Summary of Product Characteristics

Carfilnat (Carfilzomib for Injection 60 mg/vial)

1. Name of the medicinal product

Carfilnat (Carfilzomib for Injection 60 mg/vial)

2. Qualitative and quantitative composition

Each vial contains 60 mg of carfilzomib.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Lyophilized Powder for Injection

A white to off white lyophilized cake or powder.

Description for Reconstituted solution: Clear, color less solution and free from extraneous visible matter

4. Clinical particulars

4.1 Therapeutic indications

Carfilnat in combination with either lenalidomide and dexamethasone or 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

Carfilnat 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%.

Carfilnat in combination with lenalidomide and dexamethasone

When combined with lenalidomide and dexamethasone, Carfilnat 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.

Carfilnat 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 Carfilnat are omitted.

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

Treatment with Carfilnat 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 Carfilnat, 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 Carfilnat.

Table 1. Carfilnat in combination with lenalidomide and dexamethasone[a]

	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**
Carfilnat (mg/m^2)	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**
Carfilnat (mg/m^2)	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**

Carfilnat (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily									-	-

Infusion time is 10 minutes and remains consistent throughout the regimen

Carfilnat in combination with dexamethasone

When combined with dexamethasone, Carfilnat 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.

Carfilnat 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 Carfilnat 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 Carfilnat.

Table 2. Carfilnat in combination with dexamethasone alone[a]

	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**
Carfilnat (mg/m^2)	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**
Carfilnat (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

Infusion time is 30 minutes and remains consistent throughout the regimen

Concomitant medicinal products

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

Thromboprophylaxis is recommended in patients being treated with Carfilnat in combination with dexamethasone or 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 Carfilnat 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 Carfilnat 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 Carfilnat toxicity. Recommended actions and dose modifications are presented in table 3. Dose level reductions are presented in table 4.

Table 3. Dose modifications during Carfilnat treatment

Haematologic toxicity	Recommended action
• Absolute neutrophil count < 0.5 x 10^9/L (see section 4.4)	• Stop dose - If recovered to ≥ 0.5 x 10^9/L, continue at same dose level • For subsequent drops to < 0.5 x 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilnat[a]
• Febrile neutropenia • Absolute neutrophil count < 0.5 x 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 x 10^9/L or evidence of bleeding with thrombocytopenia (see section 4.4)	• Stop dose - If recovered to ≥ 10 x 10^9/L and/or bleeding is controlled continue at same dose level

	• For subsequent drops to < 10 x 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilnat[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) - Carfilnat 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 Carfilnat, 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]

ee table 4 for dose level reductions

Table 4. Dose level reductions for Carfilnat

Regimen	Carfilnat Dose	First Carfilnat dose reduction	Second Carfilnat dose reduction	Third Carfilnat dose reduction
Carfilnat, lenalidomide, and dexamethasone	27 mg/m^2	20 mg/m^2	15 mg/m^2 [a]	—
Carfilnat and dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2 [a]

Note: Carfilnat infusion times remain unchanged during dose reduction(s)

[a.] If symptoms do not resolve, discontinue Carfilnat treatment

Special populations

Renal impairment

Patients with moderate or severe renal impairment were enrolled in Carfilnat-dexamethasone combination studies, but were excluded from Carfilnat-lenalidomide combination studies. Thus, there are limited data for Carfilnat 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 Carfilnat 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 3). There are limited efficacy and safety data on patients with baseline creatinine clearance < 30 mL/min.

Since dialysis clearance of Carfilnat 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 Carfilnat studies in combination with either lenalidomide and dexamethasone or dexamethasone alone.

The pharmacokinetics of Carfilnat 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 3). 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 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 Carfilnat in paediatric patients have not been established. No data are available.

Method of administration

Carfilnat 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.

Carfilnat 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 Carfilnat administration.

Do not mix Carfilnat 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 Carfilnat 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 Carfilnat 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 Carfilnat. As lenalidomide may be used in combination with Carfilnat, 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 Carfilnat. Death due to cardiac arrest has occurred within a day of Carfilnat 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 Carfilnat for grade 3 or 4 cardiac events until recovery and consider whether to restart Carfilnat 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.

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 Carfilnat. 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. An effect of Carfilnat 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 Carfilnat. Some of these events have been fatal. Evaluate and stop Carfilnat until resolved and consider whether to restart Carfilnat based on a benefit/risk assessment (see section 4.2).

Pulmonary hypertension

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

Dyspnoea

Dyspnoea was commonly reported in patients treated with Carfilnat. Evaluate dyspnoea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Carfilnat for grade 3 and 4 dyspnoea until resolved or returned to baseline and consider whether to restart Carfilnat 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 Carfilnat. Some of these events have been fatal. It is recommended to control hypertension prior to starting treatment. All patients should be routinely evaluated for hypertension while on Carfilnat and treated as needed. If the hypertension cannot be controlled, the Carfilnat dose should be reduced. In case of hypertensive crises, stop Carfilnat until resolved or returned to baseline and consider whether to restart Carfilnat 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 Carfilnat. 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 Carfilnat 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 Carfilnat. 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 Carfilnat 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 Carfilnat until TLS is resolved (see section 4.2).

Infusion reactions

Infusion reactions, including life-threatening reactions, have been reported in patients who received Carfilnat. 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 Carfilnat. Dexamethasone should be administered prior to Carfilnat 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 Carfilnat, often associated with thrombocytopenia. Some of these events have been fatal (see section 4.8).

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

Venous thrombosis

Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received Carfilnat.

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. Carfilnat 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 Carfilnat. Some of these events have been fatal. Signs and symptoms of TTP/HUS should be monitored for. If the diagnosis is suspected, stop Carfilnat and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, Carfilnat can be restarted. The safety of reinitiating Carfilnat 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 Carfilnat. 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. Carfilnat should be discontinued if PRES is suspected. The safety of reinitiating Carfilnat 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 per mL of reconstituted solution. 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 human hepatocytes. A clinical trial using oral midazolam as a CYP3A probe conducted with carfilzomib at a dose of 27 mg/m^2 (2-10 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 trial 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 CYP11 -A2, 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 Carfilnat 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 = 2.01 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 IC50 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 childbearing potential/Contraception in males and females

Female patients of child bearing potential treated with Carfilnat (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, Carfilnat can cause foetal harm when administered to a pregnant woman. Carfilnat should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus. If Carfilnat 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 Carfilnat.

Fertility

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

4.7 Effects on ability to drive and use machines

Carfilnat 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 Carfilnat 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 Carfilnat 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, PRES, thrombotic microangiopathy and TTP/HUS. In clinical studies with Carfilnat, cardiac toxicity and dyspnoea typically occurred early in the course of Carfilnat 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 Carfilnat and dexamethasone (Kd) arm of study 2011-003 vs the Carfilnat, 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%).

Tabulated list of adverse reactions

Adverse reactions are presented below by system organ class and frequency category (table 5). Frequency categories were determined from the crude incidence rate reported for each adverse reaction in a dataset of pooled clinical studies (n = 2,944). Within each system organ class and frequency category, adverse reactions are presented in order of decreasing seriousness.

Table 5. 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	
Immune system disorders			Drug hypersensitivity	
Blood and lymphatic system disorders	Thrombocytopenia Neutropenia Anaemia Lymphopenia Leukopenia	Febrile neutropenia	HUS	TTP Thrombotic microangiopathy

Metabolism and nutrition disorders	Hypokalaemia Hyperglycaemia Decreased appetite	Dehydration Hyperkalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia Hypocalcaemia Hypophosphataemia Hyperuricaemia Hypoalbuminaemia	Tumour lysis syndrome	
Psychiatric disorders	Insomnia	Anxiety 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 Myocardial ischaemia Pericarditis Pericardial effusion	
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	

Hepatobiliary disorders		Increased alanine aminotransferase Increased aspartate aminotransferase Gamma-glutamyltransferase increased Hyperbilirubinaemia	Hepatic failure Cholestasis	
Skin and subcutaneous tissue disorders		Rash Pruritus Erythema Hyperhidrosis		
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Pain in extremity Muscle spasms	Musculoskeletal pain Musculoskeletal chest pain Bone pain Myalgia Muscular weakness		
Renal and urinary disorders	Increased blood creatinine	Acute kidney injury Renal failure Renal impairment Decreased creatinine renal clearance		
General disorders and administration site conditions	Pyrexia Peripheral oedema Asthenia Fatigue Chills	Chest pain Pain Infusion site reactions Influenza like illness Malaise	Multi-organ dysfunction syndrome	
Investigations		Increased c-reactive protein Increased blood uric acid		
Injury, poisoning and procedural complications		Infusion related reaction		

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

Description of selected adverse reactions

Cardiac failure, myocardial infarction and myocardial ischaemia

In clinical studies with Carfilnat, cardiac failure was reported in approximately 7% of subjects (5% of subjects had grade ≥ 3 events), myocardial infarction was reported in approximately

2% of subjects (1.5% of subjects had grade ≥ 3 events) and myocardial ischaemia was reported in approximately 1% of subjects (< 1% of subjects had grade ≥ 3 events). These events typically occurred early in the course of Carfilnat therapy (< 5 cycles). For clinical management of cardiac disorders during Carfilnat treatment, see section 4.4.

Dyspnoea

Dyspnoea was reported in approximately 30% of subjects in clinical studies with Carfilnat. 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 Carfilnat treatment, see section 4.4.

Hypertension including hypertensive crises

Hypertensive crises (hypertensive urgency or hypertensive emergency) have occurred following administration of Carfilnat. Some of these events have been fatal. In clinical studies, hypertension adverse events occurred in approximately 20% of subjects and 7.5% 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 Carfilnat treatment, see section 4.4.

Thrombocytopenia

Thrombocytopenia was reported in approximately 34% of subjects in clinical studies with Carfilnat and approximately 20% of subjects had grade ≥ 3 events. Carfilnat 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 Carfilnat 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 Carfilnat (see section 4.4). The overall incidence of venous thromboembolic events was higher in the Carfilnat arms of two 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.

Hepatic failure

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

Peripheral neuropathy

In a randomised, open-label multicentre study in patients receiving Carfilnat 20/56 mg/m^2 infused over 30 minutes in combination with dexamethasone (Kd, n = 464) vs 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.

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 Carfilnat was higher for patients who were ≥ 75 years of age compared to patients who were < 75 years of age.

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 Carfilnat 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 Carfilnat 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/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

Carfilnat 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 Carfilnat were evaluated in a randomised, open-label, multicentre study of 792 patients with relapsed multiple myeloma, which evaluated the combination of Carfilnat with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone, randomised 1:1.

This study evaluated Carfilnat 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. Carfilnat 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 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.

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 6 and in figure 1 and figure 2.

Table 6. 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	

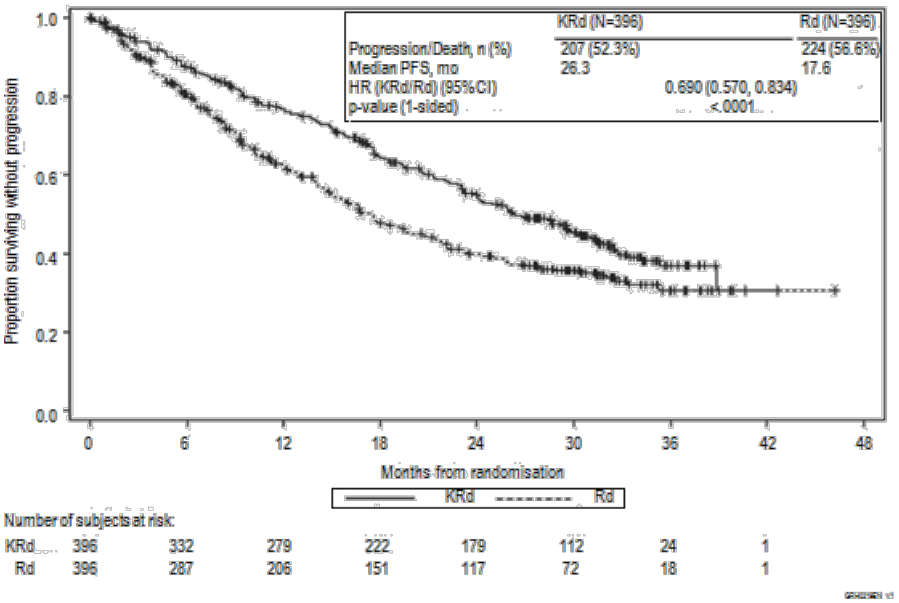
KRd = Carfilnat, lenalidomide and dexamethasone; Rd = lenalidomide and dexamethasone; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; OS = overall survival; ORR = overall response rate; sCR = stringent complete response; CR = complete response; VGPR = very good partial response; 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 Carfilnat, 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]

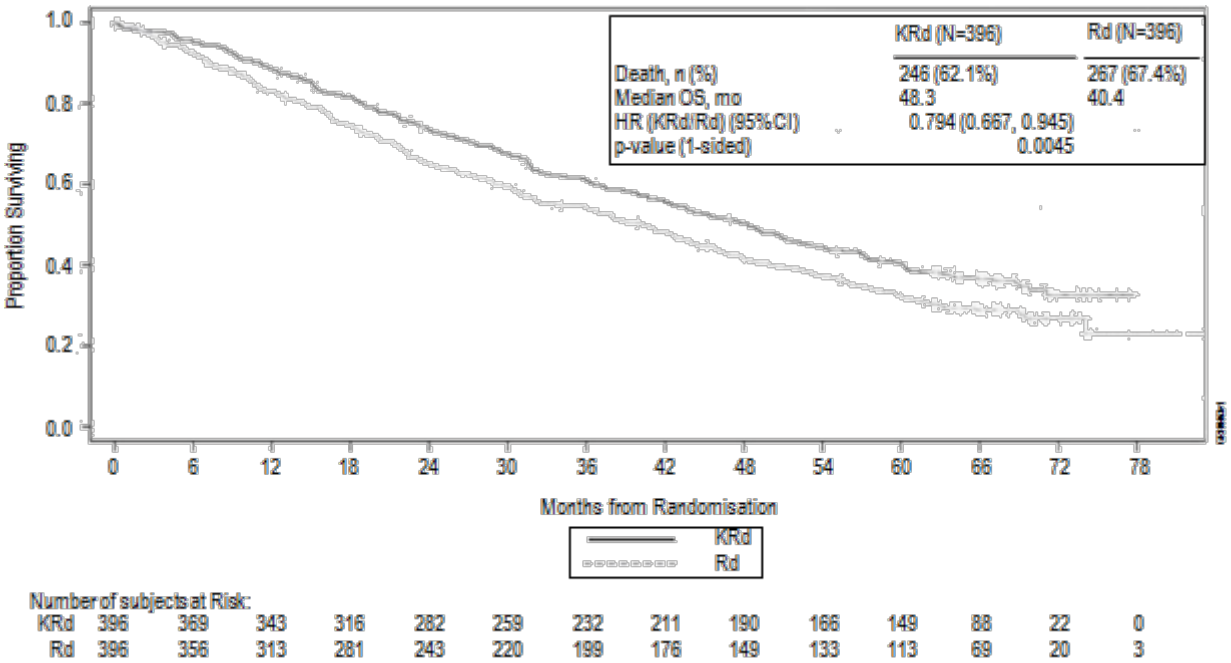


KRd = Carfilnat, lenalidomide and dexamethasone; Rd = lenalidomide, dexamethasone; PFS = progression-free survival; HR = hazard ratio; CI = confidence interval; IMWG = International Myeloma Working Group; EBMT = European blood and marrow transplantation; mo = months
Note: The response and PD outcomes 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 6 and Figure 2).

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



KRd = Carfilnat, 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.

Carfilnat in combination with dexamethasone for the treatment of patients with relapsed multiple myeloma – study 2011-003 (ENDEAVOR)

The safety and efficacy of Carfilnat were evaluated in a phase 3, randomised, open-label, multicentre study of Carfilnat 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 Carfilnat 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 trial: 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 7.

Table 7. 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 = Carfilnat 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).

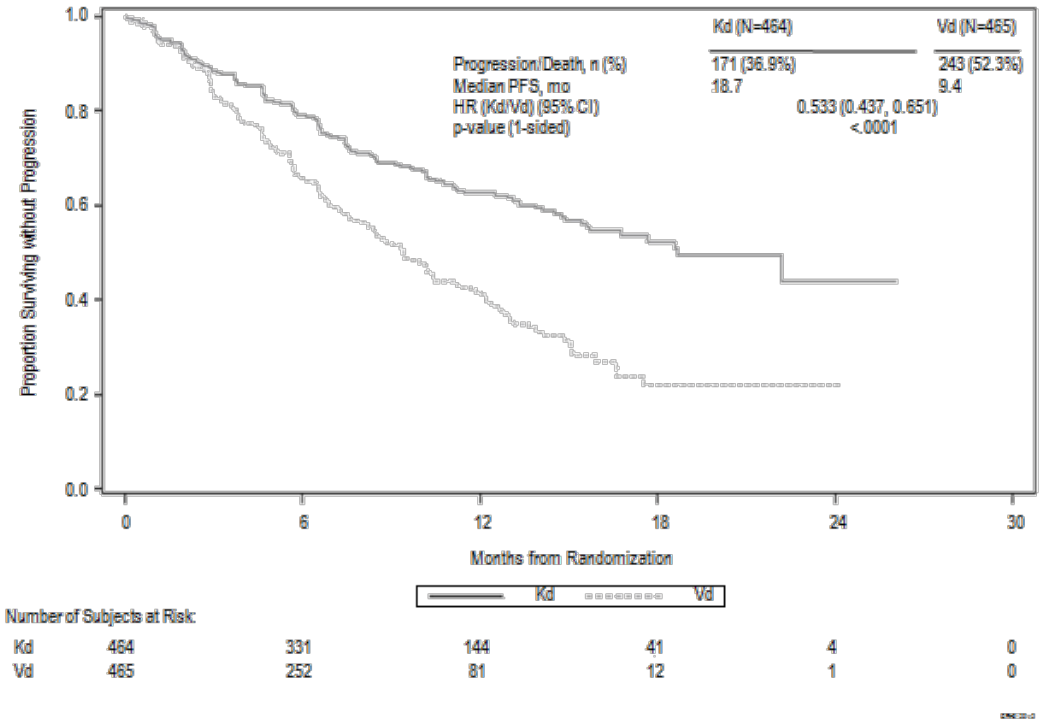
Similar PFS results were observed in patients who had received prior treatment with bortezomib (HR 0.56, 95% CI: 0.44, 0.73) and patients who had not received prior treatment with bortezomib (HR 0.48, 95% CI: 0.36, 0.66).

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%.

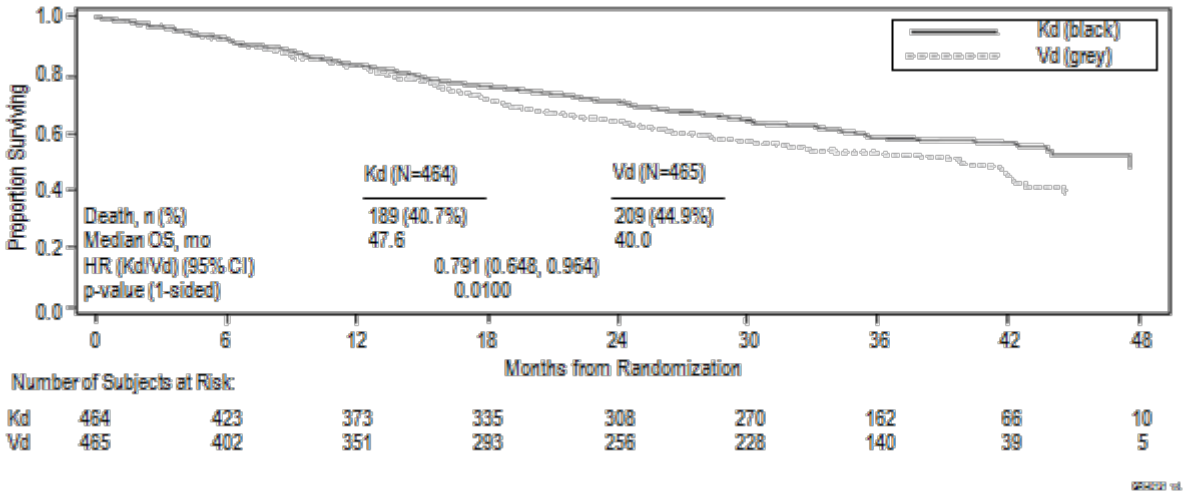
Figure 3. Kaplan-Meier plot of progression-free survival as determined by the IRC (intent-to-treat population) study 2011-003



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

Carfilnat monotherapy in patients with relapsed and refractory multiple myeloma

Additional clinical experience has been generated with Carfilnat 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 Carfilnat monotherapy versus a control arm (corticosteroids and cyclophosphamide). The study did not meet its primary efficacy endpoint of demonstrating superiority of Carfilnat 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 Carfilnat 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_{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 Carfilnat 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.

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 x ULN or AST > ULN, but bilirubin ≤ ULN, n = 14), or moderate hepatic impairment (bilirubin > 1.5-3 x ULN; any AST, n = 9). The pharmacokinetics of carfilzomib has not been studied in patients with severe hepatic impairment (bilirubin > 3 x ULN and any AST). Carfilnat, 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). Carfilnat, 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 (Emprove ® Bio)

6.2 Incompatibilities

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

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

6.3 Shelf life

2 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 and store in the original carton in order to protect from light”.

6.5 Nature and Contents of Container

50mL clear lyo vial with a 20mm double slotted rubber stoppers and sealed with 20 mm flip-off seals Ivory coloured button and then placed in a carton.

6.6 Special precautions for disposal and other handling

Reconstitution and preparation for intravenous administration

Carfilnat 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/m^2) and number of vials of Carfilnat 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%.

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. Carfilnat 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. Manufactured by

Natco Pharma Limited
Pharma Division
Kothur – 509 228
Rangareddy District
Telangana, India.

8. Date of revision of text

April, 2022