ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

### 1. NAME OF THE MEDICINAL PRODUCT

Kyprolis 60 mg powder for solution for infusion

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 60 mg of carfilzomib.

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

Excipient with known effect
Each mL of reconstituted solution contains 7 mg of sodium.

For the full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white lyophilised powder.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

Kyprolis in combination with lenalidomide and dexamethasone 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**

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). Each 28-day period is considered one treatment cycle. Kyprolis is administered at a starting dose of 20 mg/m² (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased to 27 mg/m² (maximum dose 60 mg) on day 8 of cycle 1. 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).

The dose is calculated using the patient’s baseline body surface area (BSA). Patients with a BSA greater than 2.2 m² should receive a dose based upon a BSA of 2.2 m². Dose adjustments do not need to be made for weight changes of less than or equal to 20%. From cycle 13, the day 8 and 9 doses of Kyprolis are omitted.
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

<table>
<thead>
<tr>
<th>Cycle 1</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyprolis (mg/m²):</td>
<td>20</td>
<td>20</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>Dexamethasone mg</td>
<td>40</td>
<td>-</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg daily</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

| Cycles 2–12 | | | |
| Kyprolis (mg/m²): | 27 | 27 | - | 27 | 27 | - | 27 | 27 | - | - | - |
| Dexamethasone mg | 40 | - | - | 40 | - | - | 40 | - | - | 40 | mg |
| Lenalidomide | 25 mg daily | - | - |

| Cycles 13 on | | | |
| Kyprolis (mg/m²): | 27 | 27 | - | - | - | - | 27 | 27 | - | - | - |
| Dexamethasone mg | 40 | - | - | 40 | - | - | 40 | - | - | 40 | mg |
| Lenalidomide | 25 mg daily | - | - |

Concomitant medicinal products

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

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

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 2. From 27 mg/m² to 20 mg/m² or from 20 mg/m² to 15 mg/m² is considered 1 dose level reduction.

Table 2 Dose modifications during Kyprolis treatment

<table>
<thead>
<tr>
<th>Haematologic toxicity</th>
<th>Recommended action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute neutrophil count &lt; 0.5 x10⁹/L (see section 4.4)</td>
<td>Stop dose</td>
</tr>
<tr>
<td>- If recovered to ≥ 0.5 x10⁹/L, continue at same dose level</td>
<td></td>
</tr>
<tr>
<td>- For subsequent drops to &lt; 0.5 x10⁹/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Stop dose</td>
</tr>
<tr>
<td>Absolute neutrophil count &lt; 0.5 x 10⁹/L and an oral temperature &gt; 38.5°C or two consecutive readings of &gt; 38.0°C for 2 hours</td>
<td>Stop dose</td>
</tr>
<tr>
<td>- If absolute neutrophil count returns to baseline grade and fever resolves, resume at the same dose level.</td>
<td></td>
</tr>
<tr>
<td>Platelet count &lt; 10 x10⁹/L or evidence of bleeding with thrombocytopenia (see section 4.4)</td>
<td>Stop dose</td>
</tr>
<tr>
<td>- If recovered to ≥ 10 x10⁹/L and/or bleeding is controlled continue at same dose level</td>
<td></td>
</tr>
<tr>
<td>- For subsequent drops to &lt; 10 x10⁹/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Kyprolis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-haematologic toxicity (renal)</th>
<th>Recommended action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine equal to or greater than 2 x baseline; or Creatinine clearance &lt; 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis (see section 4.4)</td>
<td>Stop dose and continue monitoring renal function (serum creatinine or creatinine clearance)</td>
</tr>
<tr>
<td>- Kyprolis should be resumed when renal function has recovered to within 25% of baseline; consider resuming at 1 dose level reduction</td>
<td></td>
</tr>
<tr>
<td>- For patients on dialysis receiving Kyprolis, the dose is to be administered after the dialysis procedure</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other non-haematologic toxicity</th>
<th>Recommended action</th>
</tr>
</thead>
<tbody>
<tr>
<td>All other grade 3 or 4 non-haematologic toxicities (see section 4.4)</td>
<td>Stop until resolved or returned to baseline</td>
</tr>
<tr>
<td>- Consider restarting the next scheduled treatment at 1 dose level reduction</td>
<td></td>
</tr>
</tbody>
</table>
Special populations

Renal impairment

Patients with moderate or severe renal impairment were excluded from Kyprolis-lenalidomide combination studies. 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 required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. Since dialysis clearance of Kyprolis concentrations has not been studied, the medicinal product should be administered after the dialysis procedure (see section 5.2). In phase 3 clinical studies the incidence of adverse events of acute renal failure was higher in subjects with lower baseline creatinine clearance than that among subjects with higher baseline creatinine clearance.

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

Hepatic impairment

Patients with hepatic impairment have not been systematically evaluated (see section 5.2). Liver enzymes and bilirubin should be monitored at treatment initiation and monthly during treatment with carfilzomib, regardless of baseline values.

Elderly patients

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

Paediatric population

The safety and efficacy of Kyprolis in paediatric patients have not been established. No data are available.

Method of administration

Kyprolis is to be administered intravenously as a 10 minute infusion. It must not be administered as a 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 is 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.

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). 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 trials. 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 medical assessment, prior to starting treatment with Kyprolis. This assessment should optimise the patient’s status, with particular attention to blood pressure 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. An effect of Kyprolis on QT interval cannot be excluded (see section 5.1).

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 section 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. All patients should be routinely evaluated for hypertension 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. 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 manage 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, 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).

Thrombocytopenia

Kyprolis causes thrombocytopenia with platelet nadirs observed between 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).

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.

Contraception

Female patients of child bearing potential (and/or their partners) must use effective contraception measures during and for one month following treatment. Male patients must use effective contraception measures during and for 3 months following treatment if their partner is pregnant or of childbearing potential and not using effective contraception (refer to section 4.6). Carfilzomib may decrease the efficacy of oral contraceptives (refer to section 4.5).

Sodium content

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

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 fresh human hepatocytes. A clinical trial using oral midazolam as a CYP3A probe 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. 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 IC50 = 2.01µM whereas it is unknown whether carfilzomib may or not inhibit other transporters OATP1B3, OAT1, OAT3, OCT2 and BSEP, at the systemic level. 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 these transporters is probably low.

The inhibition of UDP glucuronosyltransferase enzymes (UGT) by carfilzomib is not established.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Female patients of child bearing potential (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 section 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 childbearing 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 for 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 childbearing 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 trials. 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

The most serious adverse reactions that may occur during Kyprolis treatment include: cardiac toxicity, pulmonary toxicities, pulmonary hypertension, dyspnoea, hypertension including hypertensive crises, acute renal failure, tumour lysis syndrome, infusion reactions, thrombocytopenia, hepatic toxicity, PRES 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, diarrhoea, thrombocytopenia, nausea, pyrexia, dyspnoea, respiratory tract infection, cough and peripheral oedema.

Tabulated list of adverse reactions

Adverse reactions are presented below by system organ class and frequency category (table 3). Frequency categories were determined from the crude incidence rate reported for each adverse reaction in a dataset of pooled clinical studies (n = 2,044). Within each system organ class and frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 3 Tabulated list of adverse reactions

<table>
<thead>
<tr>
<th>MedDRA system organ class</th>
<th>Very common (≥ 1/10)</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Rare (≥ 1/10,000 to &lt; 1/1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Pneumonia</td>
<td>Sepsis</td>
<td>Drug hypersensitivity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Respiratory tract infection</td>
<td>Influenza</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Nasopharyngitis</td>
<td>Urinary tract infection</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Bronchitis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Viral infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Thrombocytopenia</td>
<td>Febrile neutropenia</td>
<td>HUS</td>
<td>TTP</td>
</tr>
<tr>
<td></td>
<td>Neutropenia</td>
<td>Leukopenia</td>
<td></td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Anaemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphopenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Hypokalaemia</td>
<td>Dehydration</td>
<td>Tumour lysis syndrome</td>
<td></td>
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<tr>
<td></td>
<td>Hyperglycaemia</td>
<td>Hyperkalaemia</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Decreased appetite</td>
<td>Hypomagnesaemia</td>
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<td></td>
<td></td>
<td>Hyperonatraemia</td>
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<td></td>
<td></td>
<td>Hypercalcaemia</td>
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<td>Hypocalcaemia</td>
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<td></td>
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<td>Hypophosphataemia</td>
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<td></td>
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<td>Hyperuricaemia</td>
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<tr>
<td></td>
<td></td>
<td>Hyperalbuminaemia</td>
<td></td>
<td></td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Insomnia</td>
<td>Anxiety</td>
<td></td>
<td></td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MedDRA system organ class</td>
<td>Very common (≥ 1/10)</td>
<td>Common (≥ 1/100 to &lt; 1/10)</td>
<td>Uncommon (≥ 1/1,000 to &lt; 1/100)</td>
<td>Rare (≥ 1/10,000 to &lt; 1/1,000)</td>
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<td>--------------------------</td>
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<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>Paraesthesia</td>
<td>Cerebrovascular accident</td>
<td>PRES</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>Hypoesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Eye disorders</td>
<td></td>
<td>Cataract</td>
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<tr>
<td></td>
<td></td>
<td>Blurred vision</td>
<td></td>
<td></td>
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<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Cardiac failure</td>
<td>Cardiac arrest</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Atrial fibrillation</td>
<td>Myocardial infarction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia</td>
<td>Myocardial ischaemia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Palpitations</td>
<td>Ejection fraction decreased</td>
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<td>Pericarditis</td>
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<td>Pericardial effusion</td>
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<td>Vascular disorders</td>
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<td>Hypertension</td>
<td>Hypertensive crisis</td>
<td>Hypertensive emergency</td>
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<td>Deep vein thrombosis</td>
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<td>Hypotension</td>
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<td>Flushing</td>
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<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Dyspnoea</td>
<td>Pulmonary embolism</td>
<td>ARDS</td>
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<td></td>
<td>Cough</td>
<td>Pulmonary oedema</td>
<td>Acute respiratory failure</td>
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<td>Epistaxis</td>
<td>Interstitial lung disease</td>
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<td>Oral pharyngeal pain</td>
<td>Pneumonitis</td>
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<td>Dysphonia</td>
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<td>Wheezing</td>
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<td>Pulmonary hypertension</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Vomiting</td>
<td>Dyspepsia</td>
<td>Gastrointestinal perforation</td>
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<td></td>
<td>Diarrhoea</td>
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<td></td>
<td>Constipation</td>
<td>Toothache</td>
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<td></td>
<td>Abdominal pain</td>
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<td>Nausea</td>
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<td>Hepatobiliary disorders</td>
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<td>Increased alanine aminotransferase</td>
<td>Hepatic failure</td>
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<td>Increased aspartate aminotransferase</td>
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<td>Gamma-glutamyltransferase</td>
<td>Cholestasis</td>
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<td></td>
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<td>increased Hyperbilirubinaemia</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
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<td>Pruritus</td>
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<td>Erythema</td>
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<td></td>
<td>Hyperhidrosis</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain</td>
<td>Musculoskeletal pain</td>
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<td></td>
<td>Arthralgia</td>
<td>Musculoskeletal pain chest</td>
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<td></td>
<td>Pain in extremity</td>
<td>pain</td>
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<td></td>
<td>Muscle spasms</td>
<td>Bone pain</td>
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<td>Myalgia</td>
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<td></td>
<td></td>
<td>Muscular weakness</td>
<td></td>
<td></td>
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<tr>
<td>MedDRA system organ class</td>
<td>Very common (≥ 1/10)</td>
<td>Common (≥ 1/100 to &lt; 1/10)</td>
<td>Uncommon (≥ 1/1,000 to &lt; 1/100)</td>
<td>Rare (≥ 1/10,000 to &lt; 1/1,000)</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Increased blood creatinine</td>
<td>Acute renal failure Renal failure Renal impairment Decreased creatinine renal clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Infusion reaction Pyrexia Peripheral oedema Asthenia Fatigue</td>
<td>Chest pain Pain Infusion site reaction Chills</td>
<td></td>
<td>Multi-organ failure</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td>Increased c-reactive protein Increased blood uric acid</td>
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</tbody>
</table>

Description of selected adverse reactions

*Cardiac failure, myocardial infarction and myocardial ischaemia*

In clinical studies with Kyprolis, cardiac failure (reported in approximately 7% of subjects), myocardial infarction (reported in approximately 2% of subjects) and myocardial ischaemia (reported in approximately 1% of subjects) typically occurred early in the course of Kyprolis therapy (< 5 cycles). Approximately 65% of cardiac failure events, 75% of myocardial infarction events, and 83% of myocardial ischaemia events were grade ≥ 3 events. For clinical management of cardiac disorders during Kyprolis treatment, see section 4.4.

*Dyspnoea*

Dyspnoea was reported in approximately 30% of subjects in clinical studies with Kyprolis. The majority of dyspnoea adverse reactions were non-serious (> 15% of dyspnoea events were 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 20% of subjects and approximately 30% of these events were grade ≥ 3, 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 40% of subjects in clinical studies with Kyprolis and approximately 60% of these events were grade ≥ 3. Kyprolis causes thrombocytopenia through inhibition of platelet budding from megakaryocytes resulting in a classic cyclical thrombocytopenia with platelet nadirs occurring around day 8 or 15 of each 28-day cycle and usually associated with recovery to baseline by the start of the next cycle. For clinical management of thrombocytopenia during Kyprolis treatment, see section 4.4.
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.

Other special populations

Elderly patients (≥ 75 years)

Overall, the subject incidence of certain adverse events (including cardiac arrhythmias, cardiac failure (see section 4.4), dyspnoea, leukopenia and thrombocytopenia) in clinical trials with Kyprolis in combination with lenalidomide and dexamethasone was higher for patients who were ≥ 75 years of age compared to patients who were < 75 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, ATC code: L01XX45

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/m² 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/m². 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.

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. Patients who had the following were excluded from the trial: 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.

Kyprolis treatment was administered for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and dexamethasone administration could continue until progression or unacceptable toxicity.

The 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 4 and in figure 1 and figure 2.
Table 4 Summary of efficacy analysis in relapsed multiple myeloma study PX-171-009

<table>
<thead>
<tr>
<th></th>
<th>KRd arma (N = 396)</th>
<th>Rd armb (N = 396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS months median (95% CI)</td>
<td>26.3 (23.3, 30.5)</td>
<td>17.6 (15.0, 20.6)</td>
</tr>
<tr>
<td>HR (95% CI); 1-sided p-valueb</td>
<td>0.69 (0.57, 0.83); &lt; 0.0001</td>
<td></td>
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<tr>
<td>OS months median (95% CI)</td>
<td>NE (NE, NE)</td>
<td>NE (32.1, NE)</td>
</tr>
<tr>
<td>HR (95% CI); 1-sided p-valuec</td>
<td>0.79 (0.63, 0.99); 0.0182</td>
<td></td>
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<tr>
<td>ORR n (%)</td>
<td>345 (87.1)</td>
<td>264 (66.7)</td>
</tr>
<tr>
<td>sCR</td>
<td>56 (14.1)</td>
<td>17 (4.3)</td>
</tr>
<tr>
<td>CR</td>
<td>70 (17.7)</td>
<td>20 (5.1)</td>
</tr>
<tr>
<td>VGPR</td>
<td>151 (38.1)</td>
<td>123 (31.1)</td>
</tr>
<tr>
<td>PR</td>
<td>68 (17.2)</td>
<td>104 (26.3)</td>
</tr>
<tr>
<td>95% CI of ORR</td>
<td>83.4, 90.3</td>
<td>61.8, 71.3</td>
</tr>
<tr>
<td>1-sided p-valuec</td>
<td>&lt; 0.0001</td>
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</table>

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; NE = not estimable; sCR = stringent complete response; CR = complete response; VGPR = very good partial response; PR = partial response; IMWG = international myeloma working group; EBMT = European blood and marrow transplantation

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

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 - < 50mL/min (n = 56).
Figure 1 Kaplan-Meier curve of progression-free survival in relapsed multiple myeloma

The Kaplan-Meier event-free rate for OS at 24 months was 73.3% (95% CI: 68.6% to 77.5%) in the KRd arm and 65.0% (95% CI: 59.9% to 69.5%) in the Rd arm.
Figure 2 Kaplan-Meier curve of interim overall survival in relapsed multiple myeloma

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

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. The p-values for ORR and Global Health Status/Quality of Life (QoL) scores are descriptive based on the pre-specified multiplicity adjustment plan

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 analyzing, via central blind reading, triplicate ECG in 154 subjects with advanced malignancies, including multiple myeloma. The effect of carfilzomib on cardiac repolarization using the QT interval with Fridericia’s correction (QTcF interval) and the analysis of concentration-QTc relationships show no clear signal of any dose-related effect. The upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcF at Cmax 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 Cmax 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).

5.2 Pharmacokinetic properties

Absorption

The \( C_{\text{max}} \) and AUC following a 2- to 10-minute intravenous infusion of 27 mg/m\(^2\) was 4,232 ng/mL and 379 ng\(\cdot\)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 36 mg/m\(^2\), there was a dose-dependent increase in exposure.

Distribution

The mean steady-state volume of distribution of a 20 mg/m\(^2\) dose of carfilzomib was 28 L. When tested \textit{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 \textit{in vitro} by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450 mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity.

Elimination

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

Special populations

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

No dedicated pharmacokinetic studies have been completed in patients with hepatic impairment (see section 4.4).

Renal function status had no effect on the clearance or exposure of carfilzomib following single or repeat-dose administration at doses up to 20 mg/m\(^2\) (see section 4.2).

5.3 Preclinical safety data

Carfilzomib was clastogenic in the \textit{in vitro} chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the \textit{in vitro} bacterial reverse mutation (Ames) test and was not clastogenic in the \textit{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/m² 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/m² which are below the recommended dose in humans of 27 mg/m².

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/m² 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
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 would not normally be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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

50 mL Type I clear glass vial, closed with fluoropolymer laminated elastomeric stopper and aluminium seal with plastic flip off cap.

Pack size of one vial.

6.6 Special precautions for disposal and other handling

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. Remove vial from refrigerator just prior to use.

2. Calculate the dose (mg/m²) and number of vials of Kyprolis required using the patient’s BSA at baseline. Patients with a BSA greater than 2.2 m² should receive a dose based upon a BSA of 2.2 m². Dose adjustments do not need to be made for weight changes of ≤ 20%.

3. Aseptically reconstitute each vial by slowly injecting 29 mL 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 discoloration prior to administration. The reconstituted product should be a clear, colourless to slightly yellow solution and should not be administered if any discoloration or particulate matter is observed.

6. Discard any unused portion left in the vial.

7. Optionally, Kyprolis can be administered in an intravenous bag.

8. When administering in an intravenous bag, withdraw the calculated dose from the vial and dilute into a 50 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
NL-4817 ZK Breda
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1060/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://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
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

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

The requirements for submission of periodic safety update reports 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 shall submit the first periodic safety update report 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 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.
A. LABELLING
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

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,
NL-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.
**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**

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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15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.
B. PACKAGE LEAFLET
Package leaflet: Information for the patient

Kyprolis 60 mg powder for solution for infusion
carfilzomib

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

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 lenalidomide and dexamethasone, which 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, 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 or bleeding from an injury, such as a cut, that takes longer than expected to stop. This can indicate you have low numbers of platelets (cells that help the blood to clot)
- Any other major disease for which you were hospitalised or received any medicine.

Conditions you need to look out for

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, liver problems, certain blood conditions, or a neurological condition known as PRES. See ‘Conditions you need to look out for’ in section 4.

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.

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, to ensure your partner does not become 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 0.3 mmol sodium (which is 7 mg sodium) per mL of reconstituted solution. This should be taken into consideration by patients on a controlled sodium diet.

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 lasts around 10 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.

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.

You will also be given lenalidomide and dexamethasone together with Kyprolis. 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 crises
• 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, weakness, shortness of breath, low blood pressure, fainting, 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
• Yellowing of your skin and eyes (jaundice), abdominal pain or swelling, nausea or vomiting, which could be symptoms of liver problems including liver failure
• 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)
• Infusion reactions
• Serious lung infection (pneumonia)
• Respiratory tract infection (infection of the airways)
• Runny nose or nasal congestion
• 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 sugar and/or 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
• Swelling of the hands, feet or ankles
• Feeling weak
• Tiredness (fatigue)

**Common side effects (may affect up to 1 in 10 people)**
• Heart failure and heart problems including rapid, strong or irregular heartbeat
• 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)
• Liver problems including an increase in liver enzymes in the blood
• Flu-like symptoms (influenza)
• 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
• Viral infection
• Changes to blood tests (decreased blood levels of sodium, magnesium, protein, calcium or phosphate, increased blood levels of calcium, uric acid, potassium, bilirubin or c-reactive protein)
• Dehydration
• Anxiety
• 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
• Chills
• Pain, swelling, irritation or discomfort where you received the injection into your vein

**Uncommon side effects (may affect up to 1 in 100 people)**
• Allergic reaction to Kyprolis
• Multi-organ failure
• Heart attack
• Reduced blood flow to the heart
• Stroke
• 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 between the lining of the heart and your 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
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

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

Kyprolis will be stored in the pharmacy.

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 to 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 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,
NL-4817 ZK Breda,
The Netherlands
Marketing Authorisation Holder:
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Minervum 7061
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The Netherlands

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

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://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 60 mg powder for solution for infusion 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. Remove vial from refrigerator just prior to use.

2. Calculate the dose (mg/m²) and number of vials of Kyprolis required using the patient’s body surface area (BSA) at baseline. Patients with a BSA greater than 2.2 m² should receive a dose based upon a BSA of 2.2 m². Dose adjustments do not need to be made for weight changes of ≤ 20%.

3. Aseptically reconstitute each vial by slowly injecting 29 mL 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. Optionally, Kyprolis can be administered in an intravenous bag.

8. When administering in an intravenous bag, withdraw the calculated dose from the vial and dilute into a 50 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 would not normally be longer than 24 hours at 2°C – 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

Disposal

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