8.4%)	29 (7.5%)	18 (4.6%)
Hyperglycaemia	49 (12.5%)	20 (5.1%)	38 (9.8%)	18 (4.6%)
Decreased Appetite	44 (11.2%)	0	35 (9.0%)	2 (0.5%)
Hypomagnesaemia	36 (9.2%)	4 (1.0%)	25 (6.4%)	0
Hyperuricaemia	20 (5.1%)	2 (0.5%)	10 (2.6%)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Muscle Spasms	104 (26.5%)	4 (1.0%)	82 (21.1%)	3 (0.8%)
Back Pain	69 (17.6%)	5 (1.3%)	80 (20.6%)	8 (2.1%)
Arthralgia	49 (12.5%)	2 (0.5%)	51 (13.1%)	2 (0.5%)
Pain In Extremity	46 (11.7%)	4 (1.0%)	41 (10.5%)	6 (1.5%)
Muscular Weakness	27 (6.9%)	5 (1.3%)	22 (5.7%)	6 (1.5%)
Musculoskeletal Pain	25 (6.4%)	5 (1.3%)	35 (9.0%)	3 (0.8%)
Musculoskeletal Chest Pain	23 (5.9%)	1 (0.3%)	28 (7.2%)	2 (0.5%)
Myalgia	22 (5.6%)	0	22 (5.7%)	0
NERVOUS SYSTEM DISORDERS				
Headache	53 (13.5%)	3 (0.8%)	31 (8.0%)	2 (0.5%)
Dizziness	48 (12.2%)	2 (0.5%)	44 (11.3%)	2 (0.5%)
Neuropathy Peripheral	29 (7.4%)	6 (1.5%)	27 (6.9%)	6 (1.5%)
Paraesthesia	25 (6.4%)	1 (0.3%)	23 (5.9%)	1 (0.3%)
PSYCHIATRIC DISORDERS				
Insomnia	77 (19.6%)	11 (2.8%)	64 (16.5%)	11 (2.8%)
Anxiety	31 (7.9%)	1 (0.3%)	16 (4.1%)	2 (0.5%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Cough	113 (28.8%)	1 (0.3%)	69 (17.7%)	0

Table 1. Adverse Reactions that Occurred in ≥ 5% of Patients in the ASPIRE Study (Safety Population)

System Organ Class / Preferred Term	KRd (N=392)		Rd (N=389)	
	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Dyspnoea	77 (19.6%)	11 (2.8%)	58 (14.9%)	7 (1.8%)
Oropharyngeal Pain	28 (7.1%)	0	21 (5.4%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	52 (13.3%)	5 (1.3%)	60 (15.4%)	6 (1.5%)
Erythema	30 (7.7%)	0	12 (3.1%)	0
Pruritus	30 (7.7%)	0	16 (4.1%)	1 (0.3%)
Hyperhidrosis	26 (6.6%)	0	18 (4.6%)	1 (0.3%)
VASCULAR DISORDERS				
Hypertension	57 (14.5%)	18 (4.6%)	29 (7.5%)	8 (2.1%)
Deep Vein Thrombosis	26 (6.6%)	7 (1.8%)	15 (3.9%)	4 (1.0%)
Hypotension	25 (6.4%)	8 (2.0%)	23 (5.9%)	4 (1.0%)

* There are no events in the Rd column, because the treatment regimen in the Rd arm was not delivered via infusion.

Less Common Clinical Trial Adverse Drug Reactions (<5%):

Blood and Lymphatic system disorders: febrile neutropenia (3.3%), lymphopenia (3.1%)

Cardiac disorders: cardiac failure (2.8%), cardiac failure congestive (2%), myocardial infarction (1.8%), cardiac arrest (0.5%), myocardial ischemia (0.3%)

Gastrointestinal disorders: toothache (4.6%), gastrointestinal hemorrhage (0.3%)

General disorders and Administration Site conditions: pain (4.1%), multi-organ failure (0.5%), infusion site reaction (0.3%)

Infections and Infestations: sepsis (1.3%)

Investigations: C - reactive protein increased (4.1%), creatinine renal clearance decreased (2.8%), aspartate aminotransferase increased (2.0%), blood uric acid increased (1.3%)

Metabolism and Nutrition Disorders: hyponatremia (3.8%), hypoalbuminemia (2.6%), hyperkalemia (2.0%), dehydration (1.5%), hypercalcemia (1.3%), tumour lysis syndrome (0.8%)

Nervous system disorders: hypoaesthesia (4.6%), intracranial hemorrhage (0.5%)

Renal and Urinary disorders: acute renal failure (3.8%), renal failure (2.6%), renal impairment (2.6%)

Respiratory, Thoracic and Mediastinal disorders: dysphonia (4.8%), epistaxis (4.8%), pulmonary embolism (3.6%), pulmonary edema (1.0%), pulmonary hemorrhage (0.3%)

Vascular disorders: hemorrhage (0.3%)

Abnormal Hematologic and Clinical Chemistry Findings

Tables 2 and 3 describes Grade 3-4 Hematologic and Laboratory abnormalities reported in the ASPIRE study.

Table 2. Abnormal Hematologic Findings in the ASPIRE Study

	Grade 3 or 4 laboratory values	
	KRd (N=392) n (%)	**Rd (N=389) n (%)**
Absolute neutrophil count (ANC) decreased	177 (45.2%)	167 (42.9%)
Hemoglobin decreased	79 (20.2%)	92 (23.7%)
Lymphocyte count decreased	202 (51.5%)	143 (36.8%)
Platelet count decreased	115 (29.3%)	75 (19.3%)
Total white blood cell (WBC) count decreased	122 (31.1%)	91 (23.4%)

Table 3. Abnormal Clinical Chemistry Findings in the ASPIRE Study

	Grade 3 or 4 laboratory values	
	KRd (N=392) n (%)	**Rd (N=389) n (%)**
ALT increased	22 (5.6%)	11 (2.8%)
ASP increased	16 (4.1%)	1 (0.3%)
Hypocalcemia	35 (8.9%)	24 (6.2%)
Hypercalcemia	8 (2.0%)	8 (2.1%)
Hypomagnesemia	10 (2.6%)	13 (3.3%)
Hypophosphatemia	145 (37.0%)	125 (32.1%)
Hypokalemia	65 (16.6%)	37 (9.5%)
Hyperkalemia	16 (4.1%)	17 (4.4%)
Serum creatinine increased	19 (4.8%)	16 (4.1%)
Hyponatremia	41 (10.5%)	32 (8.2%)
Total bilirubin increased	21 (5.4%)	7 (1.8%)

Post-Market Adverse Drug Reactions

The following additional adverse reactions were reported in the post-marketing experience. This includes spontaneous case reports as well as adverse reactions from other clinical studies.

Blood and Lymphatic System Disorders: thrombotic microangiopathy, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)

Cardiac disorders: tachycardia, atrial fibrillation, pericarditis, pericardial effusion

Gastrointestinal Disorders: gastrointestinal perforation

Hepatobiliary disorders: hepatic failure, cholestasis, hyperbilirubinemia

Immune system disorders: drug hypersensitivity

Investigations: gamma-glutamyltransferase increased, ejection fraction decreased

Musculoskeletal and connective tissue disorders: bone pain

Nervous system disorders: cerebrovascular accident, posterior reversible encephalopathy syndrome (PRES)

Respiratory, Thoracic, and Mediastinal Disorders: pulmonary hypertension, pneumonitis, interstitial lung disease, acute respiratory distress syndrome, acute respiratory failure, wheezing

Vascular Disorders: hypertensive crisis, hypertensive emergency, flushing

DRUG INTERACTIONS

Overview

Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers (see **ACTION AND CLINICAL PHARMACOLOGY)**.

Drug-Drug Interactions

Based on *in vitro* studies, carfilzomib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6, therefore, it is not expected to influence exposure of other drugs that are substrates of these enzymes as a result of inhibition.

In vitro studies indicated that carfilzomib does not induce CYP3A4/5 at the highest concentration tested (2.5 µM) in cultured human hepatocytes. In an *in vitro* study using human liver microsomes, carfilzomib showed modest direct (Ki = 1.7 micromolar) and time-dependent inhibition (Ki = 11 micromolar) of human cytochrome CYP3A4/5.

An open-label, Phase 1, non-randomized, fixed-sequence, drug-drug interaction study enrolled 18 evaluable patients with solid tumours in order to assess the effects of KYPROLIS on the pharmacokinetics of the CYP3A substrate midazolam. Repeated administration of KYPROLIS (27 mg/m^2) did not result in a significant interaction on the pharmacokinetics of midazolam indicating that carfilzomib is not expected to inhibit the metabolism of CYP3A4/5 substrates and is not a CYP3A4 inducer in patients.

It is unknown whether carfilzomib is an inducer of CYP1A2, 2C8, 2C9, 2C19 and 2B6 at therapeutic concentrations. Caution should be observed when carfilzomib is combined with medicinal products that are substrates of these enzymes, including oral contraceptives.

In vitro, carfilzomib inhibited the efflux transport of P-gp substrate digoxin by 25% in a Caco-2 monolayer system when tested at 3 µM. Carfilzomib is a P-glycoprotein (P-gp) substrate. However, given that carfilzomib is administrated intravenously and is extensively metabolized, the pharmacokinetic profile of carfilzomib is unlikely to be affected by P-gp inhibitors or inducers.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

Patients treated with KYPROLIS may experience fatigue, dizziness and a drop in blood pressure that could affect their ability to drive or operate machines.

DOSAGE AND ADMINISTRATION

Administration Precautions

KYPROLIS vials contain no antimicrobial preservatives and are intended for single use only. Proper aseptic technique must be observed.

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

Dosing Considerations

Concomitant Medications

Consider antiviral prophylaxis in patients being treated with KYPROLIS to decrease the risk of herpes zoster reactivation.

Thromboprophylaxis is recommended in patients being treated with KYPROLIS in combination with lenalidomide and dexamethasone, and the choice of antithrombotic agent should be based on an assessment of the patient's underlying risks and clinical status. Refer to REVLIMID and dexamethasone Product Monographs for other concomitant medications that may be required with those agents.

Sodium content

Following reconstitution, each mL of this medicinal product contains 0.3 mmols (7 mg) of sodium. This should be taken into consideration for patients on a controlled sodium diet.

Hydration and Fluid Monitoring

Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity. All patients should be monitored for evidence of volume overload and fluid requirements should be tailored to individual patient needs. The total volume of fluids may be adjusted as clinically indicated in patients with baseline cardiac failure or who are at high risk for cardiac failure (see **WARNINGS AND PRECAUTIONS**).

Recommended hydration includes both oral fluids (30 mL/kg/day for 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). Give an additional 250 mL to 500 mL of intravenous fluids as needed following KYPROLIS administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles.

Recommended Dose and Dosage Adjustment

KYPROLIS is administered by intravenous (IV) infusion over 10 minutes, on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28) for the first 12 treatment cycles. Each 28-day period is considered one treatment cycle. For cycles 13 onwards, KYPROLIS is administered on Days 1, 2, 15 and 16 followed by the 12-day rest period (*i.e.* the Days 8 and 9 KYPROLIS doses are omitted).

KYPROLIS is administered at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, the dose should be escalated to a target dose of 27 mg/m^2 on Day 8 of Cycle 1. Treatment may be continued until disease progression or until unacceptable toxicity occurs.

The dose is calculated using the patient's baseline body surface area (BSA). Patients with a body surface area greater than 2.2 m^2 should receive a dose based upon a body surface area of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.

In combination with KYPROLIS, lenalidomide is administered as 25 mg orally on Days 1–21 and dexamethasone is administered as 40 mg orally/intravenously on Days 1, 8, 15, and 22 of the 28 day cycles.

Consult the REVLIMID and dexamethasone Product Monographs prior to using KYPROLIS in combination with these agents. Appropriate dose reduction for the starting dose of lenalidomide should be considered according to the recommendations in the REVLIMID Product Monograph, for example, with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before KYPROLIS. The dosage regimen is outlined in Table 4.

Table 4. KYPROLIS in Combination with Lenalidomide and Dexamethasone

	Cycle 1										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
KYPROLIS (mg/m^2):	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone	40 mg	-	-	40 mg	-	-	40 mg	-	-	40 mg	-
Lenalidomide	25 mg daily									-	-
	Cycles 2-12										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
KYPROLIS (mg/m^2):	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone	40 mg	-	-	40 mg	-	-	40 mg	-	-	40 mg	-
Lenalidomide	25 mg daily									-	-
	Cycles 13 on										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
KYPROLIS (mg/m^2):	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone	40 mg	-	-	40 mg	-	-	40 mg	-	-	40 mg	-
Lenalidomide	25 mg daily									-	-

Recommended Dose Modifications:

Modify dosing based on toxicity. Recommended actions and dose modifications are presented in Table 5.

Table 5. Dose Modifications During KYPROLIS Treatment

Hematologic Toxicity	Recommended Action
• Absolute neutrophil count $< 0.5 \times 10^9$/L	• Withhold dose • If recovered to $\geq 0.5 \times 10^9$/L, continue at the same dose level • For subsequent drops to $< 0.5 \times 10^9$/L, follow the same recommendations as above and consider 1 dose level reduction when restarting KYPROLIS
• Febrile neutropenia ANC $< 0.5 \times 10^9$/L and an oral temperature > 38.5°C or two consecutive readings of > 38.0°C for 2 hours	• Withhold dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level.

• Platelets $<10 \times 10^9$ /L or evidence of bleeding with thrombocytopenia	• Withhold dose
	  • If recovered to $\geq 10 \times 10^9$ /L and/or bleeding is controlled, continue at the same dose level
	  • For subsequent drops to $< 10 \times 10^9$ /L, follow the same recommendations as above and consider 1 dose level reduction when restarting KYPROLIS or discontinue therapy in patients receiving 15 mg/m^2

Renal Toxicity	**Recommended Action**

• Serum creatinine equal to or greater than 2 × baseline, or
• Creatinine clearance < 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis
	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance)
	  • If attributable to KYPROLIS, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction or discontinue therapy in patients receiving 15 mg/m^2
	  • If not attributable to KYPROLIS, dosing may be resumed at the discretion of the physician
	• If tolerated, the reduced dose may be increased to the previous dose at the discretion of the physician
	• For patients on dialysis receiving KYPROLIS, the dose is to be administered after the dialysis procedure

Other Non-hematologic Toxicity	**Recommended Action**
• All other Grade 3 or 4 non-hematological toxicities	• Withhold until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction or discontinue therapy in patients receiving 15 mg/m^2 • If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician

Table 6. Recommended Dose Level Reductions for KYPROLIS

Dose Level Reductions from 27 mg/m^2	
1 Dose Level Reduction	20 mg/m^2
2 Dose Level Reduction	15 mg/m^2
If unable to tolerate 15 mg/m^2	Discontinue KYPROLIS
Dose Level Reductions from 20 mg/m^2	
1 Dose Level Reduction	15 mg/m^2
If unable to tolerate 15 mg/m^2	Discontinue KYPROLIS

Administration

Administer KYPROLIS intravenously (IV) as a 10 minute infusion. KYPROLIS should not be administered as a bolus. The intravenous administration line should be flushed with normal saline or 5% dextrose injection immediately before and after KYPROLIS administration.

Do not mix KYPROLIS with or administer as an infusion with other medicinal products.

Reconstitution:

The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. Read the complete preparation instructions prior to reconstitution.

1. Remove vial from refrigerator just prior to use.
2. Calculate the dose (mg/m^2) and number of vials of KYPROLIS required using the patient's body surface area (BSA) at baseline. Patients with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of ≤ 20%.
3. Use only a 21-gauge or larger gauge hypodermic needle (0.8 mm or smaller external diameter needle) to aseptically reconstitute each vial by slowly injecting 29 mL Sterile Water for Injection through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming.
4. Gently swirl and/or invert the vial slowly for approximately 1 minute, or until complete dissolution. DO NOT SHAKE. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear.
5. Visually inspect for particulate matter and discoloration prior to administration. The reconstituted product should be a clear, colorless solution and should not be administered if any discoloration or particulate matter is observed.
6. Withdraw the calculated dose from the vial and discard any unused portion left in the vial.

7. Optionally, KYPROLIS can be administered in an IV bag. When administering in an IV bag, use only a 21-gauge or larger gauge hypodermic needle (0.8 mm or smaller external diameter needle) to withdraw the calculated dose from the vial and dilute into a 50 or 100 mL IV bag containing 5% Dextrose Injection (D5W). Reconstituted KYPROLIS for injection should not be diluted into a 0.9% sodium chloride IV bag for IV administration.

OVERDOSAGE

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of KYPROLIS administered in error.

There is no known specific antidote for KYPROLIS overdose. In the event of an overdose, the patient should be monitored, specifically for the side effects and/or adverse drug reactions listed in the **ADVERSE REACTIONS** section of the Product Monograph.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N terminal threonine containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib has antiproliferative and proapoptotic activities in preclinical models. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic, and solid tumors. *In vitro*, carfilzomib was found to have minimal inhibition against a panel of twenty-one non-proteasomal proteases.

Pharmacodynamics

Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like (CT-L) activity when measured in blood 1 hour after the first dose. Doses of $\geq$ 15 mg/m^2 inhibited the CT-L activity ($\geq$ 80%) of the proteasome. In addition, carfilzomib administration at 20 mg/m^2 resulted in inhibition of the low molecular mass polypeptide 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the immunoproteasome ranging from 26% to 32% and 41% to 49%, respectively. Proteasome inhibition (CT-L activity) in the blood and PBMC was maintained for $\geq$ 48 hours following the first dose of carfilzomib for each week of dosing. Combination dosing with lenalidomide and dexamethasone did not affect proteasome inhibition.

Pharmacokinetics

Absorption:

The mean C_{max} and AUC following a 2- to 10- minute IV infusion of 15 mg/m^2, 20 mg/m^{2}and 27 mg/m^{2}are shown in Table 7.

Table 7. Summary of Carfilzomib PK Parameters Over 2- to 10-minute IV Infusion

	15 mg/m^2 (n = 8)	20 mg/m^2 (n = 30)	27 mg/m^2 (n = 5)
C_{max} (ng/mL)	2077 (91.4)	2390 (104)	4232 (48.8)
$AUC_{0\text{-last}}$ (ng.hr/mL)	187 (75.3)	251 (92.0)	379 (24.8)

Values presented are geometric mean (geometric CV%).

At doses between 15 and 27 mg/m^2, there was a dose-dependent increase in exposure. Following repeated doses of carfilzomib at 15 and 20 mg/m^2, systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, suggesting there was no systemic carfilzomib accumulation.

Distribution:

The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib on Day 1 of Cycle 1 was 28 L. When tested *in vitro*, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 µM.

Metabolism:

Carfilzomib is rapidly and extensively metabolized. Three predominant metabolites were identified in human plasma and urine. Two metabolites (M14 and M15) result from peptide hydrolysis of carfilzomib while the third metabolite (M16) of similar molecular mass to carfilzomib is formed by hydrolysis of the epoxyketone ring. The metabolites have no known biologic activity.

Excretion:

Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour consistent with its rapid metabolism and distribution to tissues. Carfilzomib is eliminated primarily via metabolism with subsequent excretion of the metabolites in urine.

Special Populations and Conditions

Age:

Population pharmacokinetic analyses indicate there are no effects of age on the pharmacokinetics of carfilzomib.

Gender:

Population pharmacokinetic analyses indicate there are no effects of gender on the pharmacokinetics of carfilzomib.

Hepatic Impairment:

No dedicated pharmacokinetic studies have been completed in patients with hepatic impairment.

Renal Impairment:

A pharmacokinetic study was conducted in which 50 multiple myeloma patients who had various degrees of renal impairment and who were classified according to their creatinine clearances (CrCL) into the following groups: normal function (CrCL > 80 mL/min, n = 12), mild impairment (CrCL 50-80 mL/min, n = 12), moderate impairment (CrCL 30-49 mL/min, n =10), severe impairment (CrCL < 30 mL/min, n = 8), and chronic dialysis (n = 8). KYPROLIS, as a single agent, was administered intravenously over 2 to 10 minutes, on two consecutive days, weekly for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period every 28 days. Pharmacokinetic data were collected from subjects following IV infusion of the 15 mg/m^2 dose in Cycle 1 and 20 mg/m^2 in Cycle 2. In this study, renal function status had no effect on the clearance or exposure of carfilzomib following single or repeat-dose administration. However, the M14 metabolite, a peptide fragment and the most abundant circulating metabolite increased 2- and 3-fold in patients with moderate and severe renal impairment, respectively, and 7.0-fold in patients requiring dialysis (based on AUC_{last}). This metabolite has no known biological activities.

Cardiac Electrophysiology

Analyses of ECG effects of carfilzomib via collection of triplicate ECG and central blind reading have been conducted in 2 clinical studies from 154 patients with advanced malignancies, including multiple myeloma. The effect of carfilzomib on cardiac repolarization using the QT interval with Fridericia's correction (QTcF interval) and the analysis of concentration-QTc relationships show no clear signal of any dose-related effect. The upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcF at C_{max} was 4.8 msec. With Bazett's correction (QTcB interval), the upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcB at C_{max} was 5.9 msec.

STORAGE AND STABILITY

Unopened vials should be stored refrigerated (2°C to 8°C). Retain in original package to protect from light. It is not necessary to protect the reconstituted or diluted product from light during administration.

Unopened vials of KYPROLIS are stable until the date indicated on the package when stored in the original package at 2°C to 8°C.

Reconstituted Solution:

The elapsed time from reconstitution to administration should not exceed 24 hours. Store reconstituted solutions in the vial, syringe, or IV bag refrigerated (2°C to 8°C) up to 24 hours or at room temperature (15°C to 30°C) for up to 4 hours.

DOSAGE FORMS, COMPOSITION AND PACKAGING

KYPROLIS is a sterile, white to off-white lyophilized powder for solution for injection.

KYPROLIS single-use vial contains 60 mg of carfilzomib. After reconstitution, each mL contains 2 mg of carfilzomib.

- Single-use 50 mL vial Type 1 clear glass vial fluoropolymer laminated elastomeric stopper and aluminum seal with plastic flip off cap
- Pack size of one vial

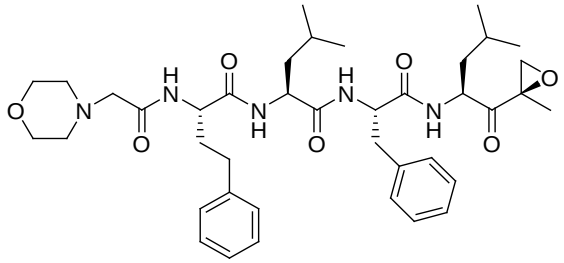
List of Excipients:

- citric acid, anhydrous
- sodium hydroxide (for pH adjustment)
- sulfobutylether beta-cyclodextrin

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	carfilzomib
Chemical name:	(2S)-N-[(1S)-1-benzyl-2-[[(1S)-3-methyl-1-[[(2R)-2-methyloxiran-2-yl]carbonyl]butyl]amino]-2-oxoethyl]-4-methyl-2-[[(2S)-2-[(morpholin-4-ylacetyl)amino]-4-phenylbutanolyl]amino]pentamide
Molecular formula and molecular mass:	$C_{40}H_{57}N_5O_7$ 719.9 g/mol
Structural formula:	
Physicochemical properties:	Carfilzomib is a modified tetrapeptidyl epoxide, isolated as the crystalline free base. Carfilzomib is practically insoluble in water, and very slightly soluble in acidic conditions.

CLINICAL TRIALS

KYPROLIS in Combination with Lenalidomide and Dexamethasone for the Treatment of Patients with Relapsed Multiple Myeloma (the ASPIRE Study; Study PX-171-009)

The safety and efficacy of KYPROLIS were evaluated in a randomized, open-label, multicenter Phase 3 study of 792 patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy (median of 2), which evaluated the combination of KYPROLIS with lenalidomide and dexamethasone (KRd) versus lenalidomide and dexamethasone alone (Rd), randomized 1:1.

The primary efficacy endpoint was progression-free survival (PFS) as determined by an Independent Review Committee (IRC) using standard objective International Myeloma Working Group (IMWG)/European Blood and Marrow Transplantation (EBMT) response criteria. Key secondary efficacy endpoints included overall survival (OS) and overall response rates (ORR).

Important exclusion criteria included: creatinine clearance rates < 50 mL/min, disease progression during the treatment with a bortezomib-containing regimen, progression during the

first 3 months of initiating treatment with lenalidomide and dexamethasone, or progression at any time during treatment with lenalidomide and dexamethasone if this was the patient's most recent line of therapy. KYPROLIS treatment was administered for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and dexamethasone administration could continue until progression or unacceptable toxicity.

The demographics and disease and baseline characteristics for the ASPIRE study are summarized in Table 8.

Table 8. Demographic, Disease and Other Baseline Characteristics

Characteristic	ASPIRE Study (PX-171-009)	
	KRd Arm (N = 396)	Rd Arm (N = 396)
Age, years		
Median (min, max)	64.0 (38, 87)	65.0 (31, 91)
Age group, years		
≥ 75, n (%)	43 (10.9)	53 (13.4)
Males, n (%)	215 (54.3)	232 (58.6)
ECOG Performance Status		
0	165 (41.7)	175 (44.2)
1	191 (48.2)	186 (47.0)
2	40 (10.1)	35 (8.8)
ISS stage, n (%)		
III	73 (18.4)	82 (20.7)
Measurable disease category, n (%)		
UPEP disease	97 (24.5)	98 (24.7)
Genetic mutations		
High-risk genetic mutations, n (%)[a]	48 (12.1)	52 (13.1)
Standard risk genetic mutations	147 (37.1)	170 (42.9)
Unknown genetic mutations	201 (50.8)	174 (43.9)
CrCL, mL/min median (min, max)	78.6 (38.7, 211.9)	79.2 (30.0, 207.8)
30 to < 50, n (%)[c]	19 (4.8)	32 (8.1)
50 to < 80, n (%)	185 (46.7)	170 (42.9)
≥ 80, n (%)	192 (48.5)	194 (49.0)
Hemoglobin, g/L median (min, max)	114.0 (71.0, 154.0)	111.0 (57.0, 166.0)
ANC, 10^9/L median (min, max)	2.6 (0.6, 11.8)	2.7 (0.7, 28.2)
Platelet count, 10^9/L median (min, max)	185.0 (32.0, 540.0)	192.5 (25.0, 597.0)
History of neuropathy, n (%)	199 (50.3)	188 (47.5)
Serum beta-2 microglobulin, mg/L median (min, max)	3.5 (1.3, 13.0)	3.6 (1.5, 31.7)
Heavy chain, n (%)		
IgG	275 (69.4)	281 (71.0)
Light chain, n (%)		
Kappa	271 (68.4)	256 (64.6)
Lambda	124 (31.3)	139 (35.1)

ECOG = Eastern Cooperative Oncology Group; ANC = absolute neutrophil count; CrCL = creatinine clearance;

IgG = immunoglobulin G; ISS = International Staging System; KRd = KYPROLIS, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone; UPEP = urine protein electrophoresis

[a] The results were based on flourescent in situ hybridization (FISH) analysis performed by a central laboratory, and the high-risk group consisted of the genetic subtypes t(4;14), t(14;16), or deletion 17p in ≥ 60% of plasma cells, based on IMF criteria.

[b] All but 2 patients had >50 mL/min CrCL at screening (as per inclusion criteria) and their reduced renal function was assessed prior to dosing. Half of these patients had a CrCL > 50 mL/min within the first two cycles.

Study results

Patients in the KYPROLIS, lenalidomide, and dexamethasone (KRd) arm demonstrated improved progression-free survival (PFS) compared with those in the lenalidomide and dexamethasone (Rd) arm (HR = 0.69, with 1-sided p-value < 0.0001). This represents a 45% improvement in PFS or a 31% reduction in the risk of disease progression or death. The median PFS was 26.3 months in the KRd arm vs. 17.6 months in the lenalidomide and dexamethasone (Rd) arm (see Table 9 and Figure 1).

The PFS benefit of KRd was consistently observed in all subgroups including those defined according to age, cytogenetic risk and number of prior lines of therapy. The results of the secondary efficacy endpoints of overall survival (OS) and overall response rates (ORR) are presented in Table 9. The overall response rate (ORR) was higher in the KRd versus the Rd arm. The interim overall survival results did not meet the protocol-specified early stopping boundary for statistical significance. Patients treated with KRd reported a statistically significant improvement in global health status, with higher Global Health Status/Quality of Life (QoL) scores compared with Rd over 18 cycles of treatment measured with the EORTC QLQ-C30, an instrument validated in multiple myeloma.

Table 9. Summary of Efficacy Analysis

	ASPIRE Study (PX-171-009)	
	KRd Arm[a] (N = 396)	**Rd Arm[a] (N = 396)**
PFS months median (95% CI)	26.3 (23.3, 30.5)	17.6 (15.0, 20.6)
HR (95% CI); 1-sided p-value[b]	0.69 (0.57, 0.83); < 0.0001	
OS months median (95% CI)	NE (NE, NE)	NE (32.1, NE)
HR (95% CI); 2-sided p-value[c]	0.79 (0.63, 0.99); 0.0364	
ORR n (%)	345 (87.1)	264 (66.7)
sCR	56 (14.1)	17 (4.3)
CR	70 (17.7)	20 (5.1)
VGPR	151 (38.1)	123 (31.1)
PR	68 (17.2)	104 (26.3)
Odds Ratio (95% CI)	3.47 (2.41,5.00)	

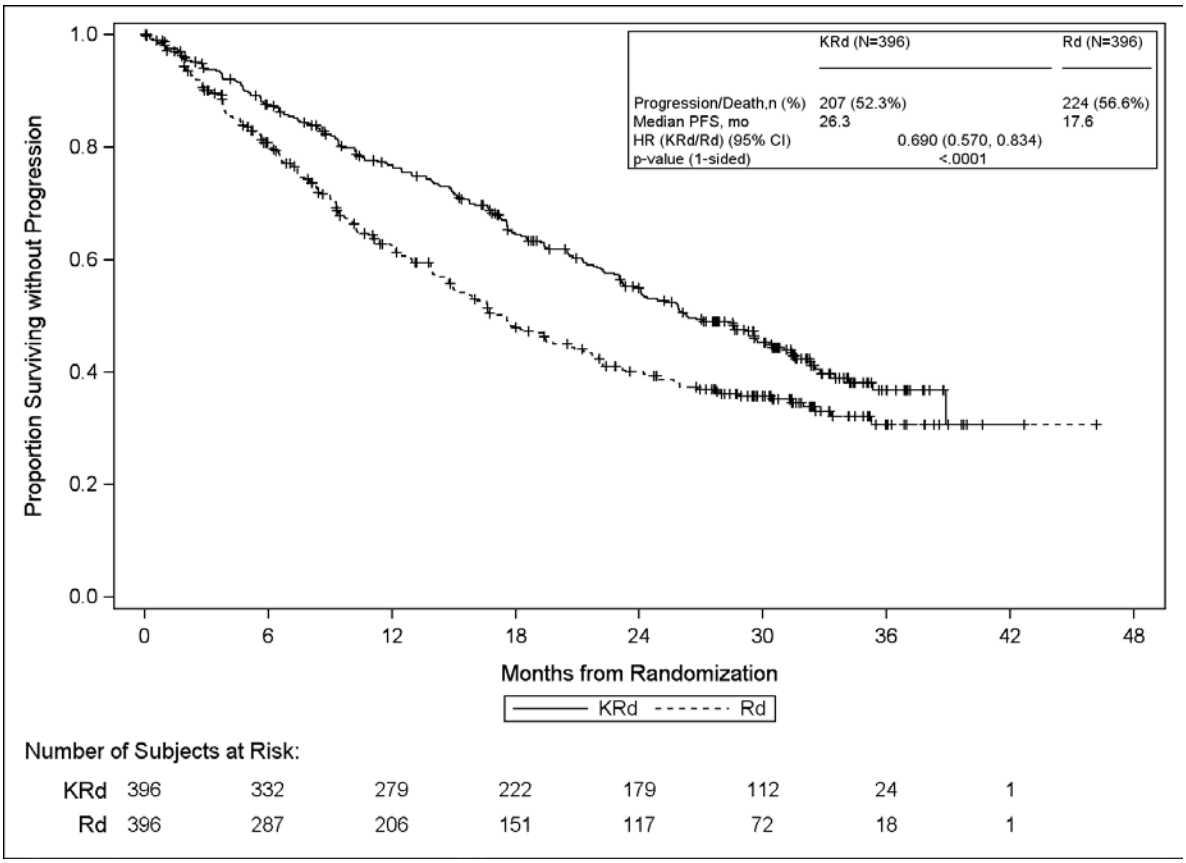
CI = confidence interval; CR = complete response; EBMT = European Blood and Marrow Transplantation; IMWG = International Myeloma Working Group; KRd = KYPROLIS, lenalidomide, and dexamethasone; NE = not estimable; OS = overall survival; ORR = overall response rate; PR = Partial Response; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; sCR = stringent complete response; VGPR = very good partial response

[a] As determined by an Independent Review Committee using standard objective IMWG/EBMT response criteria.

[b] Statistically significant.

[c] The interim OS analysis did not meet the protocol-specified early stopping boundary for OS (p = 0.0051).

Figure 1. Kaplan-Meier Curve of Progression-Free Survival in the ASPIRE Study



CI = confidence interval; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; KRd = KYPROLIS, lenalidomide, and dexamethasone; mo = months; PFS = progression-free survival; Rd = lenalidomide and dexamethasone arm

Note: The response and PD outcomes were determined using standard objective IMWG/EBMT response criteria.

DETAILED PHARMACOLOGY

The activity of carfilzomib was assessed in mice, rats and monkeys and utilized bolus IV administration and dosing schedules similar to those used in clinical studies.

A dose-dependent inhibition of proteasome activity in whole blood and tissues of animals was observed with no proteasome inhibition detected in brain. A ≥ 80% proteasome inhibition in rats and monkeys was achieved at tolerated doses (1 and 0.5 mg/kg in rats and monkeys, respectively) of carfilzomib. Proteasome inhibition in blood and tissues from rats receiving a 30-minute infusion of carfilzomib was similar to samples from rats receiving bolus administration of the same dose.

The antitumour efficacy of carfilzomib has been evaluated in immunocompromised mice implanted with a number of human tumor cell lines. In one model, a statistically significant reduction in tumour size was seen when carfilzomib was administered at 5 mg/kg on a twice-weekly schedule of Day 1/Day 2 (the clinical dosing schedule of carfilzomib) but not when administered Day 1/Day 4 or on a once-weekly schedule using a higher dose. In humans, doses of 20 and 27 mg/m^2 given on consecutive days result in prolonged proteasome inhibition of >80% in peripheral blood mononuclear cells (PBMCs).

TOXICOLOGY

Animal Toxicology

Acute Dose Toxicity

Carfilzomib was toxic following single bolus injections in rats and monkeys at similar or lower exposures (based on AUC) achieved clinically in humans receiving 27 mg/m^2. Rats administered ≥7 mg/kg showing signs of lethargy and piloerection at 1 and 4 hours after the bolus injection, respectively, with deaths reported in animals administered 9 mg/kg. Single carfilzomib doses of 4 mg/kg in monkeys resulted in considerable toxicity including deaths. Signs of nephrotoxicity and changes consistent with an acute phase response (APR) including increased C-reactive protein (CRP), neutrophils, monocytes and fibrinogen and decreased albumin in rats and pericardial effusion in monkeys along with congestion of the livers and kidneys and discolouration of the GI tract were observed. The toxicities were more severe in the rat than in the monkey, possibly owing to higher exposures of carfilzomib in these animals.

Repeat Dose Toxicity

Repeat-dose toxicity studies of 4-weeks and 3/6-months in rats and of 1, 4-weeks and 9-months in monkeys were conducted. The 3/6-month study in rats and 9-month study in monkeys used dosing schedules (days 1, 2, 8, 9, 15 and 16 of a 28-day cycle) similar to those used clinically. Intravenous administration of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys, approximating human equivalent exposures of ≥0.3 and 0.1 times, respectively (based on AUC_{last}), resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/ degeneration), gastrointestinal (necrosis/hemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (hemorrhage/ inflammation) systems. Carfilzomib achieved higher systemic concentrations in rats compared to monkeys at similar starting doses (based on mg/kg) and mortalities generally occurred early in rats than in monkeys. A summary of the toxicology findings is described in Table 10.

Table 10. Summary of Single-Dose and Repeat Dose Toxicology Studies

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
Single Dose			
Pharmacodynamics and Toxicity of Carfilzomib in Rats: Effect of Infusion Delivery	Sprague-Dawley rats/ 3 to 10M/group	Single doses Carfilzomib: 8 mg/kg IV bolus or 10 minute IV infusion. 8, 10, 12 mg/kg: 30 minute IV infusion. Bortezomib: 0.5 mg/kg IV bolus. Control: IV bolus	Mortality: Carfilzomib: 8 mg/kg bolus: 14/32; 8 mg/kg 10 minute infusion: 1/8; none at the 30 minute infusion. 10 and 12 mg/kg 30 minute infusions: 1/6 and 4/6, respectively. Bortezomib 4/6 at 0.5 mg/kg. Bolus carfilzomib and bortezomib and infusion of carfilzomib at 12 mg/kg resulted in lethargy, dyspnea, pale ears, ruffled fur and/or cold to touch. At 8 mg/kg 10 minute infusion, pale ears and ruffled fur was observed and at the 30 minute infusion, only ruffled fur was observed. ↑ BUN and creatinine 24 hours post dose at 8 mg/kg bolus carfilzomib. Increased dose for a 30 minute infusion or a 10 minute infusion at 8 mg/kg resulted in similar elevations and magnitude was dose-related. Carfilzomib at 8 mg/kg for 30 minutes resulted in the lowest ↑ in BUN and no change in creatinine. Increased BUN and creatinine were seen with bortezomib. All changes recovered by 72 hours post dose. ↑ neutrophils at 24 hr and ↓platelets at 24 and 72 hours was similar between bolus and infusion of carfilzomib. Proteasome inhibition in blood and tissues after carfilzomib by bolus or infusion MTD of carfilzomib was 8 mg/kg.
Dose Range Finding Toxicity Study of PR-171 in Male Cynomolgus Monkeys	Cynomolgus monkey/ 2 or 3M/group	Single Dose IV at 0, 1, 1.16, 2, 4 mg/kg. 5 consecutive doses at 4 mg/kg	Single Dose: Mortality at 1 mg/kg in 1/3 monkeys likely due to concomitant anesthesia. Treatment-related mortality at 4 mg/kg in 1/3 monkeys. At necropsy there was pleural and pericardial effusion, liver and kidney congestion, and GI mucosal lesions, Histopathology performed on the heart showed possible myocardial toxicity and there was GI mucosal degeneration. Emesis at 1 and 4 mg/kg and hunched posture at 4 mg/kg. ↓platelets at 1 and 4 mg/kg at 72 hr, full recovery 2 weeks post-dose. ↑monocytes ≥ 1.16 mg/kg, with full recovery, except for partial recovery at 4 mg/kg. ↑BUN and creatinine 4-mg/kg; ↓albumin at all doses, with recovery at 1 mg/kg by 72 hours post-dose.Multiple-dose: ↓platelets with full recovery; ↑monocytes with full recovery.
Repeat-Dose			
A 4-Week Repeat Dose Intravenous Toxicity Study of PR-171 in Rats	Sprague-Dawley rats/ Main study: 13 sex/group at 1, 2, 4, and 6 mg/kg; 10/sex/group at 0.5 and 1 mg/kg. TK/PD: 8 sex/group	Once-daily IV for 2 cycles (5 days dosing, 9 days off en followed by a second 5-day dosing period	Mortality at dosages ≥ 1 mg/kg (main study). 1, 2, and 1 males at 1, 4, and 6 mg/kg and 1 female each at 2, 4, and 6 mg/kg was likely due to cardiac failure (cardiomyopathy) or pulmonary interstitial inflammation. ↓ food consumption and fecal volume. Anogenital staining,in some animals, decreased activity and tachypnea during dosing, with recovery during non-dosing periods.

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
		at 0, 0.5, 1, 2, 4, 6 mg/kg	NOAEL was 0.5 mg/kg.
A 3/6 Month Intravenous Toxicity Study Of Carfilzomib in Rats With an 8-Week Recovery Period	Sprague-Dawley rats/ Main study: 4 groups with 25/sex/group: Interim: 10/sex/group, Terminal: 10/sex/group, Recovery: 5/sex/group. TK: 3 groups of 8/sex/group for TK	IV for 3 or 6 cycles (each cycle was 2 consecutive days of dosing per week for 3-weeks followed by a 12-day non-dosing period) at 0, 1, 2, 4 mg/kg	Mortality at ≥ 2 mg/kg (M) and 4 mg/kg (F); due to cardiac fibrosis, cardiac failure, gastrointestinal hemorrhage/necrosis, and/or renal tubular necrosis. Clinical signs in surviving animals at 2 and/or 4 mg/kg included ↓ food consumption, body weights (males only) and fecal volumes, anogenital staining, decreased activity,chromodacryorrhea, hunched appearance, piloerection. Transient ↓ platelets (24 hours after last dose but not at 12 or 47 days after dosing) ↑Reticulocyte counts (all doses) and bone marrow hypercellularity at ≥ 1 mg/kg ↑Neutrophil, monocyte counts, ↑fibrinogen (24 hours after last dose) ≥ 1 mg/kg ↑Serum phosphorus (day 12 after last interim dose), ↑ liver weights and microscopic findings at ≥ 1 mg/kg in the kidney (chronic progressive nephropathy), liver (periportal vacuolation and hepatocellular hypertrophy), spleen (decreased marginal zone cellularity at ≥ 2 mg/kg), and mesenteric lymph nodes (increased mast cells at 4 mg/kg. The STD10 was considered to be 2 mg/kg (12 mg/m^2) based upon mortality of > 10% in the 4 mg/kg dose group.
A Two Dose, Seven Day Intravenous Toxicity Study of Carfilzomib in Cynomolgus Monkeys	Cynomologus monkey 6 males/ group	IV bolus on 2 consecutive days followed by an observation period before necropsy on day 7 at 0 and 2 mg/kg	↓ Activity, ↑ tremors (2 to 4 hours post dose 1/6M); ↑ troponin I, ↑ AST, ALT, left ventricle red discoloration and moderate myocardial degeneration (1/6M). Transient ↑ troponin I (4/6 animals beginning on day 3 to 4). ↓erythroid mass and reticulocyte counts on days 4 or 5 with recovery of reticulocyte counts by day 7 and mild erythroid bone marrow hypercellularity on day 7, ↓ platelet counts on days 2 to 4 were recovered by day 7. Mild to moderate ↑ in BUN on day 2, associated with ↑ serum creatinine and increased urine specific gravity, which recovered by day 3. ↓ in serum albumin, ↑plasma fibrinogen and serum CRP consistent with acute phase response on day 2 or 4. Albumin, fibrinogen, and CRP changes were resolved by day 7. > 90% inhibition of whole blood proteasome activity by day 2.
A 4-Week Repeat Dose Intravenous Toxicity Study of PR-171 in Cynomolgus Monkeys	Cynomolgus monkey/ 5 sex/group	IV for up to 2 cycles (5 days dosing followed by 9 days off, then followed by a second 5-day dosing period at 0, 0.5, 1, 2 mg/kg Animals at 2 mg/kg received 1 cycle due to mortality/toxicity	Mortality at 2 mg/kg (6/10 animals) due to lung and heart changes (fluid in pericardium and thorax, hemorrhage and microscopically, inflammation heart and lungs). ↓erythroid parameters (RBC, hemoglobin, and hematocrit) and/or reticuloctyes counts at ≥ 1 mg/kg with recovery during non-treatment periods. ↓platelet counts at 1 and 2 mg/kg at the end of treatment period(s), with recovery and increased bone marrow megakaryocytes following the non-dosing period(s). Minimal intra-alveolar hemorrhage and edema and inflammation of the heart and inflammation in the lung at ≥1 mg/kg. On day 28, changes were limited to reparative changes (minimal ↑ cellularity in 1 male and 1 female and slight multifocal fibrosis in 1 female) in the heart at 2 mg/kg; there were no findings at 0.5 or 1 mg/kg. The HNSTD was determined to be 1 mg/kg based on the severe toxicity at 2 mg/kg (24 mg/m^2) .
A 9-Month Intravenous Toxicity	Cynomolgus monkey/ Main	IV 9 cycles (2	Mortality at 2 mg/kg (2 of 12 animals), due to multi-organ toxicity including

Study Title	Species/ Number of Animals	Dosage/Route	Principal Findings
Study of Carfilzomib in Cynomolgus Monkeys with an 8-Week Recovery Period	study: 4 sex/group Recovery: 2 sex/group at 0, 2 mg/kg	consecutive daily doses followed by 12 non-dosing days) at 0, 0.5, 1, 2 mg/kg	cardiac inflammation, pulmonary inflammation and edema, and renal dysfunction or declining physical condition and severe non-regenerative anemia associated with ↓bone marrow cellularity, severe hypoalbuminemia associated with subcutaneous swelling, and moderate ↑ in serum enzymes (ALT and ALKP). ↑ heart weights (associated with ECG changes compatible with left ventricular enlargement in 1 male) were associated with inflammation, myocardial hypertrophy, and myocyte degeneration. ↓ erythroid parameters (RBC, hemoglobin, and hematocrit) at ≥ 0.5 mg/kg with recovery during non-treatment periods and associated with ↑ reticulocyte counts. ↓ platelet counts after cycle 8 and 9 at 2 mg/kg, ↑increased platelet counts at the end of cycles (after 12-day non-dosing period). ↑ BUN and serum creatinine at 2 mg/kg and ↑ BUN at ≥ 1 mg/kg immediately following dosing associated with proteinuria, hematuria and ↑kidney weights, and microscopic changes in the kidney (interstitial inflammation, altered tubule size, glomerulopathy and intratubular RBC casts). Other microscopic changes; interstitial lung inflammation and inflammation with myocyte degeneration (1M) in the heart occurred at ≥ 1 mg/kg. Inflammation, edema and perivascular hemorrhage were present most frequently used injection sites. Increased cellularity was noted in the bone marrow. Partial recovery of lung, heart, and kidney changes; all other findings recovered. The HNSTD was considered to be 0.5 mg/kg (6 mg/m^2).

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity studies have not been conducted with KYPROLIS.

Carfilzomib was clastogenic in the *in vitro* chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test (Table 11).

Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28-day repeat-dose rat and monkey toxicity studies or in 6-month rat and 9-month monkey chronic toxicity studies. Carfilzomib caused embryo-foetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Carfilzomib administered to pregnant rats during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day, which is approximately half the recommended dose in humans of 27 mg/m^2 based on body surface area (see Table 12).

Table 11. Summary of Mutagenicity Studies

Study Title	Species/Number of Animals	Dosage/Route	Principal Findings
Carfilzomib Bacterial Reverse Mutation Test	*S. typhimurium*: TA1535, TA1537, TA98, TA100; *E. coli*: WP *uvr*A (pKM101)	In vitro 5 – 5000 µg/plate	Carfilzomib showed no mutagenic potential
Carfilzomib: In Vitro Chromosome Aberration Test in Human Lymphocytes	Human lymphocytes	In vitro 0.001 to 2500 µg/mL	Carfilzomib caused an increase in the frequency of structural chromosome aberrations.
Carfilzomib : Mouse Micronucleus Test	CD-1 Mice/5 sex/group	IV injections at 0.31 to 7 mg/mg	Carfilzomib showed no evidence for causing an increase in the induction of micronucleated polychromatic erythrocytes or of causing bone marrow cell toxicity

Table 12. Summary of Embryo Fetal Development Studies

Study Title	Species/Number of Animals	Dosage/Route	Principal Findings
Carfilzomib: An Intravenous Embryo-fetal Toxicity Study in Rats (GLP)	Time-mated Sprague-Dawley rats/ 22 females/group for controls, 28/group for carfilzomib groups	Daily IV from gestation day 6 to 17 inclusive at 0, 0.5, 1.0, 2.0 mg/kg	Mortality at 2 mg/kg (2 females) on gestation day (GD) 9 and GD 15. Thin fluid in the thoracic cavities, distended colon, discolored jejunal serosa, small spleen, and enlarged heart at necropsy. At ≥ 1 mg/kg, there was decreased activity, anogenital staining, pallor, and labored breathing ↓ body weight gain was associated with ↓ food consumption from GD 6 through 18 with recovery and increased body weight gain from GD 18 through GD20 at ≥ 1 mg/kg. There were no effects on percent pre- or post-implantation loss, on placental or fetal weight, or on the incidence of external, visceral, or skeletal malformations. The maternal NOAEL was 0.5 mg/kg and the NOAEL for embryo-fetal toxicity was 2 mg/kg.
Carfilzomib: Preliminary Intravenous Embryo-fetal Toxicity Study in Rabbits (Non-GLP)	Time-mated New Zealand White rabbits/8 females/group	Daily IV from gestation day 6 to 19 inclusive at 0, 0.2, 0.4, 0.8 mg/kg	Mortality at 0.8 mg/kg (one female) preceded by ↓ food consumption and accumulation of thin, red fluid in the thoracic and pericardial cavities, edema in the pericardium and thymus, and enlarged mediastinal lymph node at necropsy. ↓ body weight, ↓body weight gain, food consumption, and/or fecal volume from GD 6 through 29 at 0.8 mg/kg. At 0.4 mg/kg, there was transient ↓ body weight and food consumption that were toxicologically insignificant. At scheduled necropsy, at 0.8 mg/kg one female had 60% post-implantation loss, signs of fetal toxicity and possible early abortion or premature delivery on GD 29. ↓fetal body weight at 0.8 mg/kg may have been secondary to the severe maternal toxicity. A NOAEL for embryo-fetal toxicity was established at 0.4 mg/kg/day, based on decreased fetal body weight at 0.8 mg/kg/day that were considered, in part, secondary to maternal toxicity.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

Kyprolis™

carfilzomib for injection

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

Serious Warnings and Precautions

KYPROLIS should be prescribed and managed by a healthcare professional experienced in the use of anticancer drugs. Serious side effects with KYPROLIS include:

- Heart problems
- Breathing problems
- Liver problems
- Blood clots in the veins (deep vein thrombosis) and lungs (pulmonary embolism)
- Blood clots in small blood vessels (thrombotic microangiopathies)
- Swelling in the back of the brain (Posterior Reversible Encephalopathy Syndrome [PRES])
- Bleeding into your organs, eg, the brain, lungs or gastrointestinal tract (stomach or bowel)

What is KYPROLIS used for?

KYPROLIS is used together with lenalidomide and dexamethasone to treat patients with multiple myeloma who have received one to three previous treatments. Multiple myeloma is a cancer of plasma cells (a type of white blood cell in the bone marrow that produces antibodies).

How does KYPROLIS work?

KYPROLIS is a proteasome inhibitor. Proteasomes play an important role in cells by breaking down proteins that are damaged or no longer needed. KYPROLIS blocks proteasomes, which can lead to a build-up of proteins within cells. KYPROLIS can cause cell death, especially in multiple myeloma cells because they contain a higher amount of abnormal proteins.

What are the ingredients in KYPROLIS?

Medicinal ingredient:

- carfilzomib

Non-medicinal ingredients:

- anhydrous citric acid
- sodium hydroxide (for pH adjustment)
- sulfobutylether beta-cyclodextrin

KYPROLIS comes in the following dosage forms:

Powder for injection: 60 mg/vial

Do not use KYPROLIS if you:

- Have ever had an allergic reaction to KYPROLIS.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KYPROLIS if you:

- Have or have had heart problems, including a history of chest pain (angina), heart attack, irregular heartbeat, or if you have ever taken a medicine for your heart
- Have or have had lung problems, including a history of shortness of breath at rest or with activity (dyspnea)
- Have or have had kidney problems, including kidney failure or if you have ever received dialysis
- Have or had liver problems, including a history of hepatitis, fatty liver, or if you have ever been told your liver is not working properly
- Have or had unusual bleeding, including easy bruising, bleeding from an injury, such as a cut that does not stop bleeding in a normal amount of time, or internal bleeding, which can indicate you have low platelets
- Have or had blood clots in your veins
- Have or have had any other major medical problem for which you were hospitalized or received medication
- Are pregnant or plan to become pregnant
- Are male and are considering fathering a child
- Are breastfeeding or plan to breastfeed
- Are on a controlled sodium diet

Other warnings you should know about:

Your healthcare professional will examine you and review your full medical history before starting treatment with KYPROLIS. You will be followed closely during treatment. Before you start KYPROLIS, and during treatment, you will have blood tests. This is to make sure you have enough blood cells and your liver and kidneys are working properly. You will also have your blood pressure checked. If your blood pressure is too high, it may need to be lowered before you begin treatment with KYPROLIS. Before you start KYPROLIS, your healthcare professional will ensure you are getting enough fluids.

Pregnancy, breastfeeding and contraception

<u>For women taking KYPROLIS</u>

KYPROLIS should not be taken if you are trying to become pregnant or are pregnant. While taking KYPROLIS treatment and for 30 days after stopping treatment, you should use a reliable

method of birth control to ensure you do not become pregnant. You should talk to your healthcare professional about reliable methods of birth control. It is important that you tell your healthcare professional if you are pregnant, think you may be pregnant, or plan on becoming pregnant. If you become pregnant while taking KYPROLIS, notify your healthcare professional immediately.

If you are breastfeeding, you should not take KYPROLIS. It is not known if KYPROLIS passes into breast milk in humans. It is important to tell your healthcare professional if you are breastfeeding or plan to do so.

For men taking KYPROLIS

While taking KYPROLIS and for 90 days after stopping treatment, you should use a reliable method of birth control to ensure your partner does not become pregnant. You should talk to your healthcare professional about reliable methods of birth control.

If your partner becomes pregnant while you are taking KYPROLIS or within 90 days after stopping treatment, notify your healthcare professional immediately.

Driving and Using Machines

Treatment with KYPROLIS may cause fatigue, dizziness and a drop in blood pressure that could affect your ability to drive or operate machines. Do not drive or perform tasks which may require special attention until you know how KYPROLIS affects you.

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

The following may interact with KYPROLIS:

- KYPROLIS may stop certain types of birth control methods (eg, oral hormonal methods) from working.
- There may be a higher risk of blood clots when KYPROLIS is used together with certain types of birth control methods (eg, hormonal methods).

How to take KYPROLIS:

KYPROLIS will be given to you by a healthcare professional. Your healthcare professional will decide how much KYPROLIS you should receive based on your height and weight and how long you should receive KYPROLIS.

Most patients will receive treatment until their disease gets worse. KYPROLIS treatment may also be stopped if you experience side effects that cannot be managed.

Usual Dose:

KYPROLIS will be infused into your vein over 10 minutes. One treatment cycle is 28 days long.

For the first 12 treatment cycles:

KYPROLIS will be given on Days 1, 2, 8, 9, 15, and 16.

For treatment cycles 13 and beyond:

KYPROLIS will be given on Days 1, 2, 15 and 16.

Overdose:

In case of drug overdose, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

It is important for you to keep all your appointments to receive KYPROLIS. If you miss an appointment, ask your healthcare professional when you should schedule your next dose.

What are possible side effects from using KYPROLIS:

These are not all the possible side effects you may feel when taking KYPROLIS. If you experience any of these side effects or side effects not listed here, contact your healthcare professional.

Side effects may include:

- Fatigue, weakness
- Low white blood cell count, which may decrease your ability to fight infection and may be associated with fever
- Diarrhea, nausea, constipation, vomiting, digestion problems, stomach pain, decreased appetite, dehydration
- Infusion site reaction (pain, redness, or swelling where you received the injection into your vein)
- Fever, chills, common cold, the flu, bronchitis
- Urinary tract infection
- Lung infection (pneumonia)
- Infection in the blood (sepsis)
- Headache, dizziness
- Stroke
- Numbness, tingling, or decreased sensation in hands and/or feet
- Nose bleed
- Change in voice or hoarseness, pain in the throat
- Blurred vision
- Toothache
- Trouble sleeping, anxiety
- Rash, red, itchy skin
- Increased sweating, feeling too hot
- Back pain, joint pain, pain in legs, arms, hands, or feet, bone pain, muscle pain, muscle spasms, muscle weakness, aching muscles

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
VERY COMMON		
Bruising or bleeding due to low platelets	√	
A reaction to KYPROLIS infusion, which can include the following symptoms: fever, chills or shaking, joint pain, muscle pain, facial flushing or swelling, weakness, shortness of breath, low blood pressure, fainting, chest tightness, or chest pain	√	
Leg pain (which could be a symptom of blood clots in the deep veins of the leg), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs)		√
COMMON		
Chest pain (angina), shortness of breath, rapid, strong or irregular heartbeat or if there is swelling of your feet, which may be symptoms of heart problems including heart failure and heart attack		√
Severe bleeding events such as coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools		√
Difficulty breathing, including shortness of breath at rest or with activity, rapid breathing, wheezing, or cough, which can be signs of lung problems		√
Swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results, which may be symptoms of kidney problems or kidney failure		√
UNCOMMON		
Irregular heartbeat , muscle spasms or twitching, passing less urine and abnormal blood tests due to rapid breakdown of cancer cells (tumour lysis syndrome)		√
Yellowing of your skin and eyes, stomach pain or swelling, nausea or vomiting due to liver problems		√
Shortness of breath with everyday activities or at rest, irregular heartbeat, fast pulse, tiredness, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension		√
Very high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis.		√

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	Stop taking drug and get immediate medical help
FREQUENCY UNKNOWN Symptoms of headaches, confusion, seizures, speech and visual loss, and high blood pressure due to swelling in the back of the brain (Posterior reversible encephalopathy syndrome [PRES]).		√
Symptoms of bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea and acute kidney failure due to blood clots in small vessels (thrombotic microangiopathies)		√

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect® (http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

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

Storage:

KYPROLIS will be stored in the pharmacy under refrigeration, in the original carton to protect from light. Protection from light is not necessary during administration.

If you want more information about KYPROLIS:

- Talk to your healthcare professional

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.amgen.ca, or by calling 1-866-50-AMGEN (1-866-502-6436).

This leaflet was prepared by Amgen Canada Inc.

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