ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Kyprolis 10 mg powder for solution for infusion
Kyprolis 30 mg powder for solution for infusion
Kyprolis 60 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Kyprolis 10 mg powder for solution for infusion
Each vial contains 10 mg of carfilzomib.

Excipient with known effect
Each vial contains 37 mg sodium.
Each vial contains 500 mg of cyclodextrin (betadex sulfobutyl ether sodium).

Kyprolis 30 mg powder for solution for infusion
Each vial contains 30 mg of carfilzomib.

Excipient with known effect
Each vial contains 109 mg sodium.
Each vial contains 1 500 mg of cyclodextrin (betadex sulfobutyl ether sodium).

Kyprolis 60 mg powder for solution for infusion
Each vial contains 60 mg of carfilzomib.

Excipient with known effect
Each vial contains 216 mg sodium.
Each vial contains 3 000 mg of cyclodextrin (betadex sulfobutyl ether sodium).

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Kyprolis in combination with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (see section 5.1).

4.2 Posology and method of administration

Kyprolis treatment should be supervised by a physician experienced in the use of anti-cancer therapy.

Posology

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

Kyprolis in combination with lenalidomide and dexamethasone

When combined with lenalidomide and dexamethasone, Kyprolis is administered intravenously as a 10 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) as shown in table 1. Each 28-day period is considered one treatment cycle.

Kyprolis is administered at a starting dose of 20 mg/m^2 (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 27 mg/m^2 (maximum dose 60 mg). From cycle 13, the day 8 and 9 doses of Kyprolis are omitted.

Treatment may be continued until disease progression or until unacceptable toxicity occurs.

Treatment with Kyprolis combined with lenalidomide and dexamethasone for longer than 18 cycles should be based on an individual benefit/risk assessment, as the data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited (see section 5.1).

In combination with Kyprolis, lenalidomide is administered as 25 mg orally on days 1-21 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 current lenalidomide summary of product characteristics, for example for patients with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Table 1. Kyprolis in combination with lenalidomide and dexamethasone

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

	Cycles 13 on										
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Day 22	Days 23-28
Kyprolis (mg/m^2)[a]	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily									-	-

[a.] Infusion time is 10 minutes and remains consistent throughout the regimen

Kyprolis in combination with dexamethasone

When combined with dexamethasone, Kyprolis is administered intravenously as 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) as shown in table 2. Each 28-day period is considered one treatment cycle.

Kyprolis is administered at a starting dose of 20 mg/m^2 (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 56 mg/m^2 (maximum dose 123 mg).

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. Kyprolis in combination with dexamethasone alone

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Day 22	Day 23	Days 24-28
Kyprolis (mg/m^2)[a]	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
	Cycle 2 and all subsequent cycles											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Day 23**	**Days 24-28**
Kyprolis (mg/m^2)[a]	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

[a.] Infusion time is 30 minutes and remains consistent throughout the regimen

Kyprolis in combination with daratumumab and dexamethasone

When combined with daratumumab and dexamethasone, Kyprolis is administered intravenously as 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) as shown in table 3. Each 28-day period is considered one treatment cycle.

Kyprolis is administered at a starting dose of 20 mg/m^2 (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 56 mg/m^2 (maximum dose 123 mg).

Treatment may be continued until disease progression or until unacceptable toxicity occurs.

Dexamethasone is administered as 20 mg orally or intravenously on days 1, 2, 8, 9, 15 and 16 and 40 mg orally or intravenously on day 22 of each 28-day cycle. For patients > 75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week. Dexamethasone should be administered 30 minutes to 4 hours before Kyprolis.

Daratumumab can be administered intravenously or subcutaneously.

If given intravenously, daratumumab is given at a dose of 16 mg/kg actual body weight; with a split dose of 8 mg/kg in cycle 1 on days 1 and 2. Afterwards, daratumumab is administered as 16 mg/kg once weekly on days 8, 15 and 22 of cycle 1 and days 1, 8, 15 and 22 of cycle 2, then every 2 weeks for 4 cycles (cycles 3 to 6) and then every 4 weeks for the remaining cycles or until disease progression.

Alternatively, daratumumab can be given subcutaneously at a dose of 1800 mg on days 1, 8, 15 and 22 of cycle 1 and days 1, 8, 15 and 22 of cycle 2, then every 2 weeks for 4 cycles (cycles 3 to 6) and then every 4 weeks for the remaining cycles or until disease progression.

Refer to the daratumumab summary of product characteristics for additional information regarding the use of the subcutaneous formulation.

On days when more than one of these medicines is administered, the recommended order of administration is as follows: dexamethasone, pre-infusion medications for daratumumab (see section *Concomitant medicinal products*), carfilzomib, daratumumab, and post-infusion medications for daratumumab (see section *Concomitant medicinal products*).

Refer to the daratumumab and dexamethasone summary of product characteristics for additional details on administration.

Table 3. Kyprolis in combination with dexamethasone and daratumumab

	Cycle 1											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24–28**
Kyprolis (mg/m^2)[a]	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)[b]	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (Intravenous **OR** Subcutaneous**)**												
IV administration (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
SC administration (mg)	1800	-	-	1800	-	-	1800	-	-	1800	-	-

	Cycle 2											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24–28
Kyprolis (mg/m^2)[a]	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)[b]	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (Intravenous **OR** Subcutaneous**)**												
IV administration (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
SC administration (mg)	1800	-	-	1800	-	-	1800	-	-	1800	-	-

	Cycles 3-6											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24–28
Kyprolis (mg/m^2)[a]	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)[b]	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (Intravenous **OR** Subcutaneous**)**												
IV administration (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
SC administration (mg)	1800	-	-	-	-	-	1800	-	-	-	-	-

	Cycles 7 and all subsequent cycles											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24–28
Kyprolis (mg/m^2)[a]	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)[b]	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (Intravenous **OR** Subcutaneous**)**												
IV administration (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-
SC administration (mg)	1800	-	-	-	-	-	-	-	-	-	-	-

[a.] Infusion time is 30 minutes and remains consistent throughout the regimen

[b.] For patients > 75 years of age, dexamethasone is administered as 20 mg orally or intravenously weekly after the first week.

Concomitant medicinal products

Antiviral prophylaxis should be considered in patients being treated with Kyprolis to decrease the risk of herpes zoster reactivation (see section 4.8).

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

In patients being treated with Kyprolis in combination with daratumumab and dexamethasone, pre-infusion medications should be administered to reduce the risk of infusion-related reactions with daratumumab.

Refer to the daratumumab summary of product characteristics for additional details on concomitant medications including pre-and post-infusion medications.

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 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 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 in cycle 1. Oral and/or intravenous hydration should be continued, as needed, in subsequent cycles.

When given in combination with intravenous daratumumab, oral and/or intravenous hydration is not required on days when intravenous daratumumab is dosed.

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 (e.g. medicinal products known to increase the risk of hypokalaemia) and associated comorbidities.

Recommended dose modifications

Dosing should be modified based on Kyprolis toxicity. Recommended actions and dose modifications are presented in table 4. Dose level reductions are presented in table 5.

Table 4. Dose modifications during Kyprolis treatment

Haematologic toxicity	Recommended action
• Absolute neutrophil count < 0.5 × 10^9/L (see section 4.4)	• Stop dose - If recovered to ≥ 0.5 × 10^9/L, continue at same dose level • For subsequent drops to < 0.5 × 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis[a]
• Febrile neutropenia • Absolute neutrophil count < 0.5 × 10^9/L and an oral temperature > 38.5°C or two consecutive readings of > 38.0°C for 2 hours	• Stop dose • If absolute neutrophil count returns to baseline grade and fever resolves, resume at the same dose level
• Platelet count < 10 × 10^9/L or evidence of bleeding with thrombocytopenia (see section 4.4)	• Stop dose - If recovered to ≥ 10 × 10^9/L and/or bleeding is controlled continue at same dose level • For subsequent drops to < 10 × 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 equal to or greater than 2 × baseline; or • Creatinine clearance < 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis (see section 4.4)	• Stop dose and continue monitoring renal function (serum creatinine or creatinine clearance) - Kyprolis should be resumed when renal function has recovered to within 25% of baseline; consider resuming at 1 dose level reduction[a] • 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-haematologic toxicities (see section 4.4)	• Stop until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction[a]

[a.] See table 5 for dose level reductions

Table 5. Dose level reductions for Kyprolis

Regimen	Kyprolis dose	First Kyprolis dose reduction	Second Kyprolis dose reduction	Third 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]
Kyprolis, daratumumab 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

Special populations

Renal impairment

Patients with moderate or severe renal impairment were enrolled in Kyprolis-dexamethasone combination studies, but were excluded from Kyprolis-lenalidomide combination studies. Thus, there are limited data for Kyprolis in combination with lenalidomide and dexamethasone in patients with creatinine clearance (CrCL < 50 mL/min). Appropriate dose reduction for the starting dose of lenalidomide in patients with baseline renal impairment should be considered according to the recommendations in the lenalidomide summary of product characteristics.

No starting dose adjustment for Kyprolis is recommended in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis based on available pharmacokinetic data (see section 5.2). However, in phase 3 clinical studies, the incidence of adverse events of acute renal failure was higher in patients with lower baseline creatinine clearance than that among patients with higher baseline creatinine clearance.

Renal function should be assessed at treatment initiation and monitored at least monthly or in accordance with accepted clinical practice guidelines, particularly in patients with lower baseline creatinine clearance (CrCL < 30 mL/min). Appropriate dose modifications based on toxicity should be made (see table 4). There are limited efficacy and safety data on patients with baseline creatinine clearance < 30 mL/min.

Since dialysis clearance of Kyprolis concentrations has not been studied, the medicinal product should be administered after the dialysis procedure.

Hepatic impairment

Patients with moderate or severe hepatic impairment were excluded from Kyprolis studies in combination with either lenalidomide and dexamethasone or dexamethasone alone.

The pharmacokinetics of Kyprolis has not been evaluated in patients with severe hepatic impairment. No starting dose adjustment is recommended in patients with mild or moderate hepatic impairment based on available pharmacokinetic data. However, higher subject incidence of hepatic function abnormalities, ≥ grade 3 adverse events and serious adverse events have been reported in patients with mild or moderate baseline hepatic impairment compared with patients with normal hepatic function (see sections 4.4 and 5.2). Liver enzymes and bilirubin should be assessed at treatment initiation and monitored monthly during treatment with carfilzomib, regardless of baseline values, and appropriate dose modifications based on toxicity should be made (see table 4). Special attention should be paid to patients with moderate and severe hepatic impairment in view of the very limited efficacy and safety data on this population.

Elderly patients

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

Paediatric population

There is no relevant use of Kyprolis in children and adolescents aged below 18 years in multiple myeloma.

Outside its authorised indications, Kyprolis has been studied in children and adolescents aged below 18 years with acute lymphoblastic leukaemia (ALL), however the primary endpoint did not meet the statistical significance for superiority for Kyprolis in combination with chemotherapy when compared to the external control arm. Currently available data are described in sections 5.1 and 5.2.

Method of administration

Kyprolis is to be administered by intravenous infusion. The 20/27 mg/m^2 dose is administered over 10 minutes. The 20/56 mg/m^2 dose must be administered over 30 minutes.

Kyprolis must not be administered as an intravenous push or bolus.

The intravenous administration line should be flushed with normal sodium chloride solution or 5% glucose solution for 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 the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Women who are breast-feeding (see section 4.6).

As Kyprolis is administered in combination with other medicinal products, refer to their summaries of product characteristics for additional contraindications.

4.4 Special warnings and precautions for use

As Kyprolis is administered in combination with other medicinal products, the summary of product characteristics of these other medicinal products must be consulted prior to initiation of treatment with Kyprolis. As lenalidomide may be used in combination with Kyprolis, particular attention to the lenalidomide pregnancy testing and prevention requirements is needed (see section 4.6).

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. For potential dose-related effects, see section 4.8.

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).

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).

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

A thorough assessment for cardiovascular risk factors prior to starting treatment is recommended.

Patients with New York Heart Association (NYHA) Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medicinal products were not eligible for the clinical studies. These patients may be at greater risk for cardiac complications. Patients with signs or symptoms of NYHA Class III or IV cardiac failure, recent history of myocardial infarction (in the last 4 months), and in patients with uncontrolled angina or arrhythmias, should have a comprehensive cardiological assessment, prior to starting treatment with Kyprolis. This assessment should optimise the patient's status, with particular attention to blood pressure control and fluid management. Subsequently patients should be treated with caution and remain under close follow-up.

Electrocardiographic changes

There have been cases of QT interval prolongation reported in clinical studies and post-marketing. Cases of ventricular tachycardia have been reported in patients receiving Kyprolis.

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).

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).

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 sections 4.2 and 4.8).

Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. Some of these events have been fatal. Hypertension was reported more frequently in patients who received Kyprolis in combination with daratumumab in study 20160275. It is recommended to control hypertension prior to starting and during treatment. 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 crises, stop Kyprolis until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment (see section 4.2).

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. 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. Reduce or stop dose as appropriate (see section 4.2).

Tumour lysis syndrome

Cases of tumour lysis syndrome (TLS), including with 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 (see section 4.2). Uric acid lowering medicinal products should be considered in patients at high risk for TLS. Evidence of TLS during treatment should be monitored for, including regular measurement of serum electrolytes, and managed promptly. Stop Kyprolis until TLS is resolved (see section 4.2).

Infusion reactions

Infusion reactions, including life-threatening reactions, have been reported in patients who received Kyprolis. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, shortness of breath, hypotension, syncope, bradycardia, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Dexamethasone should be administered prior to Kyprolis to reduce the incidence and severity of reactions (see section 4.2).

Haemorrhage and thrombocytopenia

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

Kyprolis causes thrombocytopenia 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). Platelet counts should be monitored frequently during treatment with Kyprolis. Reduce or stop dose as appropriate (see section 4.2).

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.

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 (e.g. smoking, hypertension and hyperlipidaemia). Caution should be used in the concomitant administration of other agents that may increase the risk of thrombosis (e.g. 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

Cases of hepatic failure, including fatal cases, have been reported. Kyprolis can cause elevations of serum transaminases (see section 4.8). Reduce or stop dose as appropriate (see section 4.2). Liver enzymes and bilirubin should be monitored at treatment initiation and monthly during treatment with carfilzomib, regardless of baseline values.

Thrombotic microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome (TTP/HUS) have been reported in patients who received Kyprolis. Some of these events have been fatal. Signs and symptoms of TTP/HUS should be monitored for. 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

Cases of posterior reversible encephalopathy syndrome (PRES) have been 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.

Hepatitis B virus (HBV) reactivation

Cases of Hepatitis B virus (HBV) reactivation have been reported in patients receiving carfilzomib.

All patients should be screened for HBV before initiation of treatment with carfilzomib. For patients with positive HBV serology, prophylaxis with antivirals should be considered. They should be monitored for clinical and laboratory signs of HBV reactivation during and after the end of treatment. Experts in the treatment of HBV infection should be consulted, as necessary. The safety of resuming carfilzomib, after HBV reactivation is adequately controlled, is not known. Therefore, resumption of therapy should be discussed with experts in managing HBV.

Progressive multifocal leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients receiving carfilzomib who have had prior or concurrent immunosuppressive therapy.

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

If PML is suspected, further administration must be suspended until PML has been excluded by a specialist with appropriate diagnostic testing. If PML is confirmed, carfilzomib must be discontinued.

Contraception

Female patients of childbearing 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 (refer to section 4.6). Carfilzomib may decrease the efficacy of oral contraceptives (refer to section 4.5).

Sodium content

Kyprolis 10 mg powder for solution for infusion
This medicinal product contains 37 mg sodium per 10 mg vial which is equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Kyprolis 30 mg powder for solution for infusion
This medicinal product contains 109 mg sodium per 30 mg vial which is equivalent to 5.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Kyprolis 60 mg powder for solution for infusion
This medicinal product contains 216 mg sodium per 60 mg vial which is equivalent to 11% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cyclodextrin content

Kyprolis 10 mg powder for solution for infusion
This medicinal product contains 500 mg cyclodextrin (betadex sulfobutyl ether sodium) per 10 mg vial which is equivalent to 88 mg/kg for a 70 kg adult.

Kyprolis 30 mg powder for solution for infusion
This medicinal product contains 1 500 mg cyclodextrin (betadex sulfobutyl ether sodium) per 30 mg vial which is equivalent to 88 mg/kg for a 70 kg adult.

Kyprolis 60 mg powder for solution for infusion
This medicinal product contains 3 000 mg cyclodextrin (betadex sulfobutyl ether sodium) per 60 mg vial which is equivalent to 88 mg/kg for a 70 kg adult.

4.5 Interaction with other medicinal products 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.

In vitro studies indicated that carfilzomib did not induce human CYP3A4 in cultured human hepatocytes. A clinical study using oral midazolam as a CYP3A probe conducted with carfilzomib at a dose of 27 mg/m^2 (2 to 10 minute infusion) demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration, indicating that carfilzomib is not expected to inhibit the metabolism of CYP3A4/5 substrates and is not a CYP3A4 inducer in human subjects. No clinical study was conducted with a dose of 56 mg/m^2. However, it is unknown whether carfilzomib is an inducer of CYP1A2, 2C8, 2C9, 2C19 and 2B6 at therapeutic concentrations. Caution should be observed when carfilzomib is combined with medicinal products that are substrates of these enzymes, such as oral contraceptives. Effective measures to avoid pregnancy should be taken (see section 4.6, and refer also to the current lenalidomide summary of product characteristics), an alternative method of effective contraception should be used if the patient is using oral contraceptives.

Carfilzomib does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 *in vitro* and is therefore not expected to influence exposure of medicinal products that are substrates of these enzymes as a result of inhibition.

Carfilzomib is a P-glycoprotein (P-gp) but not a BCRP substrate. However, given that Kyprolis is administrated intravenously and is extensively metabolised, the pharmacokinetic profile of carfilzomib is unlikely to be affected by P-gp or BCRP inhibitors or inducers. *In vitro*, at concentrations (3 μM) lower than those expected at therapeutic doses, carfilzomib inhibits the efflux transport of digoxin, a P-gp substrate, by 25%. Caution should be observed when carfilzomib is combined with substrates of P-gp (e.g. digoxin, colchicine).

In vitro, carfilzomib inhibits OATP1B1 with an IC_{50} = 2.01 μM whereas it is unknown whether carfilzomib may or not inhibit other transporters OATP1B3, OAT1, OAT3, OCT2 and BSEP, at the systemic level. Carfilzomib does not inhibit human UGT2B7 but inhibits human UGT1A1 with an IC_{50} of 5.5 μM. Nonetheless, considering the fast elimination of carfilzomib, notably a rapid decline in systemic concentration 5 minutes after the end of infusion, the risk of clinically relevant interactions with substrates of OATP1B1 and UGT1A1 is probably low.

4.6 Fertility, pregnancy and lactation

Women of child bearing potential/Contraception in males and females

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

It cannot be excluded that the efficacy of oral contraceptives may be reduced during carfilzomib treatment (see section 4.5). In addition, due to an increased risk of venous thromboembolic events associated with carfilzomib, females should avoid the use of hormonal contraceptives that are associated with a risk of thrombosis during treatment with carfilzomib (see sections 4.4 and 4.8). If a patient is currently using oral contraceptives or a hormonal method of contraception that is associated with a risk of thrombosis, the patient should switch to an alternative method of effective contraception.

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

Pregnancy

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

Studies in animals have shown reproductive toxicity (see section 5.3).

Based on its mechanism of action and findings in animals, Kyprolis can cause foetal harm when administered to a pregnant woman. Kyprolis should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. If Kyprolis is used during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be apprised of the potential hazard to the foetus.

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected. The conditions of the Pregnancy Prevention Programme for lenalidomide must be fulfilled for all patients unless there is reliable evidence that the patient does not have child bearing potential. Please refer to the current lenalidomide summary of product characteristics.

Breast-feeding

It is unknown whether carfilzomib or its metabolites are excreted in human milk. Based on its pharmacological properties, a risk to the suckling child cannot be excluded. Consequently, as a precautionary measure, breast-feeding is contra-indicated during and for at least 2 days after treatment with Kyprolis.

Fertility

No fertility studies have been performed in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

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

Fatigue, dizziness, fainting, blurred vision, somnolence and/or a drop in blood pressure have been observed in clinical studies. Patients being treated with Kyprolis should be advised not to drive or operate machines in the event that 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 crises, acute kidney injury, tumour lysis syndrome, infusion related reaction, gastrointestinal haemorrhage, intracranial haemorrhage, pulmonary haemorrhage, thrombocytopenia, hepatic failure, hepatitis B virus reactivation, PRES, thrombotic microangiopathy and TTP/HUS. In clinical studies with Kyprolis, cardiac toxicity and dyspnoea typically occurred early in the course of Kyprolis therapy (see section 4.4). The most common adverse reactions (occurring in > 20% of subjects) were: anaemia, fatigue, thrombocytopenia, nausea, diarrhoea, pyrexia, dyspnoea, respiratory tract infection, cough and neutropenia.

Following initial doses of carfilzomib at 20 mg/m^2, the dose was increased to 27 mg/m^2 in study PX-171-009 and to 56 mg/m^2 in study 2011-003 (see section 5.1). A cross-study comparison of the adverse reactions occurring in the Kyprolis and dexamethasone (Kd) arm of study 2011-003 versus the Kyprolis, lenalidomide and dexamethasone (KRd) arm of study PX-171-009 suggest that there may be a potential dose relationship for the following adverse reactions: cardiac failure (Kd 8.2%, KRd 6.4%), dyspnoea (Kd 30.9%, KRd 22.7%), hypertension (Kd 25.9%, KRd 15.8%), and pulmonary hypertension (Kd 1.3%, KRd 0.8%).

In study 20160275 (see section 5.1), in which the administration of Kyprolis in combination with daratumumab and dexamethasone (KdD) was compared to Kyprolis in combination with dexamethasone (Kd), deaths due to adverse events within 30 days of the last dose of any study treatment occurred in 10% of patients in the KdD arm compared with 5% of patients in the Kd arm. The most common cause of death occurring in patients in the two arms (KdD versus Kd) was infections (5% versus 3%). The risk of fatal treatment-emergent adverse events was higher among subjects ≥ 65 years of age. Serious adverse events were reported in 56% of the patients in the KdD arm and 46% of the patients in the Kd arm. The most common serious adverse events reported in the KdD arm as compared with the Kd arm were anaemia (2% versus 1%), diarrhoea (2% versus 0%), pyrexia (4% versus 2%), pneumonia (12% versus 9%), influenza (4% versus 1%), sepsis (4% versus 1%) and bronchitis (2% versus 0%).

Tabulated list of adverse reactions

Adverse reactions are presented below by system organ class and frequency category (see table 6). Frequency categories were determined from the crude incidence rate reported for each adverse reaction in a dataset of pooled clinical studies (n = 3 878). Within each system organ class and frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 6. Tabulated list 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 < 1/1 000)**
Infections and infestations	Pneumonia Respiratory tract infection	Sepsis Lung infection Influenza Herpes zoster* Urinary tract infection Bronchitis Gastroenteritis Viral infection Nasopharyngitis Rhinitis	Clostridium difficile colitis Cytomegalovirus infection Hepatitis B virus reactivation	
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 Decreased appetite	Dehydration Hyperkalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia Hypocalcaemia Hypophosphataemia Hyperuricaemia Hypoalbuminaemia Hyperglycaemia	Tumour lysis syndrome	

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 < 1/1 000)**
Psychiatric disorders	Insomnia	Anxiety Confusional state		
Nervous system disorders	Dizziness Peripheral neuropathy Headache	Paraesthesia Hypoaesthesia	Intracranial haemorrhage Cerebrovascular accident PRES	
Eye disorders		Cataract Blurred vision		
Ear and labyrinth disorders		Tinnitus		
Cardiac disorders		Cardiac failure Myocardial infarction Atrial fibrillation Tachycardia Ejection fraction decreased Palpitations	Cardiac arrest Cardiomyopathy Myocardial ischaemia Pericarditis Pericardial effusion Ventricular tachycardia	
Vascular disorders	Hypertension	Deep vein thrombosis Hypotension Flushing	Hypertensive crisis Haemorrhage	Hypertensive emergency
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	
Gastrointestinal disorders	Vomiting Diarrhoea Constipation Abdominal pain Nausea	Gastrointestinal haemorrhage Dyspepsia Toothache	Gastrointestinal perforation Pancreatitis acute	
Hepatobiliary disorders		Increased alanine aminotransferase Increased aspartate aminotransferase Gamma-glutamyltransferase increased Hyperbilirubinaemia	Hepatic failure Cholestasis	
Skin and subcutaneous tissue disorders		Rash Pruritus Erythema Hyperhidrosis		Angioedema
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		

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 < 1/1 000)
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		

* Frequency is calculated based on data from clinical studies in which most patients used prophylaxis

Description of selected adverse reactions

Cardiac failure, myocardial infarction and myocardial ischaemia

In clinical studies with Kyprolis, cardiac failure was reported in approximately 5% of subjects (approximately 3% of subjects had grade ≥ 3 events), myocardial infarction was reported in approximately 1% of subjects (approximately 1% of subjects had grade ≥ 3 events) and myocardial ischaemia was reported in < 1% of subjects (< 1% of subjects had grade ≥ 3 events). These events typically occurred early in the course of Kyprolis therapy (< 5 cycles).

In study 20160275, the overall incidence of cardiac disorders (any and all grade events) in the subgroup of patients with baseline vascular disorders or baseline hypertension was 29.9% versus 19.8% (KdD versus Kd), and 30.6% versus 18.1%, respectively. For fatal cardiac events, the incidence was 1.9% versus 0.0% (KdD versus Kd) and 1.5% versus 0.0%, respectively. No single type of cardiac event accounted for the difference reported between the KdD versus Kd arms in the subgroup of patients with baseline vascular disorders or baseline hypertension.

For clinical management of cardiac disorders during Kyprolis treatment, see section 4.4.

Dyspnoea

Dyspnoea was reported in approximately 24% 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.

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 21% of subjects and 8% 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.

Thrombocytopenia

Thrombocytopenia was reported in approximately 33% of subjects in clinical studies with Kyprolis and approximately 20% of subjects had grade ≥ 3 events. In study 20160275, the incidence of grade ≥ 3 thrombocytopenia was 24.4% in the KdD arm and 16.3% in the Kd arm. Kyprolis causes thrombocytopenia through inhibition of platelet budding from megakaryocytes resulting in a classic

cyclical thrombocytopenia with platelet nadirs occurring on 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.

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). The overall incidence of venous thromboembolic events was higher in the Kyprolis arms of three phase 3 studies. In study PX-171-009 the incidence of venous thromboembolic events was 15.6% 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 bortezomib plus 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. In study 20160275 the incidence of venous thromboembolic events was 6.2% in the KdD arm and 11.1% in the Kd arm. Grade ≥ 3 venous thromboembolic events were reported in 1.9% of patients in the KdD arm and 6.5% of patients in the Kd arm.

Hepatic failure

Cases of hepatic failure, including fatal cases, have been reported in < 1% of subjects in clinical studies with Kyprolis. For clinical management of hepatic toxicity during Kyprolis treatment, see section 4.4.

Peripheral neuropathy

In a randomised, open-label, multicentre study in patients receiving Kyprolis 20/56 mg/m^2 infused over 30 minutes in combination with dexamethasone (Kd, n = 464) versus bortezomib plus dexamethasone (Vd, n = 465), cases of grade 2 and higher peripheral neuropathy were reported in 7% of patients with relapsed multiple myeloma in the Kd arm, compared with 35% in the Vd arm at the time of the pre-planned OS analysis. In study 20160275, cases of grade 2 and higher peripheral neuropathy were reported in 10.1% of patients with relapsed multiple myeloma in the KdD arm compared with 3.9% in the Kd arm.

Infusion reaction

In study 20160275, there was a higher risk of infusion reaction when carfilzomib is administered with daratumumab.

Respiratory tract infections

In study 20160275, respiratory tract infections reported as serious adverse reactions occurred in each treatment group (27.6% in KdD arm and 15.0% in Kd arm). In study 20160275, pneumonia reported as serious adverse reactions occurred in each treatment group (15.3% in KdD arm and 9.8% in Kd arm). 1.3% and 0% events have been fatal in the KdD and Kd arms, respectively.

Secondary primary malignancies

In study 20160275, secondary primary malignancies in each treatment group (1.9% in KdD arm and 1.3% in Kd arm) have been reported.

Opportunistic infections

In study 20160275, opportunistic infections in each treatment group (9.4% in KdD arm and 3.9% in Kd arm) have been reported. Opportunistic infections occurring in ≥ 1% of subjects in the KdD arm included herpes zoster, oral candidiasis, oral herpes, and herpes simplex.

Hepatitis B reactivation

In study 20160275, the incidence of hepatitis B reactivation was 0.6% in the KdD arm versus 0% in the Kd arm.

Other special populations

Elderly patients

Overall, the subject incidence of certain adverse events (including cardiac arrhythmias, cardiac failure (see section 4.4), dyspnoea, leukopenia and thrombocytopenia) in clinical studies with Kyprolis was higher for patients who were ≥ 75 years of age compared to patients who were < 75 years of age.

In study 20160275, 47% of the 308 patients who received KdD 20/56 mg/m^2 twice weekly were ≥ 65 years of age. In the KdD arm of the study, fatal treatment-emergent adverse events occurred in 6% of patients < 65 years of age and 14% of patients ≥ 65 years of age. In the Kd arm, these events occurred in 8% of patients < 65 years of age and 3% of patients ≥ 65 years of age.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is currently insufficient information to draw conclusions about the safety of doses higher than those evaluated in clinical studies. Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error.

There is no known specific antidote for carfilzomib overdose. In the event of an overdose, the patient should be monitored, specifically for the adverse reactions to Kyprolis listed in section 4.8.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XG02

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 haematologic tumours. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumour growth in models of multiple myeloma. *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 ≥ 15 mg/m^2 consistently

induced an (≥ 80%) inhibition of the CT-L activity of the proteasome. In addition, carfilzomib administration resulted in inhibition of the latent membrane protein 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the immunoproteasome ranging from 26% to 32% and 41% to 49%, respectively, at 20 mg/m^2. 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 proteasome inhibition.

At the higher dose of 56 mg/m^2, there was not only a greater inhibition of CT-L subunits (≥ 90%) compared to those at 15 to 20 mg/m^2, but also a greater inhibition of other proteasome subunits (LMP7, MECL1, and LMP2). There was an approximately 8%, 23% and 34% increase in the inhibition of LMP7, MECL1, and LMP2 subunits respectively at the dose of 56 mg/m^2 compared to those at 15 to 20 mg/m^2. Similar proteasome inhibition by carfilzomib was achieved with 2 to 10 minute and 30 minute infusions at the 2 dose levels (20 and 36 mg/m^2) at which it was tested.

Clinical efficacy and safety

Kyprolis in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed 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 with relapsed multiple myeloma, which evaluated the combination of Kyprolis with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone, randomised 1:1.

This study evaluated Kyprolis at an initial dose of 20 mg/m^2, which was increased to 27 mg/m^2 on cycle 1, day 8, administered twice weekly for 3 out of 4 weeks as a 10 minute infusion. 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.

Patients who had the following were excluded from the study: creatinine clearance rates < 50 mL/min, NYHA Class III to IV congestive heart failure, or myocardial infarction within the last 4 months, disease progression during the treatment with a bortezomib-containing regimen, or progression during the first 3 months of initiating treatment with lenalidomide and dexamethasone, or progression at any time during treatment with lenalidomide and dexamethasone if this was the subject's most recent line of therapy. Study eligibility criteria allowed a small subset of patients with myeloma refractory to bortezomib (n = 118) or lenalidomide (n = 57) to be enrolled. Enrolled subjects were defined as refractory to a therapy if they met any of the following 3 criteria: nonresponsive (< minimal response) to any regimen; progression during any regimen; or progression within 60 days of completion of any regimen. This study did not evaluate the benefit/risk ratio in the broader refractory population.

The disease status and other baseline characteristics were well-balanced between the two arms, including age (64 years, range 31-91 years), gender (56% male), ECOG performance status (48% with performance status 1), high risk genetic mutations, consisting of the genetic subtypes t(4;14), t(14;16), or deletion 17p in ≥ 60% of plasma cells (13%), unknown-risk genetic mutations, which included subjects with results not collected or not analysed (47%), and baseline ISS stage III disease (20%). Subjects had received 1 to 3 prior lines of therapy (median of 2), including prior treatment with bortezomib (66%), thalidomide (44%) and lenalidomide (20%).

The results of study PX-171-009 are summarised in table 7 and in figure 1 and figure 2.

Table 7. Summary of efficacy analysis in relapsed multiple myeloma 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)	48.3 (42.4, 52.8)	40.4 (33.6, 44.4)
HR (95% CI); 1-sided p-value[b]	0.79 (0.67, 0.95); 0.0045	
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	< 0.0001	

KRd = Kyprolis, lenalidomide and dexamethasone; Rd = lenalidomide and dexamethasone;
PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; OS = overall survival;
ORR = overall response rate; sCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; IMWG = International Myeloma Working Group; EBMT = European Society for Blood and Marrow Transplantation

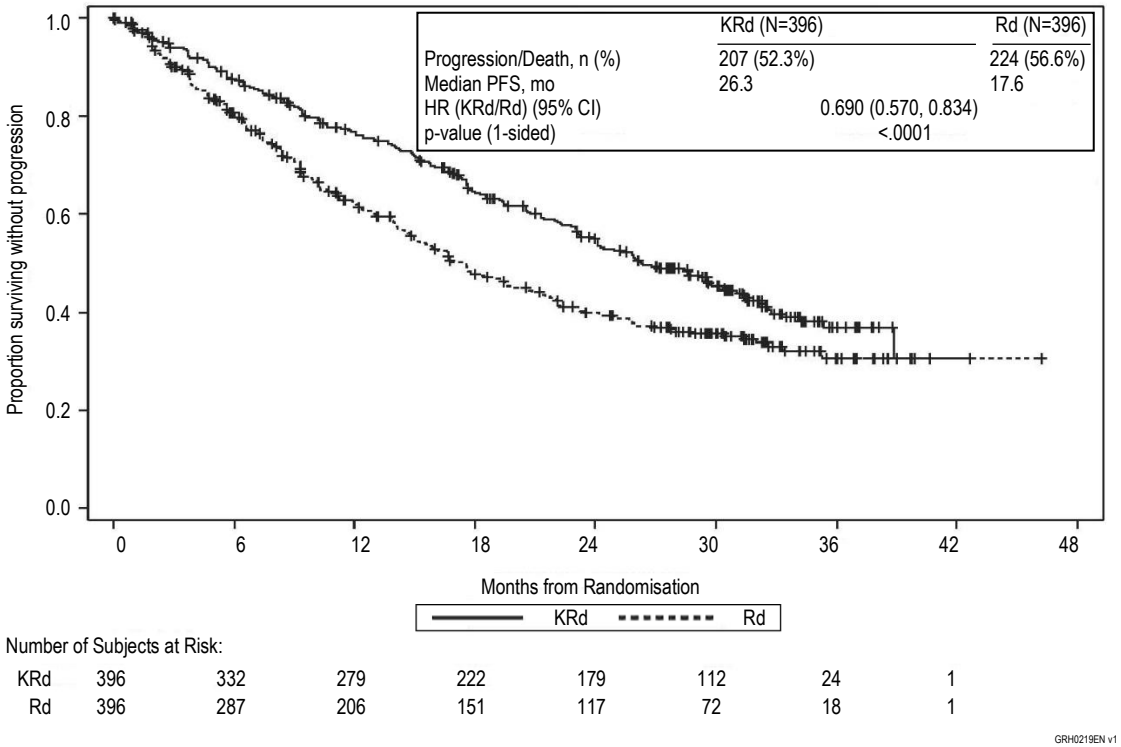
[a.] As determined by an Independent Review Committee using standard objective IMWG/EBMT response criteria

[b.] Statistically significant

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) which 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 PFS benefit of KRd was consistently observed in all subgroups, including patients ≥ 75 years of age (n = 96), patients with high risk (n = 100) or unknown (n = 375) risk genetic mutations, and patients with baseline creatinine clearance of 30 - < 50 mL/min (n = 56).

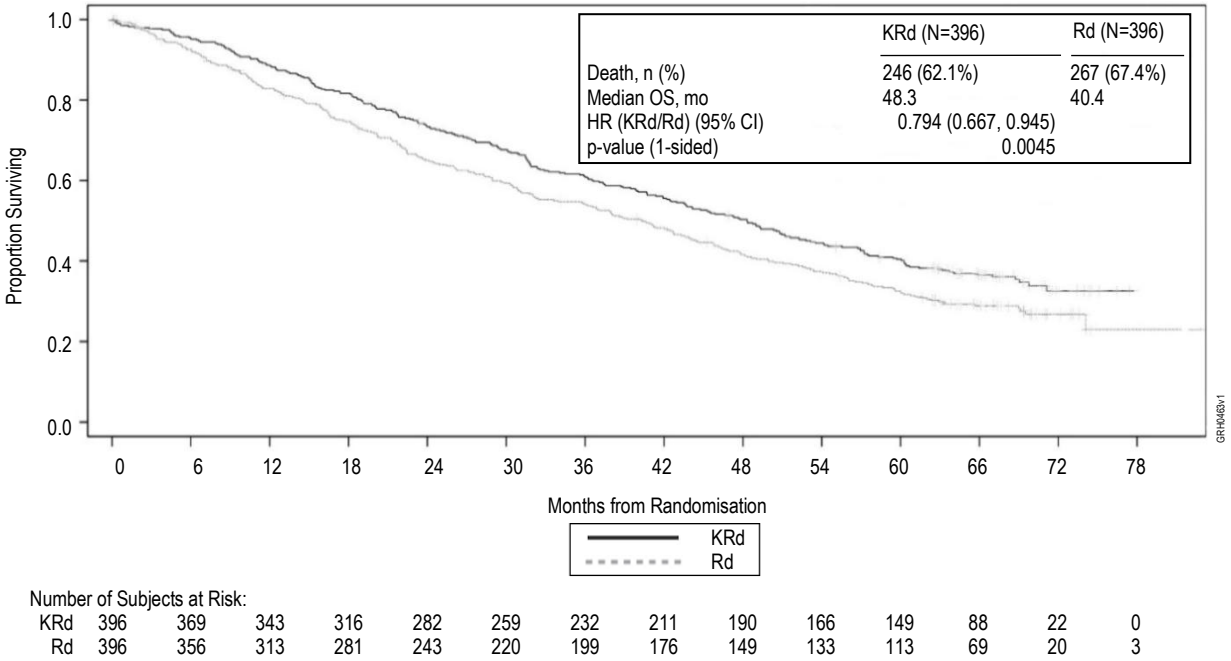
Figure 1. Kaplan-Meier curve of progression-free survival in relapsed multiple myeloma[a]



KRd = Kyprolis, lenalidomide and dexamethasone; Rd = lenalidomide, dexamethasone; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; IMWG = International Myeloma Working Group; EBMT = European Blood and Marrow Transplantation; mo = months
Note: The response and PD outcomes were determined using standard objective IMWG/EBMT response criteria.
[a.] Study PX-171-009

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 7 and figure 2).

Figure 2. Kaplan-Meier curve of overall survival in relapsed multiple myeloma[a]



Number of Subjects at Risk:

KRd	396	369	343	316	282	259	232	211	190	166	149	88	22	0
Rd	396	356	313	281	243	220	199	176	149	133	113	69	20	3

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

[a.] Study PX-171-009

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 (multiplicity unadjusted 1-sided p-value = 0.0001) measured with the EORTC QLQ-C30, an instrument validated in multiple myeloma.

Kyprolis in combination with dexamethasone for the treatment of patients with relapsed multiple myeloma – 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 or refractory 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).

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

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 study: creatinine clearance rates < 15 mL/min, NYHA Class III to IV congestive heart failure, myocardial infarction within the last 4 months or those with left ventricular ejection fraction (LVEF) < 40%. Study eligibility criteria allowed patients previously treated with carfilzomib (n = 3) or bortezomib (n = 502) to be enrolled as long as patients had at least a partial response (PR) to prior proteasome inhibitor therapy, were not removed from proteasome inhibitor therapy due to toxicity, and had at least a 6-month proteasome inhibitor treatment-free interval from last dose.

The demographics and baseline characteristics for study 2011-003 were well-balanced between the two arms, including prior treatment with bortezomib (54%), prior treatment with lenalidomide (38%), lenalidomide refractory (25%), age (65 years, range 30-89 years), gender (51% male), ECOG performance status (45% with performance status 1), high risk genetic mutations, consisting of the genetic subtypes t(4;14) or t(14;16) in 10% or more of screened plasma cells, or deletion 17p in ≥ 20%

of plasma cells (23%) unknown-risk genetic mutations, which included subjects with results not collected or not analysed (9%) and baseline ISS stage III disease (24%).

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

Table 8. Summary of efficacy analysis in relapsed multiple myeloma study 2011-003

	Kd Arm (N = 464)	**Vd Arm (N = 465)**
PFS months median (95% CI)[a]	18.7 (15.6, NE)	9.4 (8.4, 10.4)
HR (95% CI); 1-sided p-value[b]	0.533 (0.44, 0.65); < 0.0001	
Overall survival months median (95% CI)	47.6 (42.5, NE)	40.0 (32.6, 42.3)
HR (95% CI); 1-sided p-value[b]	0.791 (0.65, 0.96); 0.010	
ORR n (%)[a, c]	357 (76.9)	291 (62.6)
≥ CR[d]	58 (12.5)	29 (6.2)
≥ VGPR[e]	252 (54.3)	133 (28.6)
95% CI of ORR	72.8, 80.7	58.0, 67.0
1-sided p-value[b]	< 0.0001	

Kd = Kyprolis plus dexamethasone; Vd = bortezomib and dexamethasone; CI = confidence interval; NE = not estimable; HR = hazard ratio; ORR = overall response rate; CR = complete response; VGPR = very good partial response

[a.] These endpoints were determined by an Independent Review Committee

[b.] Statistically significant

[c.] Overall response is defined as achieving a best overall response of PR, VGPR, CR, or sCR

[d.] Statistically significant, 1-sided p-value = 0.0005

[e.] Statistically significant, 1-sided p-value = 0.0001

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]) (see figure 3).

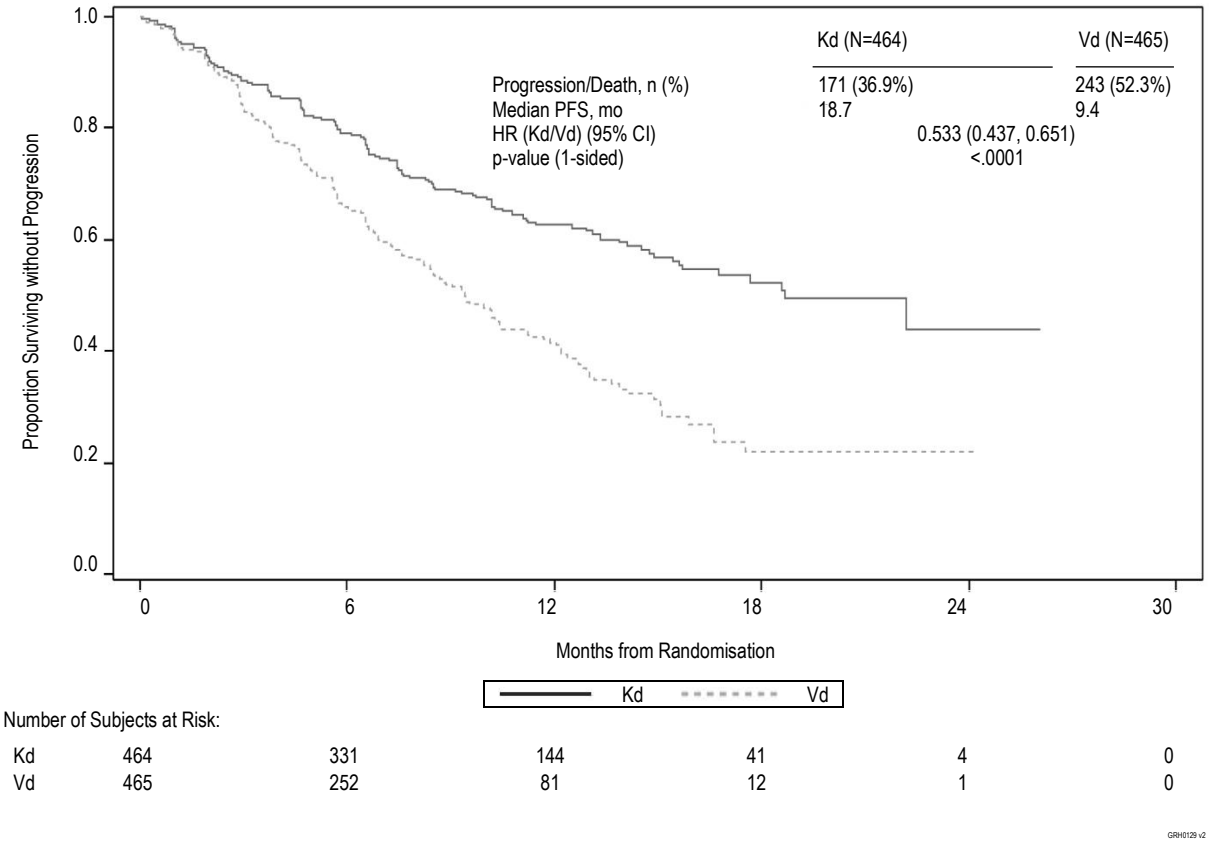
Similar PFS results were observed in patients who had received prior treatment with bortezomib (HR 0.56, 95% CI: 0.44, 0.73) and patients who had not received prior treatment with bortezomib (HR 0.48, 95% CI: 0.36, 0.66).

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).

In patients who received prior bortezomib (54%), median PFS was 15.6 months in the Kd arm versus 8.1 months in the Vd arm (HR = 0.56, 95% CI: 0.44, 0.73), ORR was 71.2% versus 60.3%.

In patients who received prior lenalidomide (38%), median PFS was 12.9 months in the Kd arm versus 7.3 months in the Vd arm (HR = 0.69, 95% CI: 0.52, 0.92), ORR was 70.1% versus 59.3%. In patients refractory to lenalidomide (25%), median PFS was 8.6 months in the Kd arm versus 6.6 months in the Vd arm (HR = 0.80, 95% CI: 0.57, 1.11), ORR was 61.9% versus 54.9%.

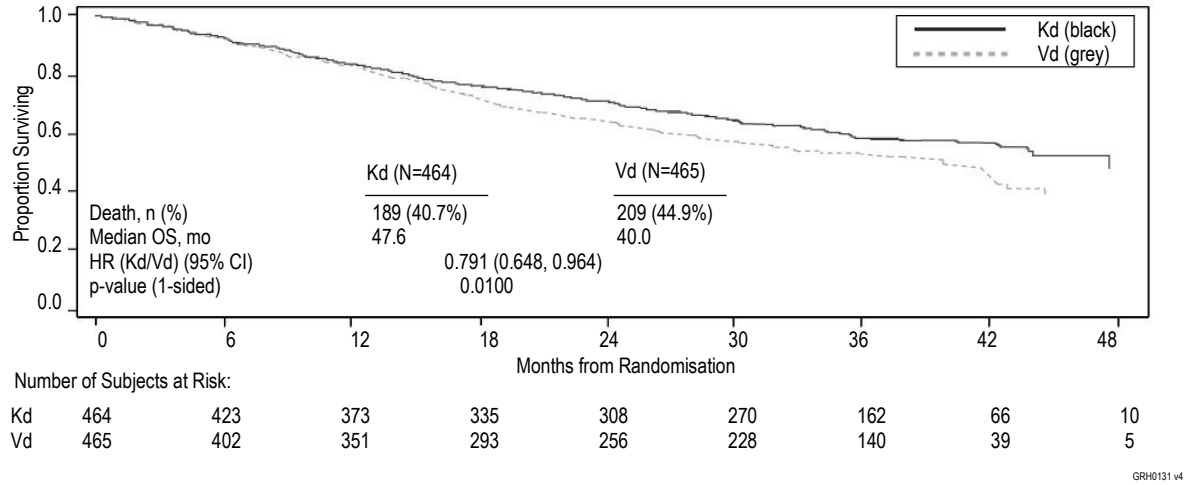
Figure 3. Kaplan-Meier plot of progression-free survival as determined by the IRC (intent-to-treat population) study 2011-003



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

A pre-planned second interim OS analysis was performed after 189 deaths in the Kd arm and 209 deaths in the Vd arm. At the time of the analysis, 80% of the targeted events were registered. 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 = 0.791; 95% CI: 0.65, 0.96; p-value = 0.010) (see figure 4).

Figure 4. Kaplan-Meier curve of overall survival in relapsed multiple myeloma study 2011-003



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

Kyprolis in combination with daratumumab and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma – study 20160275 (CANDOR)

The safety and efficacy of Kyprolis were evaluated in a phase 3, randomised, open-label, multicentre superiority trial of Kyprolis with daratumumab plus dexamethasone (KdD) versus Kyprolis plus dexamethasone (Kd). A total of 466 patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy were enrolled and randomised in a 2:1 randomisation (312 in KdD arm and 154 in Kd arm).

In the KdD and Kd arms, Kyprolis was evaluated at a starting dose of 20 mg/m^2, which was increased to 56 mg/m^2 on cycle 1, day 8 administered twice weekly for 3 out of 4 weeks as a 30 minute infusion.

Patients who had the following were excluded from the trial: known moderate or severe persistent asthma within the past 2 years, known chronic obstructive pulmonary disease (COPD) with a FEV1 < 50% of predicted normal, active congestive heart failure.

Demographics and baseline characteristics were generally consistent between the two arms, including gender (57.5% male), race (78.5% white subjects), age (64 years, range 29-84 years), prior treatment with bortezomib (90%), bortezomib refractory (29%), high risk genetic mutations, consisting of the genetic subtypes t(4; 14), t(14; 16), or deletion17p (16%) and unknown-risk genetic-mutations which included subjects with results not done, failed or quantity insufficient (51%). A smaller proportion of subjects were aged ≥ 75 years in the KdD group (9.0%) than in the Kd group (14.3%). Subjects had a median (range) of 2.0 (1 to 4) prior lines of therapy. A higher percent of subjects had a prior transplant in the KdD group (62.5%) compared with the Kd group (48.7%). Only 1 patient in KdD group received previous anti-CD38 monoclonal antibody therapy.

The results of the primary analysis of study 20160275 are summarised in table 9 and figure 5 and figure 6.

Table 9. Summary of efficacy in study 20160275 at primary analysis

	KdD arm (N = 312)	**Kd arm (N = 154)**
PFS months median (95% CI)[a]	NE (NE, NE)	15.8 (12.1, NE)
HR (95% CI); 1-sided p-value[b]	0.630 (0.464, 0.854); 0.0014	
ORR (%) (95% CI)[a, c]	84.3 (79.8, 88.1)	74.7 (67.0, 81.3)
Response category, n(%)		
N with response	263	115
CR	89 (28.5)	16 (10.4)
MRD [-] CR	43 (13.8)	5 (3.2)
VGPR	127 (40.7)	59 (38.3)
PR	47 (15.1)	40 (26.0)
Odds ratio	1.925 (1.184, 3.129)	
1-sided p-value[b]	0.0040	
MRD[-]CR at 12 months	12.5 (9.0, 16.7)	1.3 (0.2, 4.6)
Odds ratio	11.329 (2.703, 47.476)	
1-sided p-value[b]	< 0.0001	

KdD = Kyprolis plus dexamethasone and daratumumab; Kd = Kyprolis plus dexamethasone; CI = confidence interval; NE = not estimable; HR = hazard ratio; ORR = overall response rate; CR = complete response;

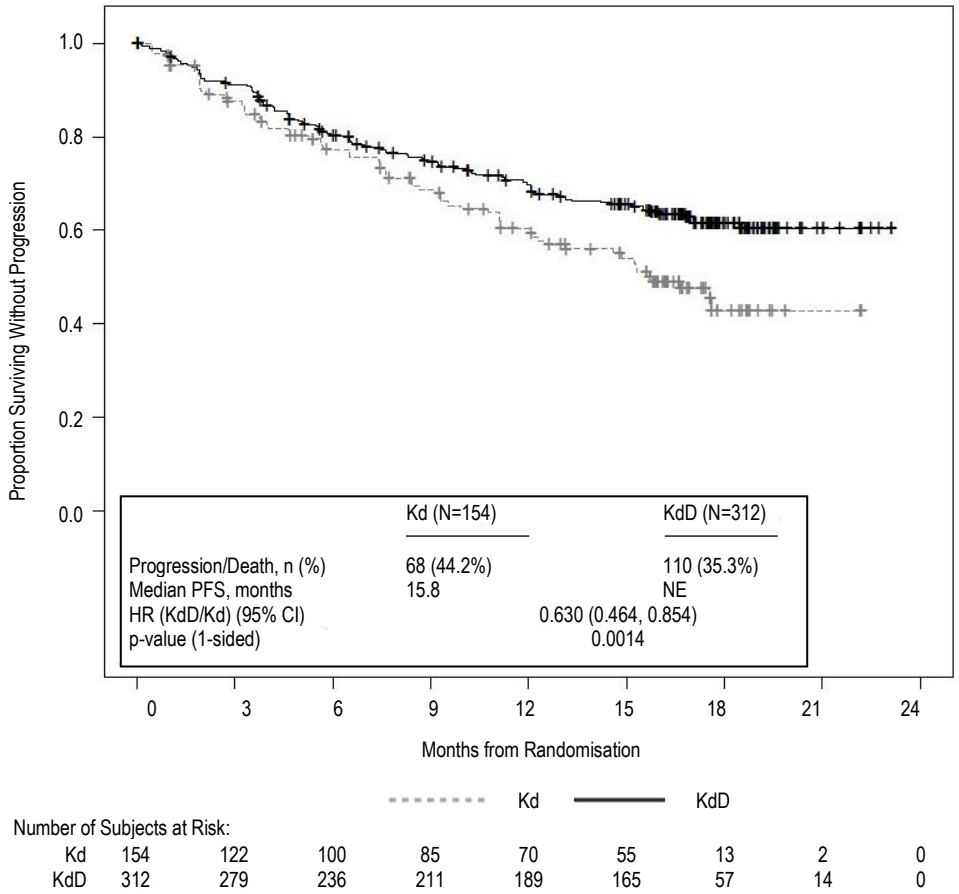
VGPR = very good partial response; MRD[-]CR = complete response with negative (or no) minimal residual disease.
[a.] These endpoints were determined by an Independent Review Committee using IMWG response criteria.
[b.] Statistically significant
[c.] Overall response is defined as achieving a best overall response of PR, VGPR, CR, or better.
Data cut off for primary analysis: 14 July 2019

At the time of the primary PFS analysis the trial demonstrated an improvement in PFS in the KdD arm as compared to the Kd arm (hazard ratio [HR] = 0.630; 95% CI: 0.464, 0.854; p = 0.0014) which represents a 37% reduction in the risk of disease progression or death in patients treated with KdD. The median PFS was not estimable for the KdD arm and was 15.8 months in the Kd arm.

In patients who received prior lenalidomide (42.3%), median PFS was NE in the KdD arm versus 12.1 months in the Kd arm (HR = 0.52, 95% CI: 0.34, 0.80), ORR was 78.9% versus 74.3% (OR = 1.29, 95% CI: 0.65, 2.54), and MRD[-]CR at 12 months was 11.4% versus 0.0% (OR = NE, 95% CI: NE, NE). In patients refractory to lenalidomide (33%), median PFS was NE in the KdD arm versus 11.1 months in the Kd arm (HR = 0.45, 95% CI: 0.28, 0.74), ORR was 79.8% versus 72.7% (OR = 1.48, 95% CI: 0.69, 3.20), and MRD[-]CR at 12 months 13.1% versus 0.0% (OR = NE, 95% CI: NE, NE).

Limited data are available in elderly patients (≥ 75 years). A total of 43 patients above 75 years of age were enrolled in study 20160275 (25 patients in the KdD group and 18 patients in the Kd group). A HR of 1.459 (95% CI: 0.504, 4.223) in PFS was observed. The risk of fatal treatment-emergent adverse events was higher among subjects ≥ 65 years of age (see section 4.8). KdD should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis.

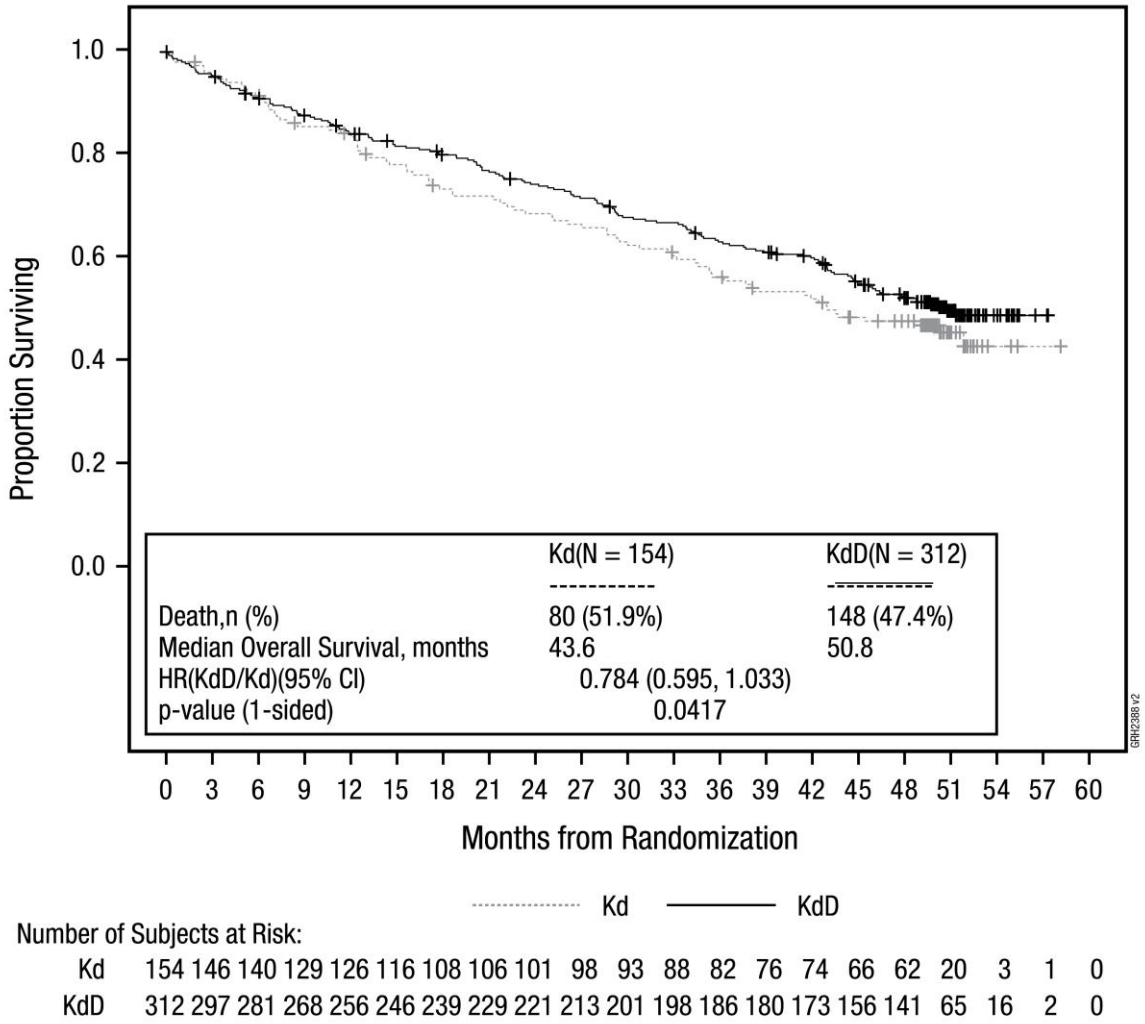
Figure 5. Kaplan-Meier plot of progression-free survival (intent-to-treat-population) as determined by IRC study 20160275



ORR was 84.3% for patients in the KdD arm and 74.7% in the Kd arm (see table 9). The median duration of response was not estimable for the KdD arm and was 16.6 months (13.9, NE) for the Kd group. The median time to response was 1.0 (1, 14) months for the KdD arm and 1.0 (1, 10) months for the Kd arm.

At the time of final analysis, 148 subjects (47.4%) in the KdD group and 80 subjects (51.9%) in the Kd group had died. Median OS (95% CI) was 50.8 (44.7, NE) months for the KdD group and 43.6 (35.3, NE) months for the Kd group, with a HR (KdD/Kd) of 0.784 (95% CI: 0.595, 1.033; 1-sided p = 0.0417). This one-sided p-value did not meet the statistical significance level of 0.021 for this final analysis. Median follow-up time was 50.6 months in the KdD group and 50.1 months in the Kd group.

Figure 6. Kaplan-Meier plot of overall survival in study 20160275



Kyprolis monotherapy in patients with relapsed and refractory multiple myeloma

Additional clinical experience has been generated with Kyprolis monotherapy in patients with relapsed and refractory multiple myeloma. Study PX-171-011 was an open-label, randomised phase 3 study (N = 315; exposure to ≥ 3 prior therapies required). Patients enrolled to study PX-171-011 were more heavily pre-treated with lower organ and marrow function as compared to those enrolled in study PX-171-009. PX-171-011 evaluated Kyprolis monotherapy versus a control arm (corticosteroids and cyclophosphamide). The study did not meet its primary efficacy endpoint of demonstrating superiority of Kyprolis monotherapy over the active control arm in overall survival (HR = 0.975 [95% CI: 0.760, 1.249]). PX-171-003A1 was a single-arm phase 2 study (N = 266; exposure to ≥ 2 prior therapies required), which met its primary efficacy endpoint of IRC-assessed ORR (22.9%).

Cardiac electrophysiology

An evaluation of possible effects of carfilzomib on cardiac function was performed by analysing, via central blind reading, triplicate ECG in 154 subjects with advanced malignancies, including multiple myeloma. The effect of carfilzomib on cardiac repolarisation using the QT interval with Fridericia's correction (QTcF interval) and the analysis of concentration-QTc relationships show no clear signal of any dose-related effect. The upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcF at C_{max} was 4.8 msec. With Bazett's correction (QTcB interval), the upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcB at C_{max} was 5.9 msec.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Kyprolis in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

The safety and effectiveness of carfilzomib in combination with chemotherapy were evaluated, but not established in an open-label, multicentre, single-arm phase 2 study (study 20140106) in paediatric patients from ages 1 year to less than 18 years of age (and adults younger than 21 years) with relapsed or refractory B-cell acute lymphoblastic leukemia/leukaemia (ALL) who have received prior targeted B-cell immune therapy or relapsed or refractory T-cell ALL compared to an external control group (selected from study 20180065).

A total of 105 patients received at least one dose of carfilzomib (61 B-cell subjects and 44 T-cell patients). Among the treated patients, 64 completed carfilzomib (37 B-cell patients, 27 T-cell patients), and 32 completed study (19 B-cell patients, 13 T-cell patients). The primary efficacy endpoint was complete remission measured by the proportion of subjects whose best response was CR at the end of induction therapy. The external control arm included 80 B-cell subjects and 60 T-cell subjects. After the propensity score weighting adjustment, the effective sample size was 59.3 B-cell subjects and 44.6 T-cell subjects in the external control arm. In B-cell subjects, the rate of complete remission (CR) was 14.8% in the carfilzomib in combination with vincristine, dexamethasone, PEG-asparaginase, and doxorubicin (CFZ-VXLD) arm, and 7.8% in external control arm. The corresponding odds ratio (OR) (95% confidence interval (CI)) was 2.039 (0.543, 7.658) comparing CFZ-VXLD arm to the external control arm. In T-cell subjects, the CR rate was 13.6% in CFZ-VXLD arm, and 9.1% in external control arm. The corresponding OR (95% CI) was 1.580 (0.470, 5.308) comparing CFZ-VXLD arm to the external control arm. This primary endpoint did not meet the statistical significance for superiority for carfilzomib in combination with chemotherapy when compared to the external control arm for each phenotype.

5.2 Pharmacokinetic properties

Absorption

The C_{max} and AUC following a 2 to 10 minute intravenous infusion of 27 mg/m^2 was 4 232 ng/mL and 379 ng•hr/mL, respectively. Following repeated doses of Kyprolis 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) was approximately 2.5-fold that observed at the 27 mg/m^2 level, and C_{max} (2 079 ng/mL) was 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 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 ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on day 1 of cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. Carfilzomib is eliminated primarily via metabolism with subsequent excretion of its metabolites in urine.

Special populations

Population pharmacokinetic analyses indicate there are no effects of age, gender or race on the pharmacokinetics of carfilzomib.

Paediatric population

The pharmacokinetics of carfilzomib was evaluated in study 20140106; however the pharmacokinetic data obtained were too limited to reliably characterise exposures in paediatrics, see sections 4.2 and 5.1.

Therefore, no conclusions can be drawn regarding pharmacokinetics behaviour of carfilzomib in this population.

Hepatic impairment

A pharmacokinetic study evaluated 33 patients with relapsed or progressive advanced malignancies (solid tumours; n = 31 or haematologic malignancies; n = 2) who had normal hepatic function (bilirubin ≤ upper limit of normal [ULN]; aspartate aminotransferase [AST] ≤ ULN, n = 10), mild hepatic impairment (bilirubin > 1-1.5 × ULN or AST > ULN, but bilirubin ≤ ULN, n = 14), or moderate hepatic impairment (bilirubin > 1.5-3 × ULN; any AST, n = 9). The pharmacokinetics of carfilzomib has not been studied in patients with severe hepatic impairment (bilirubin > 3 × ULN and any AST). Kyprolis, as a single agent, was administered intravenously over 30 minutes at 20 mg/m^2 on days 1 and 2 and at 27 mg/m^2 on days 8, 9, 15 and 16 of cycle 1. If tolerated, patients received 56 mg/m^2 starting in cycle 2. Baseline hepatic function status had no marked effect on the total systemic exposure (AUC_{last}) of carfilzomib following single or repeat-dose administration (geometric mean ratio in AUC_{last} at the 27 mg/m^2 dose in cycle 1, day 16 for mild and moderate impairment versus normal hepatic function were 144.4% and 126.1%, respectively; and at the 56 mg/m^2 dose in cycle 2, day 1 were 144.7% and 121.1%). However, in patients with mild or moderate baseline hepatic impairment, all of whom had solid tumours, there was a higher subject incidence of hepatic function abnormalities, ≥ grade 3 adverse events and serious adverse events compared with subjects with normal hepatic function (see section 4.2).

Renal impairment

The pharmacokinetics of carfilzomib was studied in two dedicated renal impairment studies.

The first study was conducted in 50 multiple myeloma patients with normal renal function (CrCL > 80 mL/min, n = 12), mild (CrCL 50-80 mL/min, n = 12), moderate (CrCL 30-49 mL/min, n = 10), and severe (CrCL < 30 mL/min, n = 8) renal impairment, and patients on chronic dialysis (n = 8). Kyprolis, as a single agent, was administered intravenously over 2 to 10 minutes at doses up to 20 mg/m^2. Pharmacokinetic data were collected from patients following the 15 mg/m^2 dose in cycle 1 and the 20 mg/m^2 dose in cycle 2. The second study was conducted in 23 relapsed multiple myeloma patients with creatinine clearance ≥ 75 mL/min (n = 13) and patients with end stage renal disease (ESRD) requiring dialysis (n = 10). Pharmacokinetic data were collected from patients following administration of a 27 mg/m^2 dose as a 30 minute infusion on cycle 1, day 16 and the 56 mg/m^2 dose on cycle 2, day 1.

Results from both studies show that renal function status had no marked effect on the exposure of carfilzomib following single or repeat-dose administration. The geometric mean ratio in AUC_{last} at the 15 mg/m^2 dose cycle 1, day 1 for mild, moderate, severe renal impairment and chronic dialysis versus normal renal function were 124.36%, 111.07%, 84.73% and 121.72%, respectively. The geometric mean ratios in AUC_{last} at the 27 mg/m^2 dose cycle 1, day 16 and at the 56 mg/m^2 dose cycle 2, day 1 for ESRD versus normal renal function were 139.72% and 132.75%, respectively. In the first study the M14 metabolite, a peptide fragment and the most abundant circulating metabolite, increased 2- and 3-fold in patients with moderate and severe renal impairment, respectively, and 7-fold in patients requiring dialysis (based on AUC_{last}). In the second study, the exposures for M14 were greater (approximately 4-fold) in subjects with ESRD than in subjects with normal renal function. This metabolite has no known biological activities. Serious adverse events related to worsening renal function were more common in subjects with baseline renal dysfunction (see section 4.2).

5.3 Preclinical safety data

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.

Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (which corresponds to 36 mg/m^2 and is similar to the recommended dose in humans of 27 mg/m^2 based on BSA) 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 BSA. The highest non-severely toxic dose of 0.5 mg/kg in monkeys resulted in interstitial inflammation in the kidney along with slight glomerulopathy and slight heart inflammation. Those findings were reported at 6 mg/m^2 which are below the recommended dose in humans of 27 mg/m^2.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Betadex sulfobutyl ether sodium
Anhydrous citric acid (E330)
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Kyprolis powder for solution for infusion must not be mixed with sodium chloride 9 mg/mL (0.9%) solution for injection.

6.3 Shelf life

Powder vial (unopened)

3 years.

Reconstituted solution

Chemical and physical in-use stability of reconstituted solutions in the vial, syringe or intravenous bag has been demonstrated for 24 hours at 2°C - 8°C or for 4 hours at 25°C. The elapsed time from reconstitution to administration should not exceed 24 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should not be longer than 24 hours at 2°C – 8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

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

6.5 Nature and contents of container

Kyprolis 10 mg powder for solution for infusion
10 mL type I clear glass vial, closed with fluoropolymer laminated elastomeric stopper and aluminium seal with a light blue plastic flip off cap.

Kyprolis 30 mg powder for solution for infusion
30 mL type I clear glass vial, closed with fluoropolymer laminated elastomeric stopper and aluminium seal with an orange plastic flip off cap.

Kyprolis 60 mg powder for solution for infusion
50 mL type I clear glass vial, closed with fluoropolymer laminated elastomeric stopper and aluminium seal with a purple plastic flip off cap.

Pack size of one vial.

6.6 Special precautions for disposal and other handling

General precautions

Carfilzomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of Kyprolis. Use of gloves and other protective equipment is recommended.

Reconstitution and preparation for intravenous administration

Kyprolis vials contain no antimicrobial preservatives and are intended for single use only. 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. Calculate the dose (mg/m^2) and number of vials of Kyprolis required using the patient's 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%.

2. Remove vial from refrigerator just prior to use.

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 5 mL (for 10 mg vial), 15 mL (for 30 mg vial) or 29 mL (for 60 mg vial) sterile water for injections through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimise foaming.

4. Gently swirl and/or invert the vial slowly for approximately 1 minute, or until complete dissolution. DO NOT SHAKE. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear.

5. Visually inspect for particulate matter and discolouration prior to administration. The reconstituted product should be a clear, colourless to slightly yellow solution and should not be administered if any discolouration or particulate matter is observed.

6. Discard any unused portion left in the vial.

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

8. When administering in an intravenous 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 intravenous bag containing 5% glucose solution for injection.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1060/002
EU/1/15/1060/003
EU/1/15/1060/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2015
Date of latest renewal: 25 June 2020

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

Amgen NV
Telecomlaan 5-7
1831 Diegem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kyprolis 10 mg powder for solution for infusion
carfilzomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 mg of carfilzomib.
After reconstitution, 1 mL of solution contains 2 mg of carfilzomib.

3. LIST OF EXCIPIENTS

Excipients: Betadex sulfobutyl ether sodium, anhydrous citric acid (E330), sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion.
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused portions in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1060/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Kyprolis 10 mg powder for solution for infusion
carfilzomib
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kyprolis 30 mg powder for solution for infusion
carfilzomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 30 mg of carfilzomib.
After reconstitution, 1 mL of solution contains 2 mg of carfilzomib.

3. LIST OF EXCIPIENTS

Excipients: Betadex sulfobutyl ether sodium, anhydrous citric acid (E330), sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion.
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused portions in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1060/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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17. UNIQUE IDENTIFIER – 2D BARCODE

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18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Kyprolis 30 mg powder for solution for infusion
carfilzomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 30 mg of carfilzomib.
After reconstitution, 1 mL of solution contains 2 mg of carfilzomib.

3. LIST OF EXCIPIENTS

Betadex sulfobutyl ether sodium, anhydrous citric acid (E330), sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused portions in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1060/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Kyprolis 60 mg powder for solution for infusion
carfilzomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 60 mg of carfilzomib.
After reconstitution, 1 mL of solution contains 2 mg of carfilzomib.

3. LIST OF EXCIPIENTS

Excipients: Betadex sulfobutyl ether sodium, anhydrous citric acid (E330), sodium hydroxide. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion.
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused portions in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1060/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Kyprolis 60 mg powder for solution for infusion
carfilzomib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 60 mg of carfilzomib.
After reconstitution, 1 mL of solution contains 2 mg of carfilzomib.

3. LIST OF EXCIPIENTS

Betadex sulfobutyl ether sodium, anhydrous citric acid (E330), sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use.
Single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard unused portions in accordance with local requirements.

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Amgen Europe B.V.
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The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1060/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Kyprolis 10 mg powder for solution for infusion
Kyprolis 30 mg powder for solution for infusion
Kyprolis 60 mg powder for solution for infusion
carfilzomib

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Kyprolis is and what it is used for
2. What you need to know before you use Kyprolis
3. How to use Kyprolis
4. Possible side effects
5. How to store Kyprolis
6. Contents of the pack and other information

1. What Kyprolis is and what it is used for

Kyprolis is a medicine that contains the active substance carfilzomib.

Carfilzomib works by blocking the proteasome. The proteasome is a system within the cells that breaks down proteins when they are damaged or no longer needed. By preventing the breakdown of proteins in cancer cells, which are more likely to contain more abnormal proteins, Kyprolis causes the death of cancer cells.

Kyprolis is used to treat adult patients with multiple myeloma who have had at least one previous treatment for this disease. Multiple myeloma is a cancer of plasma cells (a type of white blood cell).

Kyprolis will be given to you together with daratumumab and dexamethasone, with lenalidomide and dexamethasone, or only with dexamethasone. Daratumumab, lenalidomide and dexamethasone are other medicines used to treat multiple myeloma.

2. What you need to know before you use Kyprolis

Your doctor will examine you and review your full medical history. You will be monitored closely during treatment. Before starting Kyprolis, and during treatment, you will undergo blood testing. This is to check that you have enough blood cells and your liver and kidneys are working properly. Your doctor or nurse will check if you are getting enough fluids.

You must read the package leaflet of all medicines that you take in combination with Kyprolis so that you understand the information related to those medicines.

Do not use Kyprolis if you are allergic to carfilzomib or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or nurse before using Kyprolis if you have any of the conditions listed below. You may need extra tests to check that your heart, kidneys and liver are working properly.

- Heart problems, including a history of chest pain (angina), heart attack, irregular heartbeat, high blood pressure or if you have ever taken a medicine for your heart
- Lung problems, including a history of shortness of breath at rest or with activity (dyspnoea)
- Kidney problems, including kidney failure or if you have ever received dialysis
- Liver problems, including a history of hepatitis, fatty liver, or if you have ever been told your liver is not working properly
- Unusual bleeding, including easy bruising, bleeding from an injury, such as a cut, that takes longer than expected to stop, or internal bleeding such as coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools; or bleeding in the brain leading to sudden numbness or paralysis on one side of the face, legs or arms, sudden severe headache or trouble seeing or difficulty speaking or swallowing. This can indicate you have low numbers of platelets (cells that help the blood to clot)
- A history of blood clots in your veins
- Leg or arm pain or swelling (which could be a symptom of blood clots in the deep veins of the leg or arm), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs)
- Any other major disease for which you were hospitalised or received any medicine.

<u>Conditions you need to look out for</u>

You must look out for certain symptoms while you are taking Kyprolis to reduce the risk of any problems. Kyprolis can make some conditions worse or cause serious side effects, which may be fatal, such as heart problems, lung problems, kidney problems, tumour lysis syndrome (a life-threatening condition that occurs when cancer cells break and release their content to the bloodstream), reactions to the Kyprolis infusion, unusual bruising or bleeding, (including internal bleeding), blood clots in your veins, liver problems, certain blood conditions, or a neurological condition known as PRES. See ‘Conditions you need to look out for’ in section 4.

Tell your doctor if you have ever had or might now have a hepatitis B infection. This is because this medicine could cause hepatitis B virus to become active again. Your doctor will check you for signs of this infection before, during and for some time after treatment with this medicine. Tell your doctor right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes.

At any time during or after your treatment, tell your doctor or nurse immediately if you: experience blurred, loss of or double vision, difficulty speaking, weakness in an arm or a leg, a change in the way you walk or problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion. These may all be symptoms of a serious and potentially fatal brain condition known as progressive multifocal leukoencephalopathy (PML). If you had these symptoms prior to treatment with carfilzomib, tell your doctor about any change in these symptoms.

Other medicines and Kyprolis

Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes any medicines obtained without a prescription, such as vitamins or herbal remedies.

Tell your doctor or nurse if you are taking medicines used to prevent pregnancy such as oral contraceptives or other hormonal contraceptives, as these may not be suitable for use with Kyprolis.

Children and adolescents

Kyprolis is not recommended for use in children and adolescents under 18 years. This is because the effectiveness of Kyprolis has not been established in paediatric patients.

Pregnancy and breast-feeding

For women taking Kyprolis

Do not take Kyprolis if you are pregnant, think you may be pregnant or are planning to have a baby. Treatment with Kyprolis has not been evaluated in pregnant women. While taking Kyprolis, and for 30 days after stopping treatment you should use a suitable method of contraception to ensure you do not become pregnant. You should talk to your doctor or nurse about suitable methods of contraception.

If you become pregnant while taking Kyprolis, notify your doctor or nurse immediately.

Do not take Kyprolis if you are breast-feeding. It is not known if Kyprolis passes into breast milk in humans.

Lenalidomide is expected to be harmful to the unborn child. As Kyprolis is given in combination with lenalidomide, you must follow the Pregnancy Prevention Programme (see package leaflet for lenalidomide for information on pregnancy prevention and discuss with your doctor, pharmacist or nurse).

For men taking Kyprolis

While taking Kyprolis and for 90 days after stopping treatment, you should use a condom even if your partner is pregnant.

If your partner becomes pregnant whilst you are taking Kyprolis or within 90 days after stopping treatment, notify your doctor or nurse immediately.

Driving and using machines

While you are being treated with Kyprolis you may experience fatigue, dizziness, fainting, and/or a drop in blood pressure. This may impair your ability to drive or operate machines. Do not drive a car or operate machines if you have these symptoms.

Kyprolis contains sodium

This medicine contains 37 mg sodium per 10 mg vial. This is equivalent to 1.9% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains 109 mg sodium per 30 mg vial. This is equivalent to 5.5% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This medicine contains 216 mg sodium per 60 mg vial. This is equivalent to 11% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Kyprolis contains cyclodextrin

This medicine contains 500 mg cyclodextrin (betadex sulfobutyl ether sodium) per 10 mg vial. This is equivalent to 88 mg/kg for a 70 kg adult.

This medicine contains 1 500 mg cyclodextrin (betadex sulfobutyl ether sodium) per 30 mg vial. This is equivalent to 88 mg/kg for a 70 kg adult.

This medicine contains 3 000 mg cyclodextrin (betadex sulfobutyl ether sodium) per 60 mg vial. This is equivalent to 88 mg/kg for a 70 kg adult.

3. How to use Kyprolis

Kyprolis will be given to you by a doctor or nurse. The dose will be calculated based on your height and weight (body surface area). Your doctor or nurse will determine the dose of Kyprolis that you receive.

Kyprolis will be given as an infusion into a vein. The infusion may last up to 30 minutes. Kyprolis is given 2 days in a row each week, for 3 weeks, followed by one week without treatment.

Each 28-day period is one treatment cycle. This means that Kyprolis will be given to you on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle. The doses on day 8 and 9 of each cycle will not be given from cycle 13 onwards if you are treated with Kyprolis in combination with lenalidomide and dexamethasone.

Most patients will receive treatment for as long as their disease improves or remains stable. However, Kyprolis treatment may also be stopped if you experience side effects that cannot be managed.

Together with Kyprolis you will also be given either lenalidomide and dexamethasone, daratumumab and dexamethasone, or only dexamethasone. You may also be given other medicines.

If you are given too much Kyprolis

As this medicine is being given by a doctor or nurse, it is unlikely that you will be given too much. However, if you are given too much Kyprolis your doctor will monitor you for side effects.

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

4. Possible side effects

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

Conditions you need to look out for

Some side effects could be serious. Tell your doctor straight away if you get notice any of the following symptoms:

- Chest pains, shortness of breath, or if there is swelling of your feet, which may be symptoms of heart problems
- Difficulty breathing, including shortness of breath at rest or with activity or a cough (dyspnoea), rapid breathing, feeling like you can't breathe in enough air, wheezing, or cough, which can be signs of lung toxicity
- Very high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis
- Shortness of breath with everyday activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting spells, which can be signs of a condition known as pulmonary hypertension
- Swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results, which may be symptoms of kidney problems or kidney failure
- A side effect called tumour lysis syndrome, which can be caused by the rapid breakdown of tumour cells and may cause irregular heartbeat, kidney failure or abnormal blood test results
- Fever, chills or shaking, joint pain, muscle pain, facial flushing, or swelling of the face, lips, tongue and/or throat which may cause difficulty breathing or swallowing (angioedema), weakness, shortness of breath, low blood pressure, fainting, slow heart rate, chest tightness, or chest pain can occur as a reaction to the infusion

- Unusual bruising or bleeding, such as a cut, that takes longer than usual to stop bleeding; or internal bleeding such as coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools; or bleeding in the brain leading to sudden numbness or paralysis on one side of the face, legs or arms, sudden severe headache or trouble seeing or difficulty speaking or swallowing
- Leg or arm pain or swelling (which could be a symptom of blood clots in the deep veins of the leg or arm), chest pain or shortness of breath (which may be a symptom of blood clots in the lungs)
- Yellowing of your skin and eyes (jaundice), abdominal pain or swelling, nausea or vomiting, which could be symptoms of liver problems including liver failure. If you have ever had hepatitis B infection, treatment with this medicine may cause the hepatitis B infection to become active again
- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhoea, and acute kidney failure, which may be signs of a blood condition known as thrombotic microangiopathy
- Headaches, confusion, seizures (fits), visual loss, and high blood pressure (hypertension), which may be symptoms of a neurologic condition known as posterior reversible encephalopathy syndrome (PRES).

Other possible side effects

Very common side effects (may affect more than 1 in 10 people)
- Serious lung infection (pneumonia)
- Respiratory tract infection (infection of the airways)
- Low platelets, which may cause easy bruising or bleeding (thrombocytopenia)
- Low white blood cell count, which may decrease your ability to fight infection and may be associated with fever
- Low red blood cell count (anaemia) which may cause tiredness and fatigue
- Changes to blood tests (decreased blood levels of potassium, increased blood levels of creatinine)
- Decreased appetite
- Difficulty sleeping (insomnia)
- Headache
- Numbness, tingling, or decreased sensation in hands and/or feet
- Dizziness
- High blood pressure (hypertension)
- Shortness of breath
- Cough
- Diarrhoea
- Nausea
- Constipation
- Vomiting
- Stomach pain
- Back pain
- Joint pain
- Pain in limbs, hands or feet
- Muscle spasms
- Fever
- Chills
- Swelling of the hands, feet or ankles
- Feeling weak
- Tiredness (fatigue)

Common side effects (may affect up to 1 in 10 people)
- Infusion reaction
- Heart failure and heart problems including rapid, strong or irregular heartbeat

- Heart attack
- Kidney problems, including kidney failure
- Blood clots in the veins (deep vein thrombosis)
- Feeling too hot
- Blood clot in the lungs
- Fluid in the lungs
- Wheezing
- Serious infection including infection in the blood (sepsis)
- Lung infection
- Liver problems including an increase in liver enzymes in the blood
- Flu-like symptoms (influenza)
- Reactivation of the chicken pox virus (shingles) that can cause a skin rash and pain (herpes zoster)
- Urinary tract infection (infection of structures that carry urine)
- Cough which could include chest tightness or pain, nasal congestion (bronchitis)
- Sore throat
- Inflammation of the nose and throat
- Runny nose, nasal congestion or sneezing
- Viral infection
- Infection of the stomach and intestine (gastroenteritis)
- Bleeding in the stomach and bowels
- Changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or phosphate, increased blood levels of calcium, uric acid, potassium, bilirubin, c-reactive protein or sugar)
- Dehydration
- Anxiety
- Feeling confused
- Blurred vision
- Cataract
- Low blood pressure (hypotension)
- Nose bleed
- Change in voice or hoarseness
- Indigestion
- Toothache
- Rash
- Bone pain, muscle pain, chest pain
- Muscle weakness
- Aching muscles
- Itchy skin
- Redness of the skin
- Increased sweating
- Pain
- Pain, swelling, irritation or discomfort where you received the injection into your vein
- Ringing in the ears (tinnitus)
- A general feeling of illness or discomfort

Uncommon side effects (may affect up to 1 in 100 people)
- Bleeding in the lungs
- Inflammation of the colon caused by a bacteria called *Clostridium difficile*
- Allergic reaction to Kyprolis
- Multi-organ failure
- Reduced blood flow to the heart
- Bleeding in the brain
- Stroke

- Difficulty breathing, rapid breathing and/or fingertips and lips looking slightly blue (acute respiratory distress syndrome)
- Swelling of the lining of the heart (pericarditis), symptoms include pain behind the breast bone, sometimes spreading across to the neck and shoulders, sometimes with a fever
- Fluid build-up in the lining of the heart (pericardial effusion), symptoms include chest pain or pressure and shortness of breath
- A blockage in the flow of bile from the liver (cholestasis), which can cause itchy skin, yellow skin, very dark urine and very pale stools
- Perforation of the digestive system
- Cytomegalovirus infection
- Hepatitis B infection activated again (viral inflammation of the liver)
- Inflammation of the pancreas

Reporting of side effects

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

5. How to store Kyprolis

Kyprolis will be stored in the pharmacy.

Keep this medicine out of the sight and reach of children.

Do not use Kyprolis after the expiry date printed on the vial and the carton. The expiry date refers to the last day of that month.

Store refrigerated (2°C - 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

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

Kyprolis is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What Kyprolis contains

- The active substance is carfilzomib. Each vial contains 10 mg, 30 mg or 60 mg of carfilzomib. After reconstitution, 1 mL of solution contains 2 mg of carfilzomib.
- The other ingredients are betadex sulfobutyl ether sodium, anhydrous citric acid (E330) and sodium hydroxide (see section 2 ‘Kyprolis contains sodium’).

What Kyprolis looks like and contents of the pack

Kyprolis is supplied in a glass vial as a white to off-white powder for solution for infusion, which is reconstituted (dissolved) before use. The reconstituted solution is a clear, colourless or slightly yellow solution.

Each pack contains 1 vial.

Marketing Authorisation Holder and Manufacturer
Amgen Europe B.V.
Minervum 7061,
4817 ZK Breda,
The Netherlands

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

Instructions for reconstitution and preparation of Kyprolis powder for solution for infusion for intravenous administration

Carfilzomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of Kyprolis. Use of gloves and other protective equipment is recommended.

Kyprolis vials contain no antimicrobial preservatives and are intended for single use only. 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. Calculate the dose (mg/m^2) and number of vials of Kyprolis required using the patient's 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%.

2. Remove vial from refrigerator just prior to use.

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 5 mL (for 10 mg vial), 15 mL (for 30 mg vial) or 29 mL (for 60 mg vial) sterile water for injections through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimise foaming.

4. Gently swirl and/or invert the vial slowly for approximately 1 minute, or until complete dissolution. DO NOT SHAKE. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear.

5. Visually inspect for particulate matter and discolouration prior to administration. The reconstituted product should be a clear, colourless to slightly yellow solution and should not be administered if any discolouration or particulate matter is observed.

6. Discard any unused portion left in the vial.

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

8. When administering in an intravenous 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 intravenous bag containing 5% glucose solution for injection.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should not be longer than 24 hours at 2°C – 8°C.

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