AUSTRALIAN PRODUCT INFORMATION – KYPROLIS® (CARFILZOMIB)

1 NAME OF THE MEDICINE

Kyprolis® is the registered trademark of Onyx Pharmaceuticals, Inc., a subsidiary of Amgen Inc., for carfilzomib.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Kyprolis (carfilzomib) is a modified tetrapeptidyl epoxide, isolated as the crystalline free base supplied as powder for injection for intravenous infusion.

Kyprolis is available as a single-use vial containing 10 mg, 30 mg or 60 mg of carfilzomib.

After reconstitution, 1 mL of solution contains 2 mg of carfilzomib.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Kyprolis is supplied as a sterile, white to off-white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Kyprolis, as part of combination therapy with dexamethasone or lenalidomide and dexamethasone, is indicated for the treatment of patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.

4.2 Dose and method of administration

Dosage (dose and interval)

Kyprolis is administered intravenously (IV) as a 10 minute or a 30 minute infusion, 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 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 ≤ 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 (Table 1). 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 Product Information, for example, with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Table 1: 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[a] (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[b] (25 mg)	Days 1-21									
dexamethasone[c] (40 mg)	Days 1, 8, 15, 22									

	Cycles 13 on									
	Week 1			**Week 2**			**Week 3**			**Week 4**
Kyprolis[a] (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[b] (25 mg)	Days 1-21									
dexamethasone[c] (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 ≤ 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 Product Information, for example with baseline renal impairment.
[c] Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Kyprolis in combination with 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 56 mg/m^2 on day 8 of cycle 1 (Table 2). The 20/56 mg/m^2 dose must be administered over 30 minutes (see Table 2). Treatment may be continued until disease progression or until unacceptable toxicity occurs.

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 cycles. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

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

	Cycle 1									
	Week 1			**Week 2**			**Week 3**			**Week 4**
Kyprolis[a]	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
(20-56 mg/m^2)	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]	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 mg/m^2)	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 ≤ 20%. Infusion time is 30 minutes.
[b] Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Concomitant medication

To decrease the risk of herpes zoster reactivation, consideration should be given to antiviral prophylaxis in patients being treated with Kyprolis. The majority of patients included in studies with Kyprolis received antiviral prophylaxis; due to this fact it is not possible to calculate the true incidence of herpes zoster infection in patients treated with Kyprolis.

Thromboprophylaxis is recommended in patients being treated with Kyprolis in combination with lenalidomide and dexamethasone, and should be based on an assessment of the patient's underlying risks and clinical status. For other concomitant medications that may be required, such as the use of antacid prophylaxis, refer to the current lenalidomide and dexamethasone Product Information.

Hydration, fluid and electrolyte monitoring

Adequate hydration is required before dose administration in cycle 1, especially in patients at high risk of tumour lysis syndrome (TLS) 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 Special warnings and precautions for use, Cardiac disorders).

Recommended hydration includes both oral fluids (30 mL/kg/day for 48 hours before day 1 of cycle 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid before 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.

Serum potassium levels should be monitored monthly, or more frequently, during treatment with Kyprolis as clinically indicated and will depend on the potassium levels measured before the start of treatment, concomitant therapy used (eg medicinal products known to increase the risk of hypokalaemia) and associated comorbidities.

Method of administration

Administer intravenously as a 10 or a 30 minute infusion. The 20/27 mg/m^2 dose is administered over 10 minutes (Table 1). The 20/56 mg/m^2 dose must be administered over 30 minutes (Table 2).

Kyprolis should not be administered as a bolus.

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

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

Reconstitution and preparation for intravenous administration

Kyprolis vials contain no antimicrobial preservatives and are for single use in one patient only. Discard any residue. Proper aseptic technique must be observed.

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 a 21G, or larger gauge, needle only to aseptically reconstitute each vial by slowly injecting Sterile Water for Injections through the stopper and directing the solution onto the **inside wall of the vial** to minimise foaming.
   - 10 mg (10 mL) vial: reconstitute with 5 mL Sterile Water for Injections
   - 30 mg (30 mL) vial: reconstitute with 15 mL Sterile Water for Injections
   - 60 mg (50 mL) vial: reconstitute with 29 mL Sterile Water for Injections
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.
   It is not necessary to protect the reconstituted product from light.
5. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration; if particulates or discolouration are observed, the contents of the container should not be used. The reconstituted product should be a clear, colourless to slightly yellow solution.
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 Kyprolis using an IV bag, use a 21G, or larger gauge, needle only to withdraw the calculated dose from the vial and dilute into a 50 or 100 mL IV bag containing 5% w/v glucose injection.
   It is not necessary to protect the diluted product from light.

Dosage adjustment

Dosing should be modified based on toxicity. The recommended actions and dose modifications are presented in Table 3. Dose level reductions are presented in Table 4.

Table 3: Dose modifications during Kyprolis treatment

Haematological toxicity	Recommended action
• Absolute neutrophil count (ANC) < 0.5 x10^9/L (see Section 4.4 Special warnings and precautions for use)	• Stop dose ○ If recovered to ≥ 0.5 x10^9/L, continue at same dose level • For subsequent drops to < 0.5 x10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
• Febrile neutropenia ANC < 0.5 x10^9/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
• Platelet count < 10 x10^9/L or evidence of bleeding with thrombocytopenia (see Section 4.4 Special warnings and precautions for use)	• Stop dose ○ If recovered to ≥ 10 x10^9/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to < 10 x10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
Non-haematological toxicity (renal)	Recommended action
• Serum creatinine ≥ 2x baseline; or • Creatinine clearance < 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis (see Section 4.4 Special warnings and precautions for use)	• 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-haematological toxicity	Recommended action
• All other grade 3 or 4 non-haematological toxicities (see Section 4.4 Special warnings and precautions for use)	• 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

[a] see Table 4 for dose level reductions

Table 4: Dose level reductions for Kyprolis

Regimen	Kyprolis Dose	1st Kyprolis dose reduction	2nd Kyprolis dose reduction	3rd Kyprolis dose reduction
Kyprolis, lenalidomide, and dexamethasone	27 mg/m^2	20 mg/m^2	15 mg/m^2 [a]	-
Kyprolis and dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2 [a]

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

Patients with renal impairment

Patients with moderate or severe renal impairment were excluded from Kyprolis-lenalidomide combination studies.

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 Pharmacokinetic properties, Special populations). In phase 3 clinical studies the incidence of adverse events of acute renal failure was higher in subjects with lower baseline creatinine clearance than that among subjects with higher baseline creatinine clearance.

Renal function should be monitored at least monthly or in accordance with accepted clinical practice guidelines, particularly in patients with lower baseline creatinine clearance.

Patients with hepatic impairment

No starting dose adjustment is required in patients with mild or moderate hepatic impairment. The pharmacokinetics of Kyprolis have not been evaluated in patients with severe hepatic impairment (see Section 5.2 Pharmacokinetic properties, Special populations). Liver enzymes and bilirubin should be monitored at treatment initiation and monthly during treatment with Kyprolis, regardless of baseline values.

4.3 Contraindications

Kyprolis is contraindicated in patients with hypersensitivity to the active substance or any of the excipients (see Section 6.1 List of excipients).

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

4.4 Special warnings and precautions for use

When Kyprolis is administered in combination with other medicinal products, refer to their Product Information 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 (eg congestive cardiac heart 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 (see Section 4.8 Adverse effects (Undesirable effects), Cardiac failure, myocardial infarction and myocardial ischaemia).

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 Section 4.2 Dose and method of administration, Hydration, fluid and electrolyte monitoring).

Kyprolis should be stopped following Grade 3 or 4 cardiac events until recovery. Consideration should be given to reducing the dose of Kyprolis by 1 dose level when recommencing Kyprolis, based on an assessment of the benefit/risk (see Section 4.2 Dose and method of administration, Dosage adjustment, Table 3 and 4).

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, and angina or arrhythmias uncontrolled by medications were not eligible for the clinical trials. As these patients may be at greater risk for cardiac complications, a comprehensive medical assessment (particularly blood pressure control and fluid management) should be conducted prior to starting treatment with Kyprolis. These patients should 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. Pulmonary toxicity should be evaluated and Kyprolis should be stopped until resolved. Consideration on whether to restart Kyprolis should be based on a benefit/risk assessment (see Section 4.2 Dose and method of administration, Dosage adjustment, Table 3 and 4).

Pulmonary hypertension

Pulmonary hypertension has been reported in patients treated with Kyprolis. Some of these events have been fatal. Pulmonary hypertension should be evaluated as appropriate. Kyprolis should be stopped 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 Dose and method of administration, Dosage adjustment, Table 3 and 4).

Dyspnoea

Dyspnoea was commonly reported in patients treated with Kyprolis. Dyspnoea should be evaluated to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Kyprolis should be stopped 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 Dose and method of administration, Dosage adjustment, Table 3 and 4 and Section 4.8 Adverse effects (Undesirable effects), Dyspnoea).

Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. Some of these events have been fatal (see Section 4.8 Adverse effects (Undesirable effects), Hypertension including hypertensive crises). It is recommended to control hypertension prior to starting Kyprolis. All patients should be routinely evaluated for hypertension whilst on Kyprolis, and treated as needed. If the hypertension cannot be controlled, the Kyprolis dose should be reduced. In case of hypertensive crises, Kyprolis should be stopped until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment (see Section 4.2 Dose and method of administration, Dosage adjustment, Table 3 and 4).

Acute renal failure

Cases of acute renal failure have been reported in patients administered 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. In phase 3 clinical studies the incidence of adverse events of acute renal failure was higher in subjects with lower baseline creatinine clearance than that among subjects with higher baseline creatinine clearance. Creatinine clearance was stable over time for the majority of patients. Renal function should be monitored at least monthly or in accordance with accepted clinical practice guidelines, particularly in patients with lower baseline creatinine clearance, and the dose reduced or stopped as appropriate (see Section 4.2 Dose and method of administration, Dosage adjustment, Table 3 and 4).

Tumour lysis syndrome

Tumour lysis syndrome (TLS) has been reported with Kyprolis use, including some fatal cases. Patients with a high tumour burden should be considered to be at greater risk for TLS. Patients should be well hydrated before administration of Kyprolis in cycle 1, and in subsequent cycles as needed (see Section 4.2 Dose and method of administration, Hydration, fluid and electrolyte monitoring). Uric acid lowering drugs should be considered in patients at high risk for TLS. Evidence of TLS during treatment should be monitored, including regular measurement of serum electrolytes, and managed promptly. Kyprolis should be stopped until TLS is resolved (see Section 4.2 Dose and method of administration, Dosage adjustment, Table 3 and 4).

Infusion reactions

Infusion reactions, including life-threatening reactions, have been reported in patients administered Kyprolis (see Section 4.8 Adverse effects (Undesirable effects), Table 6). Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial 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 Dose and method of administration).

Haemorrhage and thrombocytopenia

There have been cases of haemorrhage (eg gastrointestinal, pulmonary and intracranial haemorrhage) reported in patients treated with Kyprolis, often associated with thrombocytopenia. Some of these events have been fatal (see Section 4.8 Adverse effects (Undesirable effects), Thrombocytopenia).

Kyprolis causes thrombocytopenia with platelet nadirs observed on day 8 or day 15 of each 28 day cycle. Platelet counts recovered to baseline levels by the start of the next cycle. Platelet counts should be monitored frequently during treatment with Kyprolis and the dose reduced or stopped as appropriate (see Section 4.2 Dose and method of administration, Dosage adjustment, Table 3 and 4).

Venous thrombosis

There have been cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, reported in patients who received Kyprolis (see Section 4.8 Adverse effects (Undesirable effects), Venous thromboembolic events).

Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (eg

smoking, hypertension and hyperlipidaemia). Caution should be used in the concomitant administration of other agents that may increase the risk of thrombosis (eg erythropoietic agents or hormone replacement therapy). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, haemoptysis, arm or leg swelling or pain.

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

Hepatic toxicity

There have been cases of hepatic failure, including fatal cases, reported in patients administered Kyprolis. Since Kyprolis can cause elevations of serum transaminases, liver enzymes should be monitored regularly, regardless of baseline values, and the dose reduced or stopped as appropriate (see Section 4.2 Dose and method of administration, Dosage adjustment, Table 3 and 4).

Thrombotic microangiopathy

There have been cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) reported in patients who received Kyprolis. Some of these events have been fatal. Patients receiving Kyprolis should be monitored 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 reinitiated. The safety of reinitiating Kyprolis therapy in patients previously experiencing TTP/HUS is not known.

Posterior reversible encephalopathy syndrome

There have been cases of posterior reversible encephalopathy syndrome (PRES) reported in patients receiving Kyprolis. PRES, formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a rare 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. Kyprolis should be discontinued if PRES is suspected. The safety of reinitiating Kyprolis therapy in patients previously experiencing PRES is not known.

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.

Cardiac impairment

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

Use in the elderly

Overall, the subject incidence of certain adverse events (including cardiac failure, see Section 4.4 Special warnings and precautions for use, Cardiac disorders) in clinical trials was higher for patients who were ≥ 75 years of age compared to patients who were < 75 years of age.

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

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.

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.

Carfilzomib is a P-glycoprotein (P-gp) substrate, and inhibited organic anion transport protein OATP1B1 in vitro. However, given that Kyprolis is administrated intravenously and is rapidly and extensively metabolised, pharmacokinetic interaction with P-gp inhibitors or inducers, or OATP1B1substrates is unlikely.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28 day repeat dose toxicity studies conducted in rats and monkeys, or in chronic toxicity studies conducted in rats for 6 months and for 9 months in monkeys.

Use in pregnancy

Pregnancy Category: C

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

Female patients of child bearing potential (and/or their partners) must use effective contraception measures during and for one month following treatment.

Male patients must use effective contraception measures during and for 3 months following treatment if their partner is pregnant or of childbearing potential and not using effective contraception.

If Kyprolis is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be informed of the potential hazard to the fetus.

It is not known if the efficacy of oral contraceptives may be reduced during Kyprolis treatment. In addition, due to an increased risk of venous thrombosis associated with Kyprolis, patients currently using oral contraceptives or a hormonal method of contraception that is associated with a risk of thrombosis should consider an alternative method of effective contraception.

Based on its mechanism of action and findings in animals, Kyprolis can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Carfilzomib administered during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. The doses of 2 mg/kg/day in rats and 0.8 mg/kg/day in rabbits are approximately 20%, respectively, of the recommended dose in humans of 56 mg/m^2 based on body surface area.

Use of Kyprolis with lenalidomide

Lenalidomide (Pregnancy Category: X) is associated with risk of fetal 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.

Use in lactation

It is unknown whether carfilzomib or its metabolites are excreted in human milk. Kyprolis should not be administered to women who are breastfeeding. As the risk to newborns or infants cannot be excluded, either breastfeeding should be discontinued, or treatment with Kyprolis should be discontinued or withheld, with consideration given to the benefit of breastfeeding for the child and the benefit of therapy to the mother.

4.7 Effects on 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 Adverse effects (Undesirable effects)

Adverse events

Results from Study PX-171-009 (ASPIRE) and Study 2011-003 (ENDEAVOR)

The following table (Table 5) describes the overall incidence of adverse events from study PX-171-009 (ASPIRE), in 392 patients with relapsed multiple myeloma who received Kyprolis in combination with lenalidomide and dexamethasone, and 2011-003 (ENDEAVOR), in 464 patients with relapsed multiple myeloma who received Kyprolis in combination with dexamethasone. Adverse events are shown in decreasing frequency of events reported in patients receiving Kyprolis in the 2011-003 study.

Table 5: Adverse events reported in ≥10% of patients treated with Kyprolis in Studies PX-171-009 and 2011-003

	PX-171-009		2011-003	
Preferred Term	**Rd (n = 389) n (%)**	**KRd (n = 392) n (%)**	**Vd (n = 456) n (%)**	**Kd (n = 463) n (%)**
Number of subjects reporting AEs	380 (97.7)	380 (96.9)	451 (98.9)	457 (98.7)
Anaemia	155 (39.8)	169 (43.1)	129 (28.3)	197 (42.5)
Diarrhoea	131 (33.7)	166 (42.3)	185 (40.6)	168 (36.3)
Pyrexia	81 (20.8)	112 (28.6)	70 (15.4)	150 (32.4)
Fatigue	120 (30.8)	129 (32.9)	140 (30.7)	149 (32.2)
Dyspnoea	58 (14.9)	77 (19.6)	62 (13.6)	149 (32.2)
Hypertension	29 (7.5)	57 (14.5)	45 (9.9)	149 (32.2)

Preferred Term	PX-171-009		2011-003	
	Rd (n = 389) n (%)	**KRd (n = 392) n (%)**	**Vd (n = 456) n (%)**	**Kd (n = 463) n (%)**
Cough	69 (17.7)	113 (28.8)	72 (15.8)	128 (27.6)
Insomnia	64 (16.5)	77 (19.6)	122 (26.8)	125 (27.0)
Upper respiratory tract infection	76 (19.5)	112 (28.6)	83 (18.2)	119 (25.7)
Oedema peripheral	75 (19.3)	85 (21.7)	87 (19.1)	116 (25.1)
Nausea	55 (14.1)	78 (19.9)	91 (20.0)	109 (23.5)
Bronchitis	54 (13.9)	74 (18.9)	48 (10.5)	108 (23.3)
Asthenia	56 (14.4)	73 (18.6)	79 (17.3)	107 (23.1)
Back pain	80 (20.6)	69 (17.6)	81 (17.8)	107 (23.1)
Thrombocytopenia	89 (22.9)	115 (29.3)	84 (18.4)	100 (21.6)
Headache	31 (8.0)	53 (13.5)	49 (10.7)	95 (20.5)
Muscle spasms	82 (21.1)	104 (26.5)	28 (6.1)	92 (19.9)
Nasopharyngitis	63 (16.2)	84 (21.4)	61 (13.4)	81 (17.5)
Vomiting	32 (8.2)	47 (12.0)	45 (9.9)	77 (16.6)
Constipation	67 (17.2)	79 (20.2)	127 (27.9)	75 (16.2)
Hypokalaemia	52 (13.4)	108 (27.6)	51 (11.2)	60 (13.0)
Arthralgia	51 (13.1)	49 (12.5)	52 (11.4)	60 (13.0)
Bone pain	36 (9.3)	40 (10.2)	40 (8.8)	55 (11.9)
Pain in extremity	41 (10.5)	46 (11.7)	50 (11.0)	55 (11.9)
Hyperglycaemia	38 (9.8)	49 (12.5)	42 (9.2)	54 (11.7)
Blood creatinine increased	18 (4.6)	26 (6.6)	28 (6.1)	53 (11.4)
Pneumonia	56 (14.4)	68 (17.3)	53 (11.6)	53 (11.4)
Respiratory tract infection	39 (10.0)	43 (11.0)	32 (7.0)	51 (11.0)
Decreased appetite	35 (9.0)	44 (11.2)	62 (13.6)	50 (10.8)
Neuropathy peripheral	27 (6.9)	29 (7.4)	130 (28.5)	49 (10.6)
Dizziness	44 (11.3)	48 (12.2)	70 (15.4)	42 (9.1)

Preferred Term	PX-171-009		2011-003	
	Rd (n = 389) n (%)	**KRd (n = 392) n (%)**	**Vd (n = 456) n (%)**	**Kd (n = 463) n (%)**
Rash	60 (15.4)	52 (13.3)	35 (7.7)	41 (8.9)
Hypophosphataemia	29 (7.5)	52 (13.3)	28 (6.1)	32 (6.9)
Neutropenia	131 (33.7)	148 (37.8)	26 (5.7)	28 (6.0)
Hypocalcaemia	46 (11.8)	63 (16.1)	19 (4.2)	27 (5.8)

AE = adverse event; Kd = carfilzomib plus dexamethasone; KRd = carfilzomib, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone; Vd = bortezomib plus dexamethasone.

Adverse reactions

Serious adverse reactions that may occur during Kyprolis treatment include: cardiac failure, myocardial infarction, cardiac arrest, myocardial ischaemia, interstitial lung disease, pneumonitis, ARDS, acute respiratory failure, pulmonary hypertension, dyspnoea, hypertension including hypertensive crises, acute renal failure, tumour lysis syndrome, infusion reactions, gastrointestinal haemorrhage, intracranial haemorrhage, pulmonary haemorrhage, thrombocytopenia, hepatic failure, PRES, thrombotic microangiopathy and TTP/HUS. In clinical studies with Kyprolis, cardiac toxicity and dyspnoea typically occurred early in the course of Kyprolis therapy. The most common adverse reactions (occurring in > 20% of subjects) were: anaemia, fatigue, diarrhoea, thrombocytopenia, nausea, pyrexia, dyspnoea, respiratory tract infection, cough and neutropenia.

Adverse reactions are presented below by system organ class and frequency category (Table 6). Frequency categories were determined from the crude incidence rate reported for each adverse reaction from a dataset of pooled clinical studies (n = 2944). Within each system organ class and frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 6: Tabulated summary of adverse reactions

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10000 to < 1/1000)
Infections and infestations	Pneumonia Respiratory tract infection	Sepsis Lung infection Influenza Urinary tract infection Bronchitis Gastroenteritis Viral infection Nasopharyngitis Rhinitis		
Immune system disorders			Drug hypersensitivity	
Blood and lymphatic system disorders	Thrombocytopenia Neutropenia Anaemia Lymphopenia Leukopenia	Febrile neutropenia	HUS	TTP Thrombotic microangiopathy
Metabolism and nutrition disorders	Hypokalaemia Hyperglycaemia Decreased appetite	Dehydration Hyperkalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia Hypocalcaemia Hypophosphataemia Hyperuricaemia Hypoalbuminaemia	Tumour lysis syndrome	
Psychiatric disorders	Insomnia	Anxiety		
Nervous system disorders	Dizziness Peripheral neuropathy Headache	Paraesthesia Hypoaesthesia	Intracranial haemorrhage Cerebrovascular accident	PRES
Eye disorders		Cataract Blurred vision		
Cardiac disorders		Cardiac failure Atrial fibrillation Tachycardia Decreased ejection fraction Palpitations	Cardiac arrest Myocardial infarction Myocardial ischaemia Pericarditis Pericardial effusion	
Vascular disorders	Hypertension	Deep vein thrombosis Hypotension Flushing	Hypertensive crisis Haemorrhage	Hypertensive emergency

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)	Rare (≥ 1/10000 to < 1/1000)
Respiratory, thoracic, and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Pulmonary oedema Epistaxis Oropharyngeal pain Dysphonia Wheezing Pulmonary hypertension	ARDS Acute respiratory failure Pulmonary haemorrhage Interstitial lung disease Pneumonitis	
Gastro intestinal disorders	Vomiting Diarrhoea Constipation Abdominal pain Nausea	Gastrointestinal haemorrhage Dyspepsia Toothache	Gastrointestinal perforation	
Hepatobiliary disorders		Increased alanine aminotransferase Increased aspartate aminotransferase Increased gamma-glutamyltransferase Hyperbilirubinaemia	Hepatic failure Cholestasis	
Skin and subcutaneous tissue disorders		Rash Pruritus Erythema Hyperhidrosis		
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Pain in extremity Muscle spasms	Musculoskeletal pain Musculoskeletal chest pain Bone pain Myalgia Muscular weakness		
Renal and urinary disorders	Increased blood creatinine	Acute kidney injury Renal failure Renal impairment Decreased creatinine renal clearance		
General disorders and administration site conditions	Pyrexia Peripheral oedema Asthenia Fatigue Chills	Chest pain Pain Infusion site reactions Influenza-like illness Malaise	Multi-organ dysfunction syndrome	
Investigations		Increased c-reactive protein Increased blood uric acid		
Injury, Poisoning and Procedural Complications		Infusion related reaction		

PRES = posterior reversible encephalopathy syndrome; HUS = haemolytic uraemic syndrome; TTP = thrombotic thrombocytopenic purpura; ARDS = Acute respiratory distress syndrome

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 Special warnings and precautions for use, 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 Special warnings and precautions for use, 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 Special warnings and precautions for use, Hypertension.

Thrombocytopenia

Thrombocytopenia was reported in approximately 34% of subjects in clinical studies with Kyprolis and approximately 20% of subjects had grade ≥ 3 events. Kyprolis causes thrombocytopenia through inhibition of platelet budding from megakaryocytes resulting in a classic cyclical thrombocytopenia 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 thrombocytopenia during Kyprolis treatment, see Section 4.4 Special warnings and precautions for use, Haemorrhage and thrombocytopenia.

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 Special warnings and precautions for use, 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 KRd arm and 9.0% in the 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 Kd arm and 3.3% in the 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.

Post-marketing experience

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 Overdose

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia and lymphopenia have been reported following administration of 200 mg Kyprolis 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 (see Section 4.8 Adverse effects (Undesirable effects)).

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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 haematological tumours. In animals, carfilzomib inhibited

proteasome activity in blood and tissue and delayed tumour growth in models of non-Hodgkin's lymphoma and colorectal adenocarcinoma.

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 ≥ 15 mg/m^2 consistently induced an (≥ 80%) inhibition of the CT-L activity of the proteasome. In addition, administration of 20 mg/m^2 carfilzomib 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 ≥ 48 hours following the first dose of carfilzomib for each week of dosing. Combination dosing with lenalidomide and dexamethasone did not affect the pharmacodynamics (proteasome activity) of carfilzomib in subjects.

Clinical trials

Study PX-171-009 (ASPIRE)

The safety and efficacy of Kyprolis were evaluated in a phase 3, randomised, open-label, multicentre 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 (25 mg) and dexamethasone (40 mg) 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.

The demographics and baseline characteristics for study PX-171-009 were well-balanced between the two arms. The study enrolled a representative relapsed multiple myeloma population; 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 FISH analysis), unknown-risk genetic mutations (47%, based on FISH analysis) and baseline ISS stage III disease (20%).

The primary endpoint of this study was progression free survival (PFS). The secondary endpoints included overall survival (OS), overall response rate (ORR), disease control rate

(DCR), duration of response (DOR), time to response (TTR) and duration of clinical benefit (DCB). The rate of clinical benefit (CBR) was an exploratory endpoint.

The results of study PX-171-009 are summarised in Table 7.

Table 7: Summary of efficacy analysis in Study PX-171-009

	KRd combination therapy	
	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); 1 sided p-value[c]	0.79 (0.63, 0.99); 0.0182	-
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)
95% CI of ORR	83.4, 90.3	61.8, 71.3
1 sided p-value[c]	< 0.0001	-
DOR months, median (95% CI)	28.6 (24.9, 31.3)	21.2 (16.7, 25.8)
TTR months, median (min, max)[d]	1 (1, 14)	1 (1, 16)
CBR n (%)	360 (90.9)	302 (76.3)
95% CI of CBR	87.6, 93.6	71.8, 80.4
DCB months, median (95% CI)	28.3 (24.3, 30.5)	20.3 (16.6, 24.0)
DCR n (%)	367 (92.7)	345 (87.1)
95% CI of DCR[c]	89.7, 95.0	83.4, 90.3

CI = confidence interval; CBR = clinical benefit rate; CR = complete response; DCB = duration of clinical benefit; DCR = disease control rate; DOR = duration of response; EBMT = European blood and marrow transplantation; HR = hazard ratio; IMWG = international myeloma working group; KRd = Kyprolis, lenalidomide and dexamethasone; NE = not estimable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; Rd = lenalidomide and dexamethasone; sCR = stringent complete response; TTR = time to response; VGPR = very good partial response

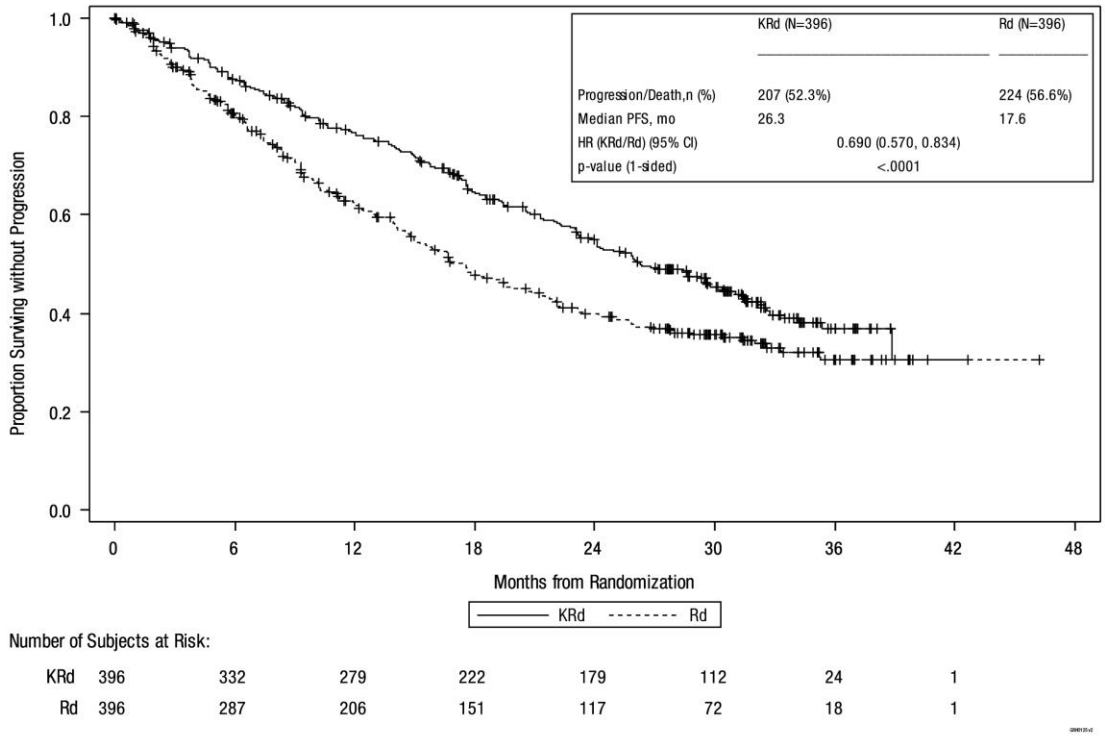
[a] As determined by an Independent Review Committee using standard objective IMWG/EBMT response criteria
[b] Statistically significant
[c] The interim OS analysis did not meet the protocol-specified early stopping boundary for OS (p = 0.0051); hence, due to the hierarchical nature of the study design all subsequent p-values are provided for descriptive purposes only
[d] Sample median

Patients in the Kyprolis, lenalidomide, and dexamethasone (KRd) arm demonstrated improved PFS compared with those in the lenalidomide and dexamethasone (Rd) arm (HR = 0.69, 1 sided p-value < 0.0001; see Figure 1). This represents a 45% improvement

in PFS or a 31% reduction in the risk of PFS 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 (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.

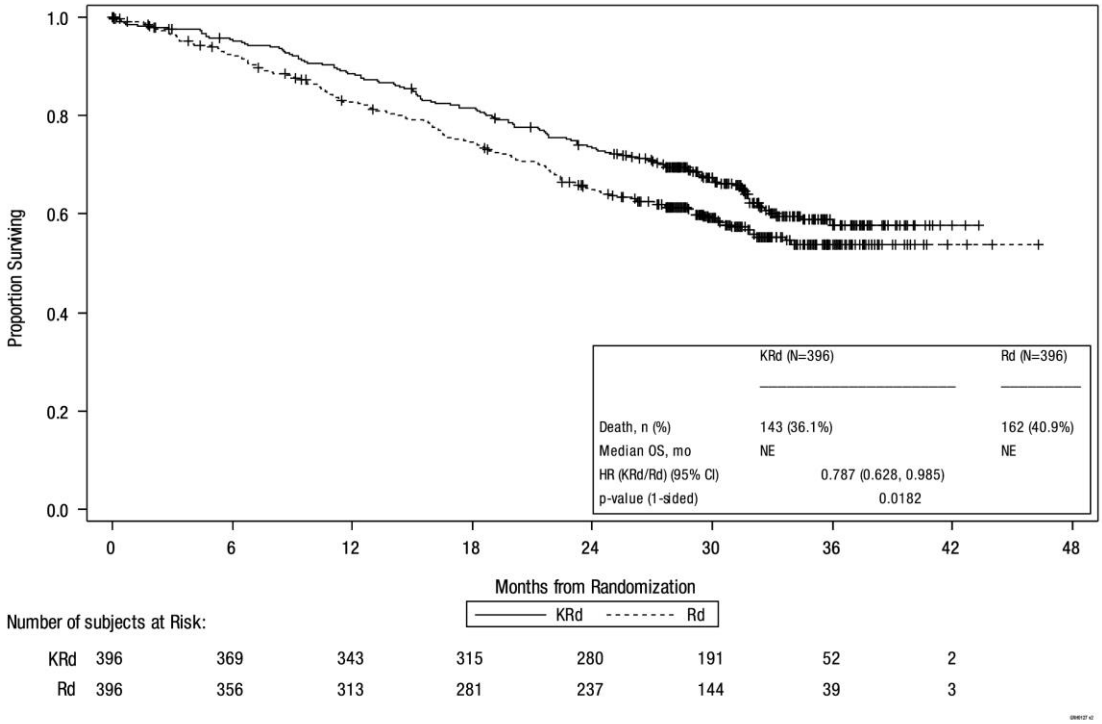
Figure 1: Kaplan-Meier curve of progression-free survival in Study PX-171-009



CI = confidence interval; EBMT = European blood and marrow transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; KRd = Kyprolis, lenalidomide and dexamethasone; PFS = progression-free survival; Rd = lenalidomide, dexamethasone
Note: The response and Progressive Disease outcomes were determined using standard objective IMWG/EBMT response criteria.

Patients in the KRd arm had a 21% reduction in the risk of death compared with those in the Rd arm (HR = 0.79, 1 sided p-value = 0.0182; Figure 2). The result did not cross the pre-specified early stopping boundary for the interim analysis of overall survival (1 sided p-value = 0.0051). The Kaplan-Meier event-free rate at 24 months was 73.3% (95% CI: 68.6%, 77.5%) in the KRd arm and 65.0% (95% CI: 59.9%, 69.5%) in the Rd arm.

Figure 2: Kaplan-Meier curve of interim overall survival in Study PX-171-009



CI = confidence interval; HR = hazard ratio; KRd = Kyprolis, lenalidomide and dexamethasone; NE = not estimable; OS = overall survival; Rd = lenalidomide and dexamethasone
Note: The interim OS analysis did not meet the protocol-specified early stopping boundary for OS (p = 0.0051).

The ORR was higher in the KRd 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% complete response (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).

Study 2011-003 (ENDEAVOR)

The safety and efficacy of Kyprolis were evaluated in a phase 3, randomised, open-label, multicentre study of Kyprolis plus dexamethasone (Kd) versus bortezomib plus dexamethasone (Vd). 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 IRC using standard objective IMWG/response criteria. The key secondary endpoints were OS, ORR, and incidence of peripheral neuropathy events (≥ grade 2).

The results of study 2011-003 are summarised in Table 8.

Table 8: Summary of key results by IRC (intent-to-treat population) Study 2011-003

	Kd Arm (n = 464)	Vd Arm (n = 465)
PFS (months)[a] median (95% CI)	18.7 (15.6, -)	9.4 (8.4, 10.4)
1 sided p-value	< 0.0001	
HR (Kd/Vd) (95% CI)	0.533 (0.44, 0.65)	
OS (months) median (95% CI)	47.6 (42.5, -)	40.0 (32.6, 42.3)
HR (Kd/Vd) (95% CI)	0.791 (0.65, 0.96)	
1 sided p-value	0.010	
ORR[a] N[b]	357	291
ORR (95% CI)	76.9 (72.8, 80.7)	62.6 (58.0, 67.0)
1 sided p-value	< 0.0001	
Odds ratio (Kd/Vd) (95% CI)	2.032 (1.519, 2.718)	
≥ CR[c] N	58	29
CR or better (95% CI)	12.5 (9.6, 15.9)	6.2 (4.2, 8.8)
1 sided p-value	0.0005	
Odds ratio (Kd/Vd) (95% CI)	2.140 (1.344, 3.408)	
≥ VGPR[c] N	252	133
VGPR or better (95% CI)	54.3 (49.7, 58.9)	28.6 (24.5, 32.9)
1 sided p-value	<0.0001	
Odds ratio (Kd/Vd) (95% CI)	3.063 (2.322, 4.040)	
DOR (months)[a], median (95% CI)[a]	21.3 (21.3, -)	10.4 (9.3, 13.9)
Grade 2+ peripheral neuropathy events[d]	463[e]	456[e]
N (%) with PN	32 (6.9)	159 (34.9)
95% CI	4.6, 9.2	30.5, 39.2
1 sided p-value	< 0.0001	
Odds Ratio (Kd/Vd) (95% CI)	0.139 (0.092, 0.208)	

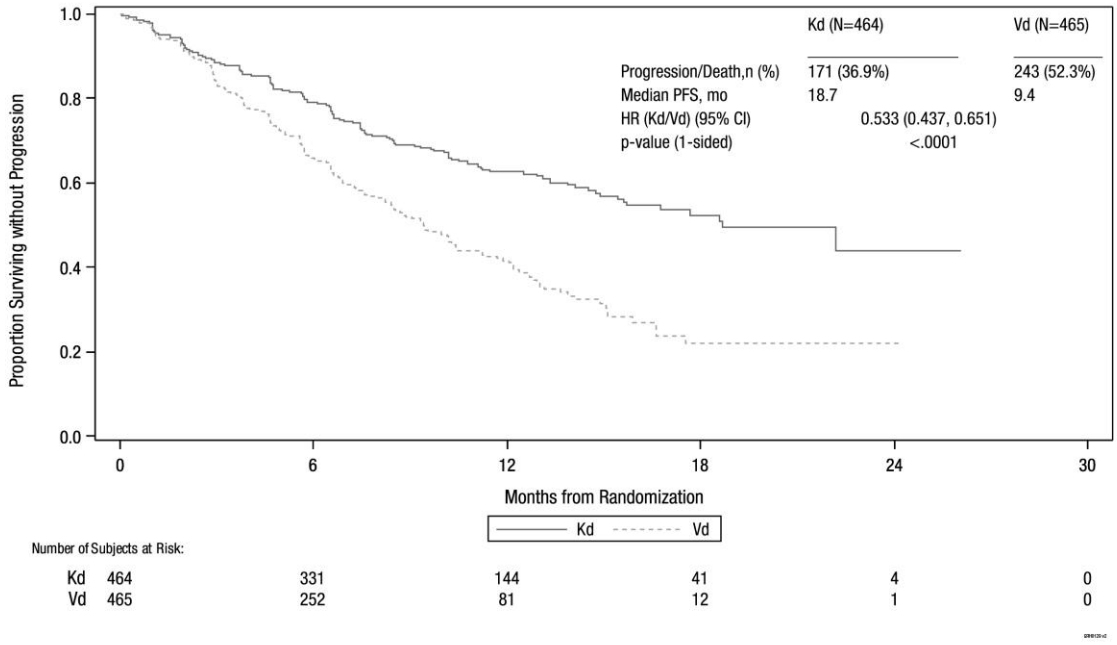
CI = confidence interval; CR = complete response; DOR = duration of response; Kd = Kyprolis plus dexamethasone; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PN = peripheral neuropathy; Vd = bortezomib and dexamethasone; VGPR = very good partial response

[a] These endpoints were determined by an Independent Review Committee.
[b] Overall response is defined as achieving a response of PR 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] Analysis of Grade 2 or higher PN events is based on safety population, the sample size of which is listed for each arm.
[e] The safety population was used to determine peripheral neuropathy events.

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 3). 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).

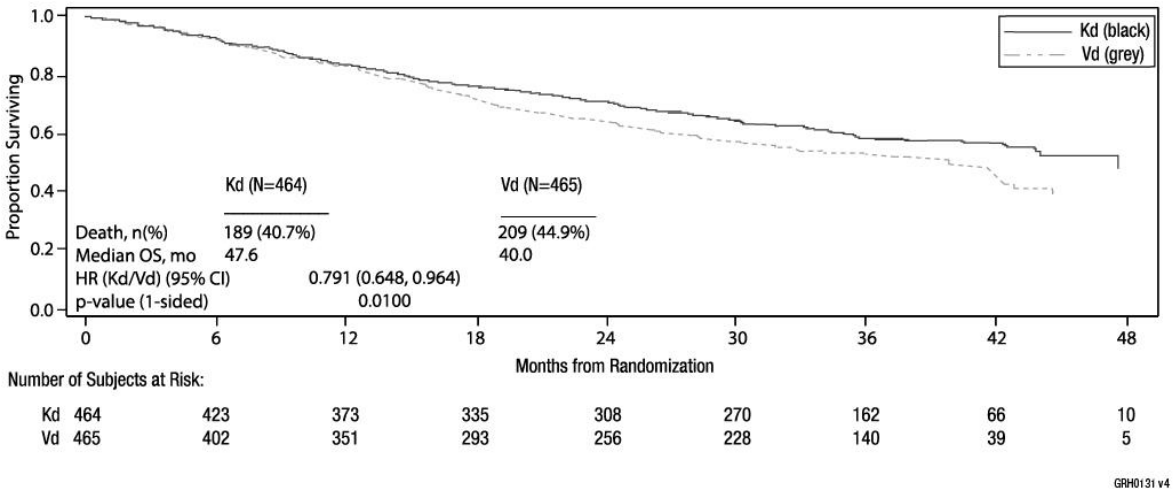
Figure 3: Kaplan-Meier plot of progression-free survival as determined by the IRC (intent-to-treat population) Study 2011-003



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

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 Table 8 and Figure 4). 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]).

Figure 4: Kaplan-Meier curve of overall survival Study 2011-003



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

5.2 Pharmacokinetic properties

Absorption

The C_{max} and AUC following a 2 to 10 minute infusion of 27 mg/m^2 presented as mean (%CV) were 4232 (49%) ng/mL and 379 (25%) ng•hr/mL, respectively. 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. At doses between 20 and 56 mg/m^2, there was a dose-dependent increase in exposure.

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. Following a 30 minute infusion of the 56 mg/m^2 dose, the AUC (948 ng•hr/mL) is approximately twice that observed at the 27 mg/m^2 level, and C_{max} (2079 ng/mL) is lower compared to that of 27 mg/m^2 over the 2 to 10 minute infusion.

Distribution

The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib was 22 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.

Metabolism

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 biological 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/h, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. Carfilzomib is eliminated primarily via metabolism with subsequent excretion in urine. In the first 24 hours, approximately 25% of the administered dose of carfilzomib was excreted in urine as metabolites. Urinary and faecal excretion of the parent compound was negligible (0.3% of total dose).

Special populations

Population pharmacokinetic analyses indicate that the pharmacokinetics of carfilzomib are not influenced by age, gender, or race.

The pharmacokinetics of carfilzomib were 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 baseline hepatic impairment. The pharmacokinetics of carfilzomib have not been studied in patients with severe hepatic impairment (see Section 4.2 Dose and method of administration, Patients with hepatic impairment).

The pharmacokinetics of carfilzomib were 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 4.2 Dose and method of administration, Patients with renal impairment).

5.3 Preclinical safety data

Genotoxicity

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.

Carcinogenicity

Carcinogenicity studies have not been conducted with carfilzomib.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each single-use vial contains:

- 10 mg vial: sulfobutyl betadex sodium (500 mg), citric acid (9.6 mg) and sodium hydroxide (for pH adjustment).
- 30 mg vial: sulfobutyl betadex sodium (1.5 g), citric acid (28.8 mg) and sodium hydroxide (for pH adjustment).
- 60 mg vial: sulfobutyl betadex sodium (3 g), citric acid (57.7 mg) and sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

Reconstituted carfilzomib for injection should not be diluted into a 0.9% sodium chloride IV bag for IV administration.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Unopened vials should be stored at 2°C to 8°C (Refrigerate. Do not freeze). Store in the original carton in order to protect from light.

Reconstituted solution

To reduce microbiological hazard, use as soon as practicable after reconstitution. If storage of the reconstituted solution is necessary, hold at 2°C to 8°C for not more than 24 hours, or below 25°C for not more than 4 hours.

It is not necessary to protect the reconstituted or diluted product from light.

6.5 Nature and contents of container

Kyprolis is supplied in a 10 mL, 30 mL or 50 mL Type I clear glass vial, fluoropolymer laminated elastomeric stopper and aluminium seal with plastic flip off cap. Each pack of Kyprolis contains a single vial.

Presentations available in Australia:

10 mL single-use vial containing 10 mg of carfilzomib

30 mL single-use vial containing 30 mg of carfilzomib

50 mL single-use vial containing 60 mg of carfilzomib

6.6 Special precautions for disposal

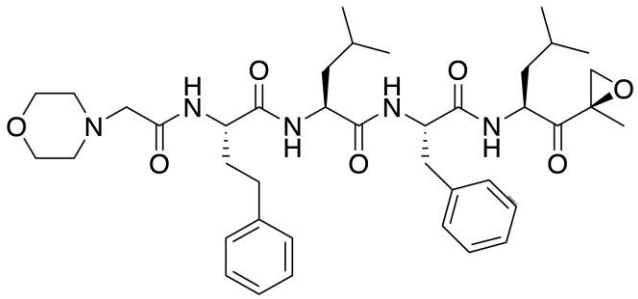
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure

The chemical name for carfilzomib is (2*S*)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide.

Carfilzomib has five chiral centres at 3*R*, 5*S*, 10*S*, 17*S* and 22*S*. It is practically insoluble in water at pH 5 (1 µg/mL), and more soluble at lower pH (10 µg/mL at pH 3 and 1.8 mg/mL at pH 1) and organic solvents (eg methanol).



$C_{40}H_{57}N_5O_7$ MW: 719.9 g/mol

CAS number

CAS Registry No. 868540-17-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Amgen Australia Pty Ltd

ABN 31 051 057 428

Level 7, 123 Epping Road

North Ryde NSW 2113

Medical Information: 1800 803 638

9 DATE OF FIRST APPROVAL

19 December 2016

10 DATE OF REVISION

3 July 2018

Summary table of changes

Section changed	Summary of new information
4.2	Editorial changes to dosing & preparation text
4.3, 4.4, 4.6	Contraindication, warnings and precaution for lenalidomide added
4.4	Additional precautions for cardiac disorder, hypertension, acute renal failure and precaution for use in combination with melphalan and prednisone in newly diagnosed transplant ineligible multiple myeloma
4.8	Updated adverse events and adverse drug reactions text and tables
5.1	Updated clinical trial (OS) data for ENDEAVOR (2011-003) study