1. KYPROLIS

Kyprolis 30 mg powder for infusion

Kyprolis 60 mg powder for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Carfilzomib 30 mg

Carfilzomib 60 mg

Excipient(s) with known effect

Each mL of reconstituted solution contains 7 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile, white to off-white lyophilised powder for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kyprolis in combination with either lenalidomide and dexamethasone, or dexamethasone alone, is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy

4.2 Dose and method of administration

Dose

Kyprolis is administered intravenously (IV) as a 10 or a 30 minute infusion either once or twice weekly based on the selected regimen (see Table 1). Treatment may be continued until disease progression or until unacceptable toxicity occurs

Table 1: Kyprolis dosing information

Regimen	Kyprolis starting dose	If tolerated, increase Kyprolis dose on day 8 of cycle1 to	Kyprolis infusion time[a]
Kyprolis in combination with lenalidomide and dexamethasone	20 mg /m^2	27 mg /m^2 twice weekly	10 minutes
	20 mg /m^2	56 mg /m^2 twice weekly	30 minutes

Kyprolis in combination with dexamethasone	20 mg /m^2	70 mg /m^2 once weekly	30 minutes

[a] Infusion time remains consistent throughout each regimen

The dose is calculated using the patient's baseline body surface area (BSA). Patients with a BSA of 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 less than or equal to 20%.

Kyprolis in combination with lenalidomide and dexamethasone

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 increased to 27 mg/m^2 on day 8 of cycle 1. Kyprolis is omitted on Days 8 and 9 of Cycles 13 and higher (see Table 2). Kyprolis 20/27 mg/m^2 is administered 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). Each 28 day period is considered one treatment cycle. The 20/27 mg/m^2 dose is administered over 10 minutes. Treatment may be continued until disease progression or until unacceptable toxicity occurs.

When given in combination with lenalidomide and dexamethasone, Kyprolis is omitted on days 8 and 9 of cycles 13 and higher. Lenalidomide is administered as 25 mg orally on days 1 to 21 and dexamethasone is administered as 40 mg orally or intravenously on days 1, 8, 15, and 22 of the 28 day cycles. Appropriate dose reduction for the starting dose of lenalidomide should be considered according to the recommendations in the lenalidomide data sheet, for example, for patients with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Table 2 Recommended dosage regimen for Kyprolis when used in combination with lenalidomide and dexamethasone

	Cycle 1									
	Week 1			**Week 2**			**Week 3**			**Week 4**
Kyprolis[a] (20-27 mg/m^2)	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
	20	20	-	27	27	-	27	27	-	-
Lenalidomide[b] (25 mg)	Days 1-21									

Dexamethasone[c] (40 mg)	Days 1, 8, 15, 22									
	Cycles 2-12									
	Week 1			**Week 2**			**Week 3**			**Week 4**
Kyprolis (27 mg/m^2)	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
	27	27	-	27	27	-	27	27	-	-
Lenalidomide (25 mg)	Days 1-21									
Dexamethasone (40 mg)	Days 1, 8, 15, 22									
	Cycles 13 on									
	Week 1			**Week 2**			**Week 3**			**Week 4**
Kyprolis (27 mg/m^2)	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
	27	27	-	-	-	-	27	27	-	-
Lenalidomide (25 mg)	Days 1-21									
Dexamethasone (40 mg)	Days 1, 8, 15, 22									

[a] The dose is calculated using the patient's baseline body surface area (BSA). Patients with a body surface area $>$ 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 $\leq$ 20%. Infusion time is 10 minutes.
[b] Appropriate dose reduction for the starting dose of lenalidomide should be considered according to the recommendations in the current lenalidomide data sheet, for example with baseline renal impairment.
[c] Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Kyprolis in combination with dexamethasone

Twice Weekly Dosing (56 mg/m^2)

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 increased to 56 mg/m^2 on day 8 of cycle 1 (see Table 3). Kyprolis 56 mg/m^2 is administered IV 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). Each 28-day period is considered one treatment cycle.

When Kyprolis is combined with dexamethasone alone, dexamethasone is administered as 20 mg orally or intravenously on days 1, 2, 8, 9, 15, 16, 22 and 23 of the 28 day cycle. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis. The 20/56 mg/m^2 dose must be administered over 30 minutes (see Table 3). Treatment may be continued until disease progression or until unacceptable toxicity occurs.

Table 3 Twice Weekly Dosing (56 mg/m^2) for Kyprolis when used in combination with dexamethasone

	Cycle 1									
	Week 1			**Week 2**			**Week 3**			**Week 4**
Kyprolis[a] (20-56 mg/m^2)	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
	20	20	-	56	56	-	56	56	-	-
Dexamethasone[b] (20 mg)	Days 1, 2, 8, 9, 15, 16, 22, 23									
	Cycle 2 and beyond									
	Week 1			**Week 2**			**Week 3**			**Week 4**
Kyprolis[a] (56 mg/m^2)	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
	56	56	-	56	56	-	56	56	-	-
Dexamethasone[b] (20 mg)	Days 1, 2, 8, 9, 15, 16, 22, 23									

[a] The dose is calculated using the patient's baseline body surface area (BSA). Patients with a body surface area $>$ 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 $\leq$ 20%. Infusion time is 30 minutes and remains consistent throughout each regimen.

[b] Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Once Weekly Dosing (70 mg/m^2)

Kyprolis is administered at a starting dose of 20 mg/m^2 in Cycle 1 on Day 1. If tolerated, the dose should be increased to 70 mg/m^2 on Day 8 of Cycle 1. Kyprolis 70 mg/m^2 is administered IV once weekly for three weeks (Days 1, 8, and 15), followed by a 13-day rest period (Days 16 to 28). Dexamethasone is administered as 40 mg orally or IV on Days 1, 8, and 15 of all cycles and on Day 22 of Cycles 1 to 9. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Table 4 Once Weekly Dosing (70 mg/m^2) for Kyprolis when used in combination with dexamethasone

	Cycle 1									
	Week 1			**Week 2**			**Week 3**			**Week 4**
Kyprolis[a] (20-70 mg/m^2)	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
	20	-	-	70	-	-	70	-	-	-
Dexamethasone[b] (40 mg)	Days 1, 8, 15, 22									

	Cycle 2 and beyond									
	Week 1			Week 2			Week 3			Week 4
Kyprolis[a] (70 mg/m^2)	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
	70	-	-	70	-	-	70	-	-	-
Dexamethasone[b] (40 mg)	Days 1, 8, 15, 22 for cycles 2-9 Days 1, 8, 15 for cycles beyond 9									

[a] The dose is calculated using the patient's baseline body surface area (BSA). Patients with a body surface area $>$ 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 $\leq$ 20%. Infusion time is 30 minutes and remains consistent throughout each regimen.

[b] Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Concomitant Medication

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

Refer to the lenalidomide and dexamethasone data sheets for other concomitant medications such as the use of anti-coagulant and antacid prophylaxis that may be required with those agents.

Hydration, Fluid and Electrolyte Monitoring

Adequate hydration is required prior to dosing in cycle 1, especially in patients at high risk of tumour 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 risk for cardiac failure [see section 4.4].

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.

Monitor serum potassium levels regularly during treatment with Kyprolis.

Recommended Dose Modifications

Modify dosing based on toxicity. Recommended actions and dose modifications are presented in Table 5. Dose level reductions are presented in Table 6.

Table 5 Dose Modifications During Kyprolis Treatment

Haematologic toxicity	**Recommended Action**
• ANC < 0.5 xx 10^9/L (see section 4.4)	• Stop dose • If recovered to ≥ 0.5 xx 10^9/L, continue at the same dose level • For subsequent drops to < 0.5 xx 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
• Febrile neutropaenia ANC < 0.5 xx 10^9/L and an oral temperature $> 38.5°C$ or two consecutive readings of $> 38.0°C$ for 2 hours	• Stop dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level.
• Platelets < 10 xx 10^9/L or evidence of bleeding with thrombocytopaenia (see section 4.4)	• Stop dose • If recovered to ≥ 10 xx 10^9/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to < 10 xx 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
Non Haematologic Toxicity (Renal)	**Recommended Action**

• Serum creatinine ≥ 2 xx baseline, or
• Creatinine clearance < 15 mL/min (or creatinine clearance decreases to $\leq 50\%$ of baseline) or need for dialysis (see section 4.4)
	• Stop 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[a]
	  • 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 haematologic Toxicity	**Recommended Action**
• All other Grade 3 or 4 non haematological toxicities (see section 4.4)	• Stop until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction[a] • If tolerated, the reduced dose may be increased to the previous dose at the discretion of the physician

ANC = absolute neutrophil count
[a] See Table 6 for dose level reductions.

Table 6 Dose Level Reductions for Kyprolis

Regimen	Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Kyprolis, Lenalidomide, and Dexamethasone	27 mg/m^2	20 mg/m^2	15 mg/m^2 [a]	—
Kyprolis plus Dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2 [a]	27 mg/m^2 [a]
	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2

Note: Infusion times remain unchanged during dose reduction(s).
[a] If symptoms do not resolve, discontinue Kyprolis treatment.

Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. Since dialysis clearance of Kyprolis concentrations has not been studied, the drug should be administered after the dialysis procedure (see section 5.2).

Hepatic Impairment

No starting dose adjustment is required in patients with mild or moderate hepatic impairment. The pharmacokinetics of Kyprolis has not been evaluated in patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and effectiveness of Kyprolis have not been established in paediatric patients.

Method of administration

Administer intravenously as a 10 minute or 30 minute infusion, depending on the Kyprolis dose regimen (see Tables 2, 3 and 4).

Kyprolis should not be administered as a bolus.

The intravenous administration line should be flushed with normal saline or glucose 5% injection immediately before and after Kyprolis administration.

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

For instructions on reconstitution of Kyprolis before administration, see section 6.6.

4.3 Contraindications

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

When Kyprolis is administered in combination with other medicinal products, refer to their data sheet before starting therapy.

4.4 Special warnings and precautions for use

When Kyprolis is administered in combination with other medicinal products, refer to their data sheet before starting therapy. When Kyprolis is used in combination with lenalidomide and dexamethasone, particular attention to the lenalidomide pregnancy prevention requirements is needed.

Cardiac Disorders

New or worsening cardiac failure (e.g., congestive cardiac failure, pulmonary oedema, decreased ejection fraction), myocardial ischaemia 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.

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 risk for cardiac failure (see section 4.2, Hydration, Fluid and Electrolyte Monitoring).

Stop Kyprolis for Grade 3 or 4 cardiac events until recovery and consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).

The risk of cardiac failure is increased in elderly patients (≥ 75 years). The risk of cardiac failure is also increased in Asian patients.

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 the clinical trials. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (particularly, blood pressure control and fluid management) prior to starting treatment with Kyprolis and remain under close follow up.

Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving Kyprolis. Some of these events have been fatal. Evaluate and stop Kyprolis until resolved, and consider whether to restart Kyprolis based

on a benefit/risk assessment (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).

Pulmonary Hypertension

Pulmonary hypertension has been reported in patients treated with Kyprolis. Some of these events have been fatal. Evaluate as appropriate. Stop Kyprolis for pulmonary hypertension until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).

Dyspnoea

Dyspnoea was commonly reported in patients treated with Kyprolis. Evaluate dyspnoea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Kyprolis for Grade 3 and 4 dyspnoea until resolved or returned to baseline, and consider whether to restart Kyprolis based on a benefit/risk assessment (see section 4.2, Recommended Dose Modifications, Tables 5 and 6; section 4.4, Cardiac Disorders; section 4.4, Pulmonary Toxicity; and section 4.8).

Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. Some of these events have been fatal. It is recommended to control hypertension prior to starting Kyprolis. All patients should be routinely evaluated for hypertension while on Kyprolis and treated as needed. If the hypertension cannot be controlled, the Kyprolis dose should be reduced. In case of hypertensive crisis, stop Kyprolis until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).

Acute Renal Failure

Cases of acute renal failure have been reported in patients who received Kyprolis. Some of these events have been fatal. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. The incidence was increased in patients with a decrease in estimated creatinine clearance, calculated using Cockcroft and Gault equation, prior to receiving Kyprolis. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or stop dose as appropriate (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).

Tumour Lysis Syndrome

Cases of tumour lysis syndrome (TLS), including fatal outcome, have been reported in patients who received Kyprolis. Patients with a high tumour 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 section 4.2). Monitor for evidence of TLS during treatment including regular measurement of serum electrolytes, and manage promptly. Interrupt Kyprolis until TLS is resolved (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).

Infusion Reactions

Infusion reactions, including life threatening reactions, have been reported in patients who received Kyprolis. Signs and symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, laryngeal oedema, 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. Dexamethasone should be administered 30 minutes to 4 hours prior to Kyprolis to reduce the incidence and severity of reactions (see section 4.2).

Haemorrhage and Thrombocytopaenia

Cases of haemorrhage (e.g. gastrointestinal, pulmonary and intracranial haemorrhage) have been reported in patients treated with Kyprolis, often associated with thrombocytopaenia. Some of these events have been fatal (see section 4.8).

Kyprolis causes thrombocytopaenia with platelet nadirs observed on day 8 or day 15 of each 28 day cycle with recovery to baseline platelet count by the start of the next cycle (see section 4.8). Monitor platelet counts frequently during treatment with Kyprolis. Reduce or stop dose as appropriate (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).

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.

Thromboprophylaxis should be considered based on an individual benefit/risk assessment.

Hepatic Toxicity

Cases of hepatic failure, including fatal cases, have been reported. Kyprolis can cause elevations of serum transaminases (see section 4.8). Monitor liver enzymes regularly, regardless of baseline values. Reduce or stop dose as appropriate (see section 4.2, Recommended Dose Modifications, Tables 5 and 6).

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopaenic purpura and haemolytic uraemic syndrome (TTP/HUS) have been reported in patients who received Kyprolis. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, Kyprolis can be restarted. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known.

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES), formerly termed reversible posterior leucoencephalopathy syndrome (RPLS), is a neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging. Cases of PRES have been reported in patients receiving Kyprolis. Discontinue Kyprolis if PRES is suspected. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known.

Hepatitis B Virus (HBV) Reactivation

Cases of Hepatitis B Virus (HBV) reactivation have been reported in patients receiving Kyprolis.

Patients should be tested for HBV infection before initiating treatment. For patients who are carriers of HBV, prophylaxis with antivirals should be considered. Carriers of HBV who require treatment with Kyprolis should be closely monitored for signs and symptoms of active HBV infection throughout and following the end of treatment. Consider consulting a specialist for patients who test positive for HBV infection prior to or during treatment.

The safety of resuming Kyprolis after HBV reactivation is adequately controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

Progressive Multifocal Leukoencephalopathy

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients treated with Kyprolis who have had prior or concurrent immunosuppressive therapy. The causal relationship with Kyprolis is unknown.

Patients should be monitored for any new or worsening neurologic, cognitive or behavioural signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders.

If PML is suspected, patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue Kyprolis if PML diagnosis is confirmed.

Increased incidence of fatal and serious adverse events in combination with melphalan and prednisone in newly diagnosed transplant ineligible multiple myeloma patients

In a clinical trial of 955 transplant-ineligible patients with newly diagnosed multiple myeloma randomised to Kyprolis (20/36 mg/m^2 by 30 minute infusion twice weekly for four weeks of each six week cycle), melphalan and prednisone (KMP) or bortezomib, melphalan and prednisone (VMP), a higher incidence of fatal adverse events (6.5% versus 4.3%), a higher incidence of serious adverse events (49.6% versus 42.1%) and a higher incidence of any grade adverse events involving cardiac failure (10.8% versus 4.3%), hypertension (24.7% versus 8.1%), acute renal failure (13.9% versus 6.2%), and dyspnoea (18.1% versus 8.5%) were observed in patients in the KMP arm compared to patients in the VMP arm. This study did not meet its primary outcome measure of superiority in PFS for the KMP arm. Kyprolis in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

Sodium content

Kyprolis contains 0.3 mmols (7 mg) of sodium per mL of reconstituted solution. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Carfilzomib is primarily metabolised 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. Carfilzomib is not expected to influence exposure of other drugs (see section 5.2, Cytochrome P450 and P-glycoprotein).

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy Category: C

There are no data on the use of Kyprolis in pregnant women.

Females and males of reproductive potential should be advised to avoid conceiving/fathering a child while being treated with Kyprolis.

Given that carfilzomib was clastogenic in the *in vitro* chromosomal aberration test in peripheral blood lymphocytes, as a precaution, females of child bearing potential treated with Kyprolis, and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with Kyprolis (see section 5.3, Carcinogenesis, Mutagenesis, and Impairment of Fertility). Male patients treated with Kyprolis 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. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the foetus. Kyprolis should only be used during pregnancy if the potential benefits to the mother outweigh the potential risks to the foetus.

It is not known if carfilzomib will reduce the efficacy of oral contraceptives.

Due to an increased risk of venous thrombosis associated with Kyprolis, patients currently using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception.

Based on its mechanism of action and findings in animals, carfilzomib can cause foetal harm when administered to a pregnant woman. 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 and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats or up to 0.8 mg/kg/day in rabbits.

Use of Kyprolis with lenalidomide

Lenalidomide (Pregnancy Risk Category X) is associated with risk of foetal harm, including severe life-threatening birth defects. Refer to the lenalidomide Product Information for additional information. When Kyprolis is used in combination with lenalidomide and dexamethasone, patients should adhere to the lenalidomide pregnancy prevention programme.

Breast-feeding

It is not known whether Kyprolis 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 breast-feeding or to discontinue Kyprolis, taking into account the potential benefit of Kyprolis to the mother.

Fertility

No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

Kyprolis has minor influence on the ability to drive and use machines.

No studies on the effects of carfilzomib on the ability to drive or use machines have been performed. Fatigue, dizziness, fainting and/or a drop in blood pressure have been observed in clinical trials. Patients being treated with Kyprolis should, therefore, be advised not to drive or operate machinery if they experience any of these symptoms.

4.8 Undesirable effects

Summary of safety profile

Serious adverse reactions that may occur during Kyprolis treatment include: cardiac failure, myocardial infarction, cardiac arrest, myocardial ischaemia, interstitial lung disease, pneumonitis, acute respiratory distress syndrome, acute respiratory failure, pulmonary hypertension, dyspnoea, hypertension including hypertensive crisis, acute kidney injury, tumour lysis syndrome, infusion related reaction, gastrointestinal haemorrhage, intracranial haemorrhage, pulmonary haemorrhage, thrombocytopaenia, hepatic failure, hepatitis B virus reactivation, PRES and thrombotic microangiopathy. The most common adverse reactions (occurring in $>$ 20% of patients) were: anaemia, thrombocytopaenia, neutropaenia, nausea, diarrhoea, fatigue, pyrexia, respiratory tract infection, dyspnoea, and cough.

Tabulated list of adverse reactions

Adverse reactions are presented in Table 7 by system organ class and frequency category. Frequency categories were determined from the crude incidence rate reported for each adverse reaction in a dataset of pooled clinical studies (N = 3,878).

Table 7 Tabulated Summary of Adverse Reactions

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1,000 to < 1/100)**	**Rare (≥ 1/10,000 to < 1/1000)**
Blood and Lymphatic System Disorders	Anaemia[b] Thrombocytopaenia[b] Neutropaenia[b] Lymphopaenia[b] Leucopaenia[b]	Febrile neutropaenia	Thrombotic microangiopathy Thrombotic thrombocytopaenic purpura	
Cardiac Disorders		Myocardial infarction[b] Cardiac failure[b] Tachycardia Palpitations Atrial fibrillation	Cardiac arrest Myocardial ischaemia Pericardial effusion Cardiomyopathy	
Ear and labyrinth disorders		Tinnitus		
Eye Disorders		Blurred vision Cataract		
Gastrointestinal Disorders	Nausea Diarrhoea Vomiting Constipation	Dyspepsia Toothache Abdominal pain[b]	Gastrointestinal haemorrhage[b] Intestinal obstruction Pancreatitis acute[a]	
General Disorders and Administration Site Conditions	Fatigue Pyrexia Oedema peripheral Asthenia	Pain Chest pain Infusion site reactions[b] Malaise Influenza-like illness Chills	Multi-organ dysfunction syndrome	
Hepatobiliary Disorders		Hyperbilirubinaemia	Cholestasis Hepatic failure	
Immune System Disorders			Drug hypersensitivity	
Infections and Infestations	Respiratory tract infection[b] Pneumonia Nasopharyngitis Bronchitis	Urinary tract infection Influenza Rhinitis Viral infection	Clostridium difficile colitis Hepatitis B Virus Reactivation[b] Septic shock	

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1000)
		Gastroenteritis Sepsis Lung infection		
Injury, Poisoning and Procedural Complications		Infusion related reaction		
Investigations	Blood creatinine increased	Alanine aminotransferase increased Aspartate aminotransferase increased Blood uric acid increased Creatinine renal clearance decreased Gamma glutamyltransferase increased C-reactive protein increased	Ejection fraction decreased	
Metabolism and Nutrition Disorders	Decreased appetite Hypokalaemia Hyperglycaemia	Hypocalcaemia Hypophosphataemia Hypomagnesaemia Hyponatraemia Hyperuricaemia Hyperkalaemia Hypercalcaemia Dehydration Hypoalbuminaemia	Tumour lysis syndrome	
Musculoskeletal and Connective Tissue Disorders	Back pain Muscle spasms Arthralgia Pain in extremity	Musculoskeletal chest pain Musculoskeletal pain Bone pain Muscular weakness Myalgia		
Nervous System Disorders	Headache Dizziness Peripheral neuropathy[b]	Paraesthesia Hypoaesthesia	Intracranial haemorrhage[b] Cerebrovascular accident PRES	
Psychiatric Disorders	Insomnia	Anxiety		
Renal and Urinary Disorders		Acute kidney injury Renal failure Renal impairment		

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1000)
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnoea Cough[b]	Epistaxis Oropharyngeal pain Wheezing Dysphonia Pulmonary embolism Pulmonary oedema Pulmonary hypertension	Pulmonary haemorrhage[b] Pneumonitis Acute respiratory distress syndrome Acute respiratory failure Interstitial lung disease	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Erythema Hyperhidrosis		
Vascular Disorders	Hypertension	Hypotension Deep vein thrombosis Flushing	Hypertensive crisis Haemorrhage	Hypertensive emergency

PRES = posterior reversible encephalopathy syndrome

[a] 'Pancreatitis acute' includes Pancreatitis and Pancreatitis acute.

[b] The following adverse drug reactions were combined:
anaemia with haematocrit decreased and haemoglobin decreased
thrombocytopaenia with platelet count decreased
neutropaenia with neutrophil count decreased
lymphopenia with lymphocyte count decreased
leucopaenia with leuocyte count decreased
cardiac failure congestive with cardiac failure
myocardial infarction' and myocardial infarction and acute myocardial infarction.
abdominal pain upper with abdominal pain
upper respiratory tract infection with respiratory tract infection, lower respiratory tract infection and viral upper respiratory tract infection.
Hepatitis B reactivation includes Acute Hepatitis B PT, Hepatitis Acute PT, Hepatitis B PT, Hepatitis B DNA Assay positive PT, Hepatitis B DNA increased PT, Hepatitis B Reactivation PT, Hepatitis Viral PT.
infusion site reaction with infusion site inflammation, infusion site pain, and infusion site erythema
peripheral neuropathy with peripheral sensory neuropathy
productive cough with cough
gastrointestinal haemorrhage with gastric haemorrhage upper gastrointestinal haemorrhage, and lower gastrointestinal haemorrhage
intracranial haemorrhage with cerebral haemorrhage, subarachnoid haemorrhage, and subdural haematoma
pulmonary haemorrhage with pulmonary alveolar haemorrhage, and haemoptysis

Description of selected adverse reactions

Cardiac failure, myocardial infarction and myocardial ischaemia

In clinical studies with Kyprolis, cardiac failure was reported in approximately 7% of subjects (< 5% of subjects had grade ≥ 3 events), myocardial infarction was reported in approximately 2% of subjects (< 1.5% of subjects had grade ≥ 3 events) and myocardial ischaemia was reported in approximately 1% of subjects (< 1% of subjects had grade ≥ 3 events). In study 2011-003, the incidence of cardiac failure events for the Kd arm was 21% (11/53) for subjects from Asian countries and 10% (40/410) for subjects from non-

Asian countries. Grade ≥ 3 cardiac failure events were reported in 11% of subjects from Asian countries and 5% of subjects from non-Asian countries. These events typically occurred early in the course of Kyprolis therapy (< 5 cycles). For clinical management of cardiac disorders during Kyprolis treatment, see section 4.4, Cardiac Disorders.

Dyspnoea

Dyspnoea was reported in approximately 30% of subjects in clinical studies with Kyprolis. The majority of dyspnoea adverse reactions were non-serious (< 5% of subjects had grade ≥ 3 events), resolved, rarely resulted in treatment discontinuation, and had an onset early in the course of study (< 3 cycles). For clinical management of dyspnoea during Kyprolis treatment, see section 4.4, Dyspnoea.

Hypertension including hypertensive crises

Hypertensive crises (hypertensive urgency or hypertensive emergency) have occurred following administration of Kyprolis. Some of these events have been fatal. In clinical studies, hypertension adverse events occurred in approximately 20% of subjects, and approximately 7% of subjects had grade ≥ 3 hypertension events, but hypertensive crises occurred in < 0.5% of subjects. The incidence of hypertension adverse events was similar between those with or without a prior medical history of hypertension. For clinical management of hypertension during Kyprolis treatment see section 4.4, Hypertension.

Thrombocytopaenia

Thrombocytopaenia was reported in approximately 34% of subjects in clinical studies with Kyprolis and approximately 20% of subjects had grade ≥ 3 events. Kyprolis causes thrombocytopaenia through inhibition of platelet budding from megacaryocytes, resulting in a classic cyclical thrombocytopaenia with platelet nadirs occurring around day 8 or 15 of each 28 day cycle, and usually associated with recovery to baseline by the start of the next cycle. For clinical management of thrombocytopaenia during Kyprolis treatment, see section 4.4, Haemorrhage and thrombocytopaenia.

Venous thromboembolic events

Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received Kyprolis (see section 4.4, Venous thrombosis). The overall incidence of venous thromboembolic events was higher in the Kyprolis arms of two phase 3 studies. In study PX-171-009 the incidence of venous thromboembolic events was 15.3% in the Kyprolis/lenalidomide/

dexamethasone (KRd) arm and 9.0% in the lenalidomide/dexamethasone (Rd) arm. Grade ≥ 3 venous thromboembolic events were reported in 5.6% of patients in the KRd arm and 3.9% of patients in the Rd arm. In study 2011-003 the incidence of venous thromboembolic events was 12.5% in the Kyprolis/dexamethasone (Kd) arm and 3.3% in the bortezomib/dexamethasone (Vd) arm. Grade ≥ 3 venous thromboembolic events were reported in 3.5% of patients in the Kd arm and 1.8% of patients in the Vd arm.

Other special populations

Geriatric population

Overall, the subject incidence of certain adverse events (including cardiac failure) in clinical trials was higher for patients who were ≥ 75 years of age compared to patients who were < 75 years of age (see section 4.4, Cardiac Disorders for additional information).

Post-Marketing Experience

The following tabulated adverse reactions have been reported during post-approval use of Kyprolis (Table 8).

Table 8 Tabulated Summary of Adverse Reactions reported during post-approval use

System Organ Class	Preferred Term	Frequency
Blood and Lymphatic System Disorders	Haemolytic Uraemic Syndrome	Rare
Cardiac Disorders	Pericarditis	Rare
Gastrointestinal Disorders	Gastrointestinal Perforation	Rare
Infections and Infestations	Cytomegalovirus Chorioretinitis	Rare
Respiratory, Thoracic and Mediastinal Disorders	Laryngeal Oedema	Rare

The maximum frequency for these adverse drug reactions can be estimated from the upper limit of 95% confidence interval for the point estimate, e.g. 3/3878 = 0.08%.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Acute onset of chills, hypotension, renal insufficiency, thrombocytopaenia, and lymphopaenia has been reported following a dose of 200 mg of Kyprolis administered in error.

There is no known specific antidote for carfilzomib overdose. In the event of an overdose, the patient should be monitored, specifically for the side effects and/or adverse drug reactions listed in section 4.8.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, ATC code: L01XX45

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that selectively and irreversibly binds to the N terminal threonine containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome, and displays little to no activity against other protease classes. Carfilzomib had antiproliferative and proapoptotic activities in preclinical models in solid and haematologic tumours. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumour growth in models of multiple myeloma, hematologic, and solid tumours. *In vitro*, carfilzomib was found to have minimal neurotoxicity and minimal reaction to non proteasomal proteases.

Pharmacodynamic effects

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 consistently induced an ($\geq$ 80%) inhibition of the CT-L activity 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 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.

Clinical efficacy and safety

Kyprolis in combination with lenalidomide and dexamethasone in multiple myeloma – study PX-171-009 (ASPIRE)

The safety and efficacy of Kyprolis were evaluated in a randomised, open label, multicentre study of 792 patients who had received 1 to 3 prior lines of therapy (median of 2), which evaluated the combination of Kyprolis with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone, randomised 1:1. Patients who had the following were excluded from the trial: creatinine clearance rates < 50 mL/min, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 4 months. 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.

Study PX-171-009 enrolled a representative relapsed multiple myeloma population; demographics, disease and other baseline characteristics were well balanced between the two arms, including age (64 years), gender (56% male), Eastern Cooperative Oncology Group (ECOG) performance status (48% with performance status 1), high-risk genetic mutations (13%, based on fluorescent in situ hybridisation (FISH) analysis), unknown-risk genetic mutations (47%, based on FISH analysis) and baseline International Staging System (ISS) stage III disease (20%).

The primary endpoint of study PX-171-009 was progression-free survival. The secondary endpoints included overall survival, overall response rate, disease control rate, duration of response, time to response, and duration of clinical benefit. The rate of clinical benefit was an exploratory endpoint. The results of this study are summarised in Table 8.

Table 8 Summary of efficacy analysis in Study PX-171-009

	KRd Combination Therapy	
	KRd Arm[a] (N = 396)	**Rd Arm[a] (N = 396)**
Progression-Free Survival 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	
Overall Survival Months, median (95% CI)	48.3 (42.4, 52.8)	40.4 (33.6, 44.4)
HR (95% CI); 1-sided p-value	0.79 (0.67, 0.95); 0.0045	
Overall Response Rate, n (%)	345 (87.1)	264 (66.7)
Stringent Complete Response	56 (14.1)	17 (4.3)
Complete Response	70 (17.7)	20 (5.1)
Very Good Partial Response	151 (38.1)	123 (31.1)
Partial Response	68 (17.2)	104 (26.3)
95% CI of Overall Response Rate	83.4, 90.3	61.8, 71.3
1-sided p-value	< 0.0001	
Duration of Response Months, median (95% CI)	28.6 (24.9, 31.3)	21.2 (16.7, 25.8)
Time to Response Months, median (min, max)[c]	1 (1, 14)	1 (1, 16)
Clinical Benefit Rate, n (%)	360 (90.9)	302 (76.3)
95% CI of Clinical Benefit Rate	87.6, 93.6	71.8, 80.4
Duration of Clinical Benefit Months, median (95% CI)	28.3 (24.3, 30.5)	20.3 (16.6, 24.0)
Disease Control Rate, n (%)	367 (92.7)	345 (87.1)
95% CI of Disease Control Rate	89.7, 95.0	83.4, 90.3

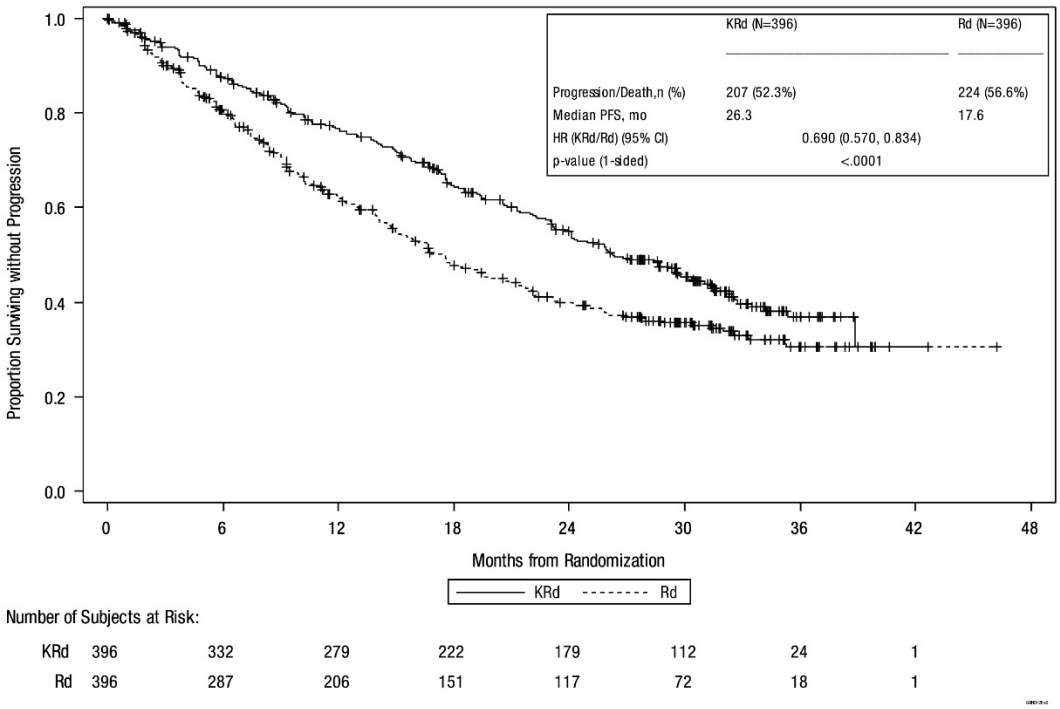
CI – confidence interval; KRd = Kyprolis/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone
[a] As determined by an Independent Review Committee using standard objective International Myeloma Working Group/European Blood and Marrow Transplantation response criteria
[b] Statistically significant
[c] This is a sample median, not a Kaplan-Meier median.

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 event as determined using standard objective International Myeloma Working Group (IMWG)/European Blood and

Marrow Transplantation (EBMT) response criteria by an Independent Review Committee (IRC).

The median PFS was 26.3 months (95% CI: 23.3, 30.5 months) in the KRd arm versus 17.6 months (95% CI: 15.0, 20.6 months) in the Rd arm, a difference of 8.7 months at the median (see Figure 1). The PFS benefit of KRd was consistently observed in all subgroups, including patients ≥ 75 years of age, patients with high risk or unknown risk genetic mutations, and patients with baseline creatinine clearance of 30 to < 50 mL/min.

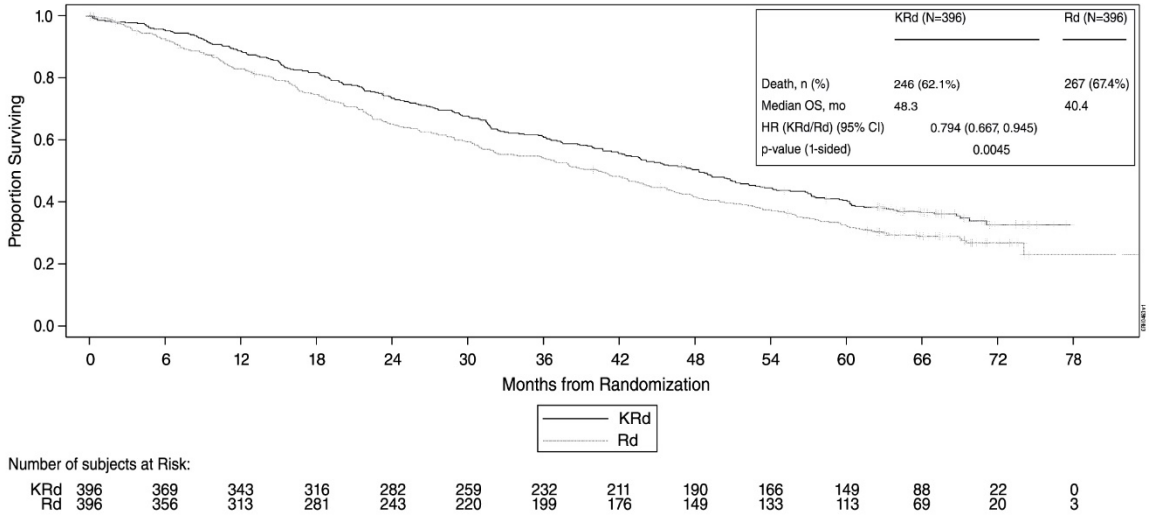
Figure 1: Kaplan-Meier Curve of Progression-Free Survival in Study PX-171-009



CI = Confidence interval; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; KRd = Kyprolis/lenalidomide/dexamethasone; mo = months; PFS = progression-free survival; Rd = lenalidomide/dexamethasone
Note: The response and PD outcomes were determined using standard objective IMWG/EBMT response criteria

A pre-planned overall survival (OS) analysis was performed after 246 deaths in the KRd arm and 267 deaths in the Rd arm. The median follow-up was approximately 67 months. A statistically significant advantage in OS was observed in patients in the KRd arm compared to patients in the Rd arm. Patients in the KRd arm had a 21% reduction in the risk of death compared with those in the Rd arm (HR = 0.79; 95% CI: 0.67, 0.95; p-value = 0.0045). The median OS improved by 7.9 months in patients in the KRd arm compared with those in the Rd arm (see Table 8 and Figure 2)

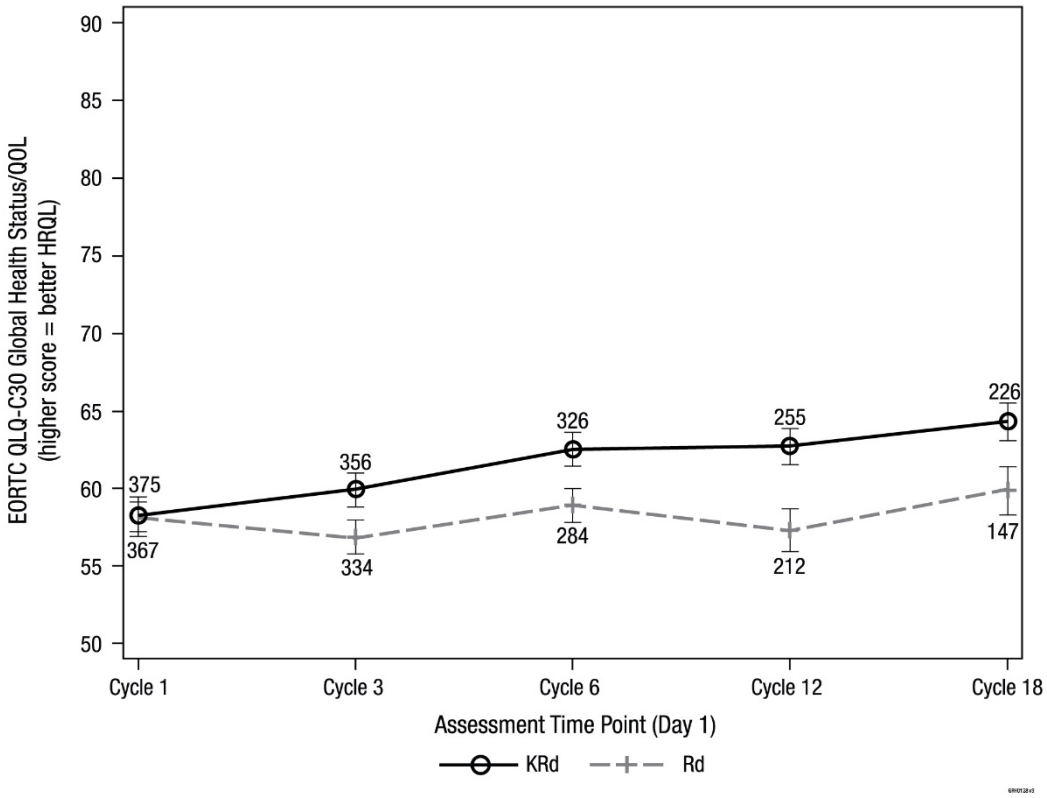
Figure 2: Kaplan Meier Curve of Overall Survival in Study PX-171-009



CI = confidence interval; HR = hazard ratio; KRd = Kyprolis/lenalidomide/dexamethasone; mo = months; OS = overall survival; Rd = lenalidomide/dexamethasone

The overall response rate (ORR) was higher in the KRd arm versus the Rd arm (87.1% versus 66.7%; 1-sided p-value < 0.0001). Rate and depth of response were increased in the KRd versus Rd arm with 31.8% CR and higher in the KRd arm (including 14.1% stringent complete response [sCR]) versus 9.3% CR and higher in the Rd arm (including 4.3% sCR). Patients treated with KRd reported improved global health status, with higher Global Health Status/Quality of Life (QoL) scores compared with Rd over 18 cycles of treatment (1-sided p-value = 0.0001) measured with the EORTC QLQ-C30, an instrument validated in multiple myeloma (see Figure 3).

Figure 3: Global QOL in Study PX-171-009



EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module; HRQL = health related quality of life; KRd = Kyprolis/lenalidomide/dexamethasone; MMRM = mixed model for repeated measures; QoL = quality of life; Rd = lenalidomide/dexamethasone
Note: a 1-sided p-value of 0.0001 for overall treatment effect was obtained based on a type 3 test for fixed effects (MMRM).

Kyprolis in Combination with Dexamethasone in multiple myeloma – Study 2011-003 (ENDEAVOR)

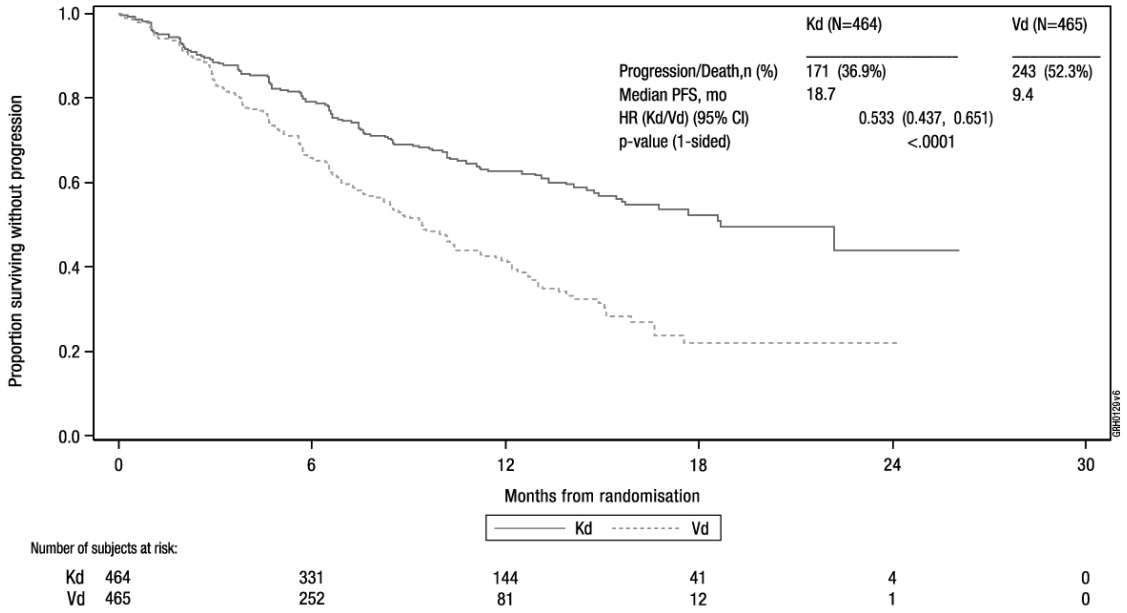
The safety and efficacy of Kyprolis 56 mg/m^2 twice weekly were evaluated in a Phase 3, randomised, open label, multicentre study of Kyprolis plus dexamethasone (Kd) versus bortezomib plus dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. A total of 929 patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy were enrolled and randomised (464 in the Kd arm; 465 in the Vd arm). Patients randomised to the Vd arm could receive bortezomib either by the intravenous (n = 108) or subcutaneous (n = 357) route. Patients who had the following were excluded from the trial: creatinine clearance rates < 15 mL/min, New York Heart Association Class III to IV congestive heart failure, myocardial infarction within the last 4 months or those with left ventricular ejection fraction (LVEF) < 40%. This study evaluated Kyprolis at an initial dose of

20 mg/m^2, which was increased to 56 mg/m^2 on day 8 of cycle 1, administered twice weekly for 3 out of 4 weeks as a 30 minute infusion until progression or unacceptable toxicity.

The study enrolled a representative relapsed multiple myeloma population; disease and other baseline characteristics were well-balanced between the two arms, including prior treatment with bortezomib (54%), prior treatment with lenalidomide (38%), age (47% < 65 years), gender (51% male), ECOG performance status (45% with performance status 1), high-risk genetic mutations consisting of genetic subtypes t(4;14) or t(14;16) in ≥ 10% of screened plasma cells or deletion of 17p in ≥ 20% of plasma cells (23%, based on FISH analysis), unknown-risk genetic mutations (9%, based on FISH analysis) and baseline ISS stage III disease (24%).

The primary endpoint of this study was PFS as determined by an Independent Review Committee (IRC) using standard objective IMWG/response criteria. The study showed significant improvement in PFS for patients in the Kd arm over those in the Vd arm (HR: 0.53, 95% CI: 0.44, 0.65 [p-value < 0.0001]), with a difference in median PFS of 9.3 months (18.7 months [95% CI: 15.6, NE] in the Kd arm versus 9.4 months [95% CI: 8.4, 10.4] in the Vd arm) (see Figure 4). Similar PFS results were observed in patients who had received prior treatment with bortezomib (HR: 0.56, 95% CI: 0.44, 0.73) and patients who had not received prior treatment with bortezomib (HR: 0.48, 95% CI: 0.36, 0.66). The PFS benefit of Kd was consistently observed in all subgroups, including patients ≥ 75 years of age (n = 143), patients with high risk (n = 210) genetic mutations, and patients with baseline creatinine clearance of 30 - < 50 mL/min (n = 128).

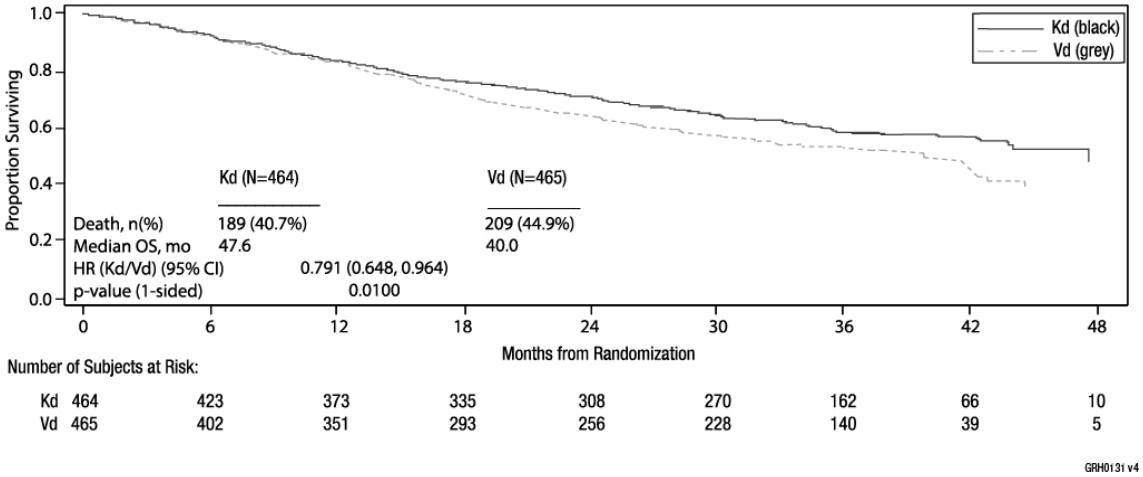
Figure 4: Kaplan Meier Plot of Progression-Free Survival as Determined by the Independent Review Committee (Intent-to-Treat Population) in Study 2011-003



HR = hazard ratio; Kd = Kyprolis/dexamethasone; mo = months; PFS = progression-free survival; Vd = bortezomib/dexamethasone

The key secondary endpoints were OS, ORR, and incidence of peripheral neuropathy events (≥ Grade 2). A pre-planned OS analysis was performed after 189 deaths in the Kd arm and 209 deaths in the Vd arm. The median follow-up was approximately 37 months. A statistically significant advantage in OS was observed in patients in the Kd arm compared to patients in the Vd arm (HR = 0.79, 95% CI: 0.65, 0.96 [p-value = 0.010]) (see Figure 5). ORR was 76.9% (95% CI: 72.8, 80.7) for patients in the Kd arm and 62.6% (95% CI: 58.0, 67.0) for patients in the Vd arm (odds ratio = 2.032, 95% CI: 1.519, 2.718), (p-value < 0.0001) (see Table 9).

Figure 5: Kaplan Meier Curve of Overall Survival in Study 2011-003



CI = confidence interval; HR = hazard ratio; Kd = Kyprolis plus dexamethasone; mo = months; OS = overall survival; Vd = bortezomib plus dexamethasone

[a] Study 2011-003

The incidence of ≥ Grade 2 peripheral neuropathy events in the Kd arm (event rate of 6.9% [95% CI: 4.6, 9.2]) was approximately 5 times lower than in the Vd arm (event rate of 34.9% [95% CI: 30.5, 39.2]) (odds ratio = 0.139; 95% CI: (0.092, 0.208); p-value < 0.0001).

Table 9 Summary of key results (intent to treat population) for Study 2011-003

	Kd Arm (N = 464)	**Vd Arm (N = 465)**
Progression-free Survival (months)[a]		
Median (95% CI)	18.7 (15.6, -)	9.4 (8.4, 10.4)
P-value (1-sided)	< 0.0001	
Hazard Ratio (Kd/Vd) (95% CI)	0.533 (0.44, 0.65)	
Overall Survival (months)		
Median (95% CI)	47.6 (42.5, -)	40.0 (32.6, 42.3)
P-value (1-sided)	0.010	
Hazard Ratio (Kd/Vd) (95% CI)	0.791 (0.65, 0.96)	
Overall Response Rate		
N with Response[b]	357	291
Overall Response Rate (95% CI)	76.9 (72.8, 80.7)	62.6 (58.0, 67.0)
P-value (1-sided)	< 0.0001	
Odds Ratio (Kd/Vd) (95% CI)	2.032 (1.519, 2.718)	
≥ Complete Response[c]		
N with ≥ Complete Response	58	29
Complete Response or Better (95% CI)	12.5 (9.6, 15.9)	6.2 (4.2, 8.8)
P-value (1-sided)	0.0005	
Odds Ratio (Kd/Vd) (95% CI)	2.140 (1.344, 3.408)	
≥ Very Good Partial Response[c]		
N with ≥ Very Good Partial Response	252	133
Very Good Partial Response or better (95% CI)	54.3 (49.7, 58.9)	28.6 (24.5, 32.9)
P-value (1-sided)	< 0.0001	
Odds Ratio (Kd/Vd) (95% CI)	3.063 (2.322, 4.040)	
Duration of Response (months)[a]		
Median (95% CI)	21.3 (21.3, -)	10.4 (9.3, 13.9)
Grade 2+ Peripheral Neuropathy Events[d]	463[e]	456[e]
n (%) with Peripheral Neuropathy	32 (6.9)	159 (34.9)
95% CI	4.6, 9.2	30.5, 39.2
P-value (1-sided)	< 0.0001	
Odds Ratio (Kd/Vd) (95% CI)	0.139 (0.092, 0.208)	

CI = confidence interval

[a] These endpoints were determined by an Independent Review Committee.
[b] Overall response is defined as achieving a response of Partial Response or above. Analysis of duration of response includes patients achieving an overall response only.
[c] The p-values presented are provided for descriptive purposes only as they are not pre-specified secondary endpoints with statistical testing.
[d] The analysis of Grade 2 or higher Peripheral Neuropathy events is based on the Safety Population, the sample size of which is listed for each arm.
[e] The safety population was used to determine peripheral neuropathy events.

Study 20140355 (A.R.R.O.W)

The safety and efficacy of Kyprolis 70 mg/m^2 once weekly were evaluated in a Phase 3, randomized open-label, multicentre study of Kd 70 mg/m^2 once weekly versus Kd 27 mg/m^2 twice weekly in patients with relapsed and refractory multiple myeloma who had received 2 to 3 prior lines of therapy. A total of 478 patients were enrolled and randomized (240 in the Kd 70 mg/m^2 arm; 238 in the Kd 27 mg/m^2 arm). This study evaluated Kyprolis at an initial dose of 20 mg/m^2, which was increased to 70 mg/m^2 on day 8 of cycle 1, administered once weekly as a 30 minute infusion until progression or unacceptable toxicity.

The study enrolled a representative relapsed multiple myeloma population; disease and other baseline characteristics were well-balanced between the two arms, including prior treatment with bortezomib (99%), prior treatment with lenalidomide (84%), age (43.5% < 65 years), gender (54% male), ECOG performance status (50.4% with performance status 1), high-risk genetic mutations consisting of genetic subtypes t(4;14) or t(14;16), or deletion of 17p (17%, based on FISH analysis), and unknown-risk genetic mutations (62%, based on FISH analysis).

The primary endpoint of this study was PFS. The key secondary endpoints were OS and ORR.

The efficacy of Kd once weekly is summarised in Table 10.

Table 10 Summary of key results by IRC (intent to treat population) for Study 20140355

	Kd 70 mg/m^2 Once Weekly Arm (N = 240)	**Kd 27 mg/m^2 Twice Weekly Arm (N = 238)**
Median (95% CI)	11.3 (8.6, 13.2)	7.6 (5.7, 8.7)
P-value (1-sided)	0.0010	
Hazard Ratio (Kd 70 mg/m^2 Once weekly/Kd 27 mg/m^2 Twice weekly) (95% CI)	0.68 (0.54, 0.87)	
N with Overall Response[b]	153	98
ORR (95% CI)	63.8 (57.3, 69.8)	41.2 (34.9, 47.7)
P-value (1-sided)	< 0.0001	
Odds Ratio (Kd 70 mg/m^2 Once weekly/Kd 27 mg/m^2 Twice weekly) (95% CI)	2.53 (1.75, 3.66)	

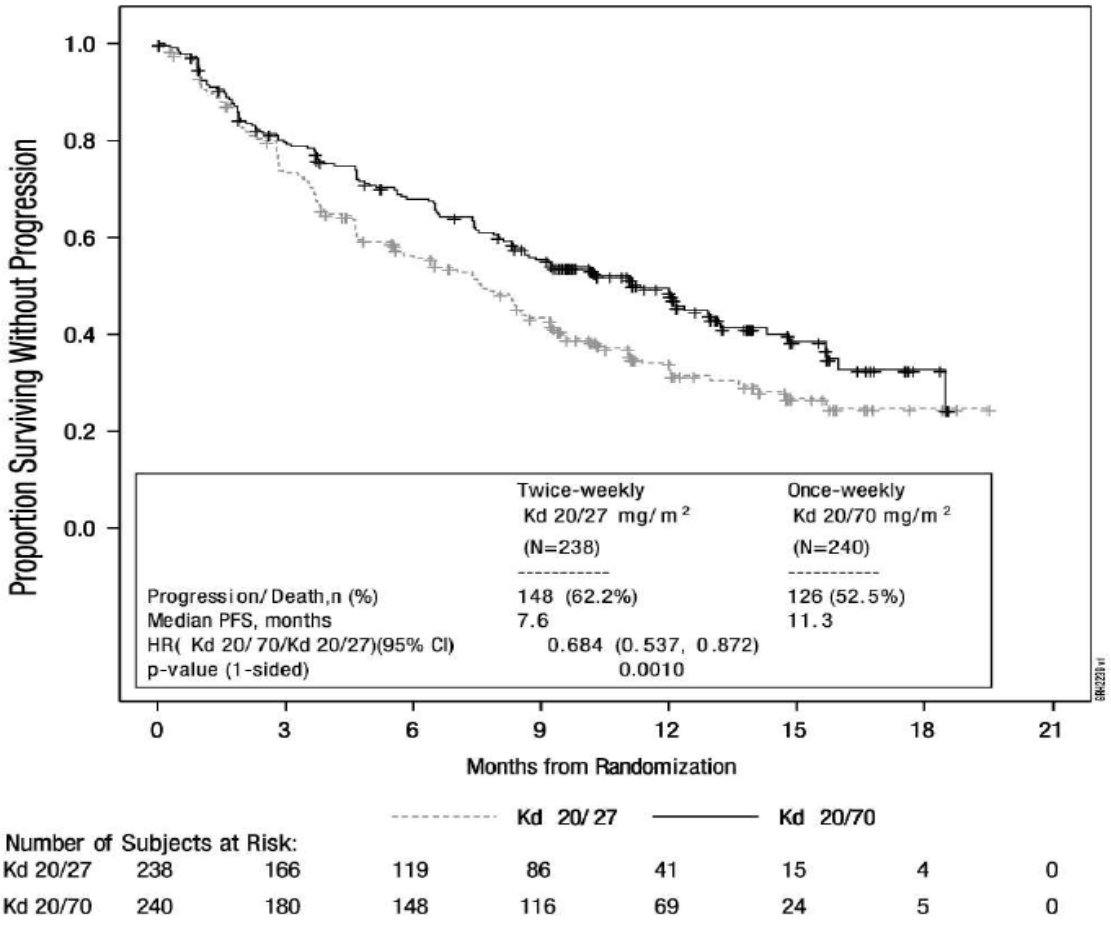
CI = confidence interval; Kd = Kyprolis/dexamethasone; ORR = overall response rate
a As determined by Independent Review Committee
b Overall response is defined as achieving a best overall response of PR, VGPR, CR or sCR or above

The study showed significantly longer duration of PFS for patients treated with Kd 70 mg/m^2 once weekly than those treated with Kd 27 mg/m^2 twice weekly (HR: 0.68, 95% CI: 0.54, 0.87 [p-value = 0.0010]), with a difference in median PFS of 3.7 months (11.3 months in the Kd 70 mg/m^2 once weekly arm versus 7.6 months in the Kd 27 mg/m^2 twice weekly arm) (see Figure 6).

ORR was 63.8% (95% CI: 57.3, 69.8) for patients in the Kd 70 mg/m^2 once weekly arm and 41.2% (95% CI: 34.9, 47.7) for patients in the Kd 27 mg/m^2 twice weekly arm (odds ratio = 2.53, 95% CI: 1.75, 3.66; p-value < 0.0001) (see Table 10).

At the time of primary analysis of PFS, the HR for OS was 0.80 (95% CI: 0.56, 1.14; 1-sided p=0.1070).

Figure 6: Kaplan-Meier Curve of Progression-Free Survival as Determined by the Independent Review Committee (Intent-to-Treat Population) in Study 20140355



CI = confidence interval; HR = hazard ratio; Kd = Kyprolis plus dexamethasone; PFS = progression-free survival

[a] Study 20140355

[b] As determined by Independent Review Committee

5.2 Pharmacokinetic properties

Absorption

At doses between 20 and 70 mg/m^2, carfilzomib administered as a 30 minute infusion resulted in dose-dependent increases in maximum plasma concentrations (C_{max}) and concentration-time curve (AUC). Following repeated administration of carfilzomib at 70 mg/m^2, systemic exposure (AUC) and half-life were similar on day 15 of cycles 1 and 2, suggesting there was no systemic carfilzomib accumulation.

A 30 minute infusion resulted in a similar half-life and AUC, but 2 to 3 fold lower C_{max} compared to that observed with a 2 to 10 minute infusion of the same dose.

Distribution

The mean steady state volume of distribution of a 20 mg/m^2 dose of carfilzomib 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 micromolar.

Biotransformation

Carfilzomib was rapidly and extensively metabolised. The predominant metabolites measured in human plasma and urine, and generated *in vitro* by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450 mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity.

Elimination

Following intravenous administration of doses $\geq$ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of $\leq$ 1 hour on day 1 of cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. Carfilzomib is eliminated primarily via metabolism with subsequent excretion in urine.

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.

Race

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

Hepatic Impairment

The pharmacokinetics of carfilzomib was studied in patients with relapsed or progressive advanced malignancies with mild or moderate chronic hepatic impairment relative to those with normal hepatic function.

No marked differences in exposures (AUC and C_{max}) were observed between patients with normal hepatic function and those with mild or moderate hepatic impairment. No starting dose adjustment is required in patients with mild or moderate baseline hepatic impairment. The pharmacokinetics of carfilzomib has not been studied in patients with severe hepatic impairment (see section 4.2, Hepatic Impairment).

Renal Impairment

The pharmacokinetics of carfilzomib was studied in relapsed multiple myeloma patients with normal renal function; mild, moderate or severe renal impairment; and patients with end stage renal disease requiring haemodialysis. Exposures of carfilzomib (AUC and C_{max}) in patients with renal impairment were similar to those with normal renal function.

No starting dose adjustment is required in patients with baseline renal impairment (see section 4.6, Renal Impairment).

Cytochrome P450

Based on *in vitro* and *in vivo* data, carfilzomib is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates. A clinical trial using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration.

P-glycoprotein

Carfilzomib is a P-glycoprotein (P-gp) substrate. However, given that carfilzomib is administered intravenously and is extensively metabolised, the pharmacokinetic profile of carfilzomib is unlikely to be affected by P-gp inhibitors or inducers.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenicity studies have not been conducted with carfilzomib.

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 and was not clastogenic in the *in vivo* mouse bone marrow micronucleus assay.

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.

Animal Toxicology and/or Pharmacology

Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (approximately 1.3 times the recommended dose in humans of 27 mg/m^2 based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin T. The repeated bolus intravenous administration of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac haemorrhage/degeneration), gastrointestinal (necrosis/haemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (haemorrhage/inflammation) systems. The dose of 2 mg/kg/dose in rats is approximately half the recommended dose in humans of 27 mg/m^2 based on body surface area. The dose of 2 mg/kg/dose in monkeys is approximately equivalent to the recommended dose in humans based on body surface area.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- sulfobutyl betadex sodium
- citric acid
- sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

Normal saline should not be used for reconstitution of carfilzomib. Reconstituted carfilzomib for injection should not be diluted into a 0.9% sodium chloride IV bag for IV administration.

6.3 Shelf life

36 months

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.

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.

6.4 Special precautions for storage

Unopened vials should be stored refrigerated (2°C to 8°C). Retain in original package to protect from light.

For storage conditions after reconstitution of the medicine, see section 6.3.

6.5 Nature and contents of container

Kyprolis 30 mg powder for infusion

- Single use 30 mL vial Type 1 clear glass vial fluoropolymer laminated elastomeric stopper and aluminum seal with plastic flip off cap
- Pack size of one vial

Kyprolis 60 mg powder for infusion

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

6.6 Special precautions for disposal and other handling

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.

Reconstitution and Preparation for Intravenous Administration

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 $\leq$ 20%.
3. Use only a 21 gauge or larger gauge needle (0.8 mm or smaller external diameter needle) to aseptically reconstitute each vial by slowly injecting 15 mL (for 30 mg vial) or 29 mL (for 60 mg vial) Sterile Water for Injection through the stopper and

directing the solution onto the INSIDE WALL OF THE VIAL to minimise foaming. Do not reconstitute Kyprolis with normal saline.

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 discolouration prior to administration. The reconstituted product should be a clear, colourless solution and should not be administered if any discoloration or particulate matter is observed.

6. Discard any unused portion left in the vial.

7. Kyprolis can be administered directly by IV infusion or optionally, administered in an IV bag. Do not administer as an IV push or bolus.

8. When administering in an IV bag, use only a 21 gauge or larger gauge 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 Glucose 5% Injection. Do not dilute Kyprolis into normal saline.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Amgen (New Zealand) Limited

Level 22, PwC Tower

15 Customs Street West

Auckland 1010

NEW ZEALAND

Telephone: 0800 443 885

Email: medinfo.JAPAC@amgen.com

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 20 December 2018

10. DATE OF REVISION OF THE TEXT

4 December 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.8	Addition of Acute Pancreatitis and relocation of some adverse reactions to 'Post-Marketing Experience' section
8	Update to the sponsor address