CARFILNAT (CARFILZOMIB) POWDER FOR SOLUTION FOR INFUSION 60 MG/ VIAL

DESCRIPTION:

Before reconstitution: A white to off white lyophilized cake or powder
After reconstitution: Clear, colorless solution and free from extraneous visible matter

COMPOSITION:

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

PHARMACODYNAMICS:

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 ($\geq 80\%$) 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.

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.

PHARMACOKINETICS:

Absorption

The Cmax 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 Cmax compared to that observed with a 2-to-10-minute infusion of the same dose. Following a 30-minute infusion of the 56 mg/m2 dose, the AUC (948 ng•hr/mL) was approximately 2.5-fold that observed at the 27 mg/m^2 level, and Cmax (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
Compared to patients with normal hepatic function, patients with mild (total bilirubin 1 to 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) and moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment had approximately 50% higher carfilzomib AUC. The pharmacokinetics of carfilzomib has not been evaluated in patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST).

Renal impairment
Relative to patients with normal renal function, ESRD patients on hemodialysis showed 33% higher carfilzomib AUC. Since hemodialysis clearance of carfilzomib concentrations have not been studied, the drug should be administered after the hemodialysis procedure.

INDICATION:
Carfilnat is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with:

- Lenalidomide and dexamethasone; or
- Dexamethasone; or
- Daratumumab and dexamethasone.

RECOMMENDED DOSAGE:

The dose is calculated using the patient's baseline body surface area (BSA). Patients with a BSA greater than 2.2m^2 should receive a dose based upon a BSA of 2.2m^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

Carfilnat is administered intravenously as a 10-minute infusion on days 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with lenalidomide and dexamethasone until Cycle 12 as shown in Table 1. Each 28-day period is considered one treatment cycle. The recommended starting dose of Carfilnat is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 on Cycle 1, Day 8. From Cycle 13, administer Carfilnat on Days 1, 2, 15, 16 until Cycle 18. Continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity occurs. Refer to the Prescribing Information for lenalidomide and dexamethasone for additional dosage information. 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.

Table 1: Carfilnat 20/27 mg/m^2 Twice Weekly (10-Minute Infusion) in Combination with Lenalidomide and Dexamethasone

	Cycle 1										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Days 23-24**
Carfilnat (mg/m^2)	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 2 to 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 23-24**
Carfilnat (mg/m^2)	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21										
	Cycles 13 and Later[a]										
	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 23-24**
Carfilnat (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-

[a] Carfilnat is administered through Cycle 18, lenalidomide and dexamethasone continue thereafter.

Carfilnat in Combination with Dexamethasone

Twice weekly 20/56 mg/m^2 regimen by 30-minute infusion

Carfilnat is administered intravenously as a 30-minute infusion on Day 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with dexamethasone until disease progression or unacceptable toxicity as shown in Table 2. The recommended starting dose of Carfilnat is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Cycle 1, Day 8. Administer dexamethasone 30 minutes to 4 hours before Carfilnat. Refer to the Prescribing Information for dexamethasone for additional dosage information.

Table 2: Carfilnat 20/ 56 mg/m^2 Twice Weekly (30-Minute Infusion) in Combination with Dexamethasone

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Day 22	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	-
	Cycles 2 and Later											
	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	-

Once weekly 20/70 mg/m^2 regimen by 30-minute infusion

Carfilnat is administered intravenously as a 30-minute infusion on Days 1, 8, and 15 of each 28-day cycle in combination with dexamethasone until disease progression or unacceptable toxicity as shown in Table 3. The recommended starting dose of Carfilnat is 20 mg/m^2 on Cycle, Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Cycle 1, Day 8. Administer dexamethasone 30 minutes to 4 hours before Carfilnat. Refer to the Prescribing Information for dexamethasone for additional dosage information.

Table 3: Carfilnat 20/ 70 mg/m^2 Once Weekly (30-Minute Infusion) in Combination with Dexamethasone

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Day 22	Day 23	Days 24-28
Carfilnat (mg/m^2)	20	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-	-
	Cycles 2 to 9											
	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)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-	-
	Cycles 10 and Later											
	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)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	-	-	-

Carfilnat in Combination with Intravenous Daratumumab and Dexamethasone

Twice weekly 20/56 mg/m^2 regimen by 30-minute infusion

Carfilnat is administered intravenously as a 30-minute infusion on Day 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with intravenous daratumumab and dexamethasone until disease progression or unacceptable toxicity as shown in Table 4. The recommended starting dose of Carfilnat is 20 mg/m^2 on Cycle 1, Day 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Cycle 1, Day 8 and thereafter. Administer dexamethasone 30 minutes to 4 hours before Carfilnat and 1 to 3 hours before intravenous daratumumab. Refer to the Prescribing Information for intravenous daratumumab and dexamethasone for additional information.

Table 4: Carfilnat 20/56 mg/m^2 Twice Weekly (30-Minute Infusion) in Combination with Intravenous Daratumumab and Dexamethasone

	Cycle 1											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilnat (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
	Cycle 2											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilnat (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
	Cycles 3 to 6											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilnat (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
	Cycles 7 and Onwards											
	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	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-

*For patients > 75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week.

Once weekly 20/70 mg/m^2 regimen by 30-minute infusion

Carfilnat is administered intravenously as a 30-minute infusion on Days 1, 8, and 15 of each 28-day cycle in combination with intravenous daratumumab and dexamethasone until disease progression or unacceptable as shown in Table 5 The recommended starting dose of Carfilnat is 20 mg/m2 on Cycle 1, Day 1. If tolerated, escalate the dose to 70 mg/m^{2}on Cycle 1, Day 8 and thereafter. Administer dexamethasone 30 minutes to 4 hours before Carfilnat and 1 to 3 hours before intravenous daratumumab. Refer to the Prescribing Information for intravenous daratumumab and dexamethasone for additional dosage information.

Table 5: Carfilnat 20/70 mg/m^2 Once Weekly (30-Minute Infusion) in Combination with Intravenous Daratumumab and Dexamethasone

	Cycle 1											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilnat (mg/m^2)	20	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
Daratumumab (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
	Cycle 2											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilnat (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
	Cycles 3 to 6											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilnat (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	40	-	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
	Cycles 7 and Thereafter											
	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)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	40	-	-	40	-	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-

*For patients > 75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week.

Dosage Modifications for Adverse Reactions

Recommended actions and dosage modifications for Carfilnat are presented in Table 6. Dose level reductions are presented in Table 7. See the lenalidomide, intravenous daratumumab, and dexamethasone Prescribing Information respectively for recommended dosage modifications associated with each product.

Table 6: Dosage Modifications for Adverse Reactions[a]

Hematologic Toxicity *[see Warnings and Precautions, Adverse Reactions]*	**Recommended Action**
• ANC less than 0.5 $\times 10^9$/L	• Withhold dose • If recovered to greater than or equal to 0.5 $\times 10^9$/L, continue at the same dose level • For subsequent drops to less than 0.5 $\times 10^9$/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilnat[a]
• Febrile neutropenia ANC less than 0.5 × 109/L and an oral temperature more than 38.5°C or two consecutive readings of more than 38.0°C for 2 hours	• Withhold dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level
• Platelets less than 10 $\times 10^9$/L or evidence of bleeding with thrombocytopenia	• Withhold dose • If recovered to greater than or equal to 10 $\times 10^9$/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to less than 10 $\times 10^9$/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilnat[a]
Renal Toxicity **[see Warnings and Precautions}**	**Recommended Action**

• Serum creatinine greater than or equal to 2 × baseline, or
• Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for hemodialysis
	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance)
	  • If attributable to Carfilnat, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction[a]
	  • If not attributable to Carfilnat, dosing may be resumed at the discretion of the healthcare provider
	  • For patients on hemodialysis receiving Carfilnat, the dose is to be administered after the hemodialysis procedure

Other Non-hematologic Toxicity **[see Adverse Reactions]**	**Recommended Action**
• All other severe or life-threatening[b] non-hematological toxicities	• Withhold until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction[a]

ANC = absolute neutrophil count
[a] See Table 7 for dose level reductions.
[b] Grade 3 and 4.

Table 7: Dose Level Reductions for Adverse Reactions

Regimen	**Dose**	**First Dose Reduction**	**Second Dose Reduction**	**Third Dose Reduction**
Carfilnat and Dexamethasone OR Carfilnat, Daratumumab and Dexamethasone (once weekly)	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^{2a}
Carfilnat and Dexamethasone OR Carfilnat, Daratumumab, and Dexamethasone (twice weekly)	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^{2a}

Carfilnat, Lenalidomide, and Dexamethasone (twice weekly)	27 mg/m^2	20 mg/m^2	15 mg/m^{2a}	-

Note: Infusion times remain unchanged during dose reduction(s).

[a] If toxicity persists, discontinue Carfilnat treatment.

Dosage Modifications for Hepatic Impairment

For patients with mild (total bilirubin > 1 to 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment, reduce the dose of Carfilnat by 25%.

Recommended Dosage for End Stage Renal Disease

For patients with end stage renal disease who are on hemodialysis, administer Carfilnat after the hemodialysis procedure.

ROUTE OF ADMINISTRATION:

For intravenous infusion.

CONTRAINDICATION:

- Hypersensitivity to the active substance or to any of the excipients.
- Women who are breast-feeding.

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

WARNINGS AND PRECAUTIONS:

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.

Cardiac disorders

New or worsening cardiac failure (e.g., congestive cardiac failure, pulmonary oedema, and decreased ejection fraction), myocardial ischaemia and infarction have occurred following administration of carfilzomib. Death due to cardiac arrest has occurred within a day of carfilzomib 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.

Stop carfilzomib for grade 3 or 4 cardiac events until recovery and consider whether to restart carfilzomib at 1 dose level reduction based on a benefit/risk assessment.

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 carfilzomib. This assessment should optimize 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 carfilzomib on QT interval cannot be excluded.

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 carfilzomib. Some of these events have been fatal. Evaluate and stop carfilzomib until resolved and consider whether to restart carfilzomib based on a benefit/risk assessment.

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

Dyspnoea
Dyspnoea was commonly reported in patients treated with carfilzomib. Evaluate dyspnoea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop carfilzomib for grade 3 and 4 dyspnoea until resolved or returned to baseline and consider whether to restart carfilzomib based on a benefit/risk assessment.

Hypertension
Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with carfilzomib. 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 carfilzomib and treated as needed. If the hypertension cannot be controlled, the carfilozmib dose should be reduced. In case of hypertensive crises, stop carfilzomib until resolved or returned to baseline and consider whether to restart carfilzomib based on a benefit/risk assessment.

Acute renal failure
Cases of acute renal failure have been reported in patients who received carfilzomib. 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 carfilzomib 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.

Tumour lysis syndrome
Cases of tumour lysis syndrome (TLS), including with fatal outcome, have been reported in patients who received carfilzomib. 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 carfilzomib in cycle 1, and in subsequent cycles as needed. 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 carfilzomib until TLS is resolved.

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

Haemorrhage and thrombocytopenia
Cases of haemorrhage (e.g., gastrointestinal, pulmonary and intracranial haemorrhage) have been reported in patients treated with carfilzomib, often associated with thrombocytopenia. Some of these events have been. Carfilzomib 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. Platelet counts should be monitored frequently during treatment with carfilzomib. Reduce or stop dose as appropriate.

Venous thrombosis
Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received carfilzomib.
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. Carfilzomib can cause elevations of serum transaminases. Reduce or stop dose as appropriate. 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 carfilzomib. Some of these events have been fatal. Signs and symptoms of TTP/HUS should be monitored for. If the diagnosis is suspected, stop carfilzomib and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, carfilzomib can be restarted. The safety of reinitiating carfilzomib 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 carfilzomib. 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. Carfilzomib should be discontinued if PRES is suspected. The safety of reinitiating carfilzomib therapy in patients previously experiencing PRES is not known.

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

Progressive Multifocal Leukoencephalopathy
Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients receiving

carfilzomib who have had prior or concurrent immunosuppressive therapy.
Patients receiving carfilzomib should be monitored for any new or worsening neurologic, cognitive or behavioural signs and symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders.
If PML is suspected, further administration must be suspended until PML has been excluded by a specialist with appropriate diagnostic testing. If PML is confirmed, carfilzomib must be discontinued.

Embryo-Fetal Toxicity
Based on the mechanism of action and findings in animals, carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib administered intravenously to pregnant rabbits during organogenesis at a dose approximately 40% of the clinical dose of 27 mg/m2 based on BSA caused post- implantation loss and a decrease in fetal weight.
Advise pregnant women of the potential risk to a fetus.

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. Carfilzomib may decrease the efficacy of oral contraceptives.

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.

Pediatric Use
The safety and effectiveness of carfilzomib in pediatric patients have not been established.

Geriatric use
The incidence of serious adverse reactions in patients 65 and over was higher than the incidence in younger patients. No overall differences in effectiveness were observed between older and younger patients.

INTERACTIONS WITH OTHER MEDICAMENTS:
Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs.

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. 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. 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.

Based on its mechanism of action and findings in animals, carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib should not be used during pregnancy unless the potential benefit outweighs the potential risk to the fetus. If carfilzomib 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 fetus.

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/ Lactation

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 carfilzomib.

Fertility

There are no data on the effect of Carfilnat on human fertility. No fertility studies have been performed in animals.

SIDE EFFECTS:

Summary of safety profile

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

Tabulated list of adverse reactions

Adverse reactions are presented at Table 8 below by system organ class and frequency category (very common, common, uncommon, rare).

Table 8: Tabulated list of adverse reactions

MedDRA system organ class	Very common	Common	Uncommon	Rare
Infections and infestations	Pneumonia Respiratory tract infection	Sepsis Lung infection Influenza Herpes zoster* Urinary tract infection Bronchitis Gastroenteritis Viral infection Nasopharyngitis Rhinitis	Clostridium difficile colitis Cytomegalovirus infection Hepatitis B virus reactivation	
Immune system disorders			Drug hypersensitivity	
Blood and lymphatic system disorders	Thrombocytopenia Neutropenia Anaemia Lymphopenia Leukopenia	Febrile neutropenia	HUS TTP	Thrombotic microangiopathy
Metabolism and nutrition disorders	Hypokalaemia Decreased appetite	Dehydration Hyperkalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia Hypocalcaemia Hypophosphataemia Hyperuricaemia Hypoalbuminaemia Hyperglycaemia	Tumour lysis syndrome	
Psychiatric disorders	Insomnia	Anxiety Confusional state		
Nervous system disorders	Dizziness Peripheral neuropathy Headache	Paraesthesia Hypoaesthesia	Intracranial haemorrhage Cerebrovascular accident PRES	
Eye disorders		Cataract Blurred vision		
Ear and labyrinth disorders		Tinnitus		
Cardiac disorders		Cardiac failure Myocardial infarction Atrial fibrillation Tachycardia Ejection fraction decreased Palpitations	Cardiac arrest Cardiomyopathy Myocardial ischaemia Pericarditis Pericardial effusion Venticular tachycardia	
Vascular disorders	Hypertension	Deep vein thrombosis Hypotension Flushing	Hypertensive crisis Haemorrhage	Hypertensive emergency

Respiratory, thoracic, and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Pulmonary oedema Epistaxis Oropharyngeal pain Dysphonia Wheezing Pulmonary hypertension	ARDS Acute respiratory failure Pulmonary haemorrhage Interstitial lung disease Pneumonitis	
Gastrointestinal disorders	Vomiting Diarrhoea Constipation Abdominal pain Nausea	Gastrointestinal haemorrhage Dyspepsia Toothache	Gastrointestinal perforation Pancreatitis acute	
Hepatobiliary disorders		Increased alanine aminotransferase Increased aspartate aminotransferase Gamma-glutamyltransferase increased Hyperbilirubinaemia	Hepatic failure Cholestasis	
Skin and subcutaneous tissue disorders		Rash Pruritus Erythema Hyperhidrosis		Angioedema
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Pain in extremity Muscle spasms	Musculoskeletal pain Musculoskeletal chest pain Bone pain Myalgia Muscular weakness		
Renal and urinary disorders	Increased blood creatinine	Acute kidney injury Renal failure Renal impairment Decreased creatinine renal clearance		
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

SYMPTOMS AND TREATMENT OF OVERDOSE:

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of carfilzomib administered in error.

There is no known specific antidote for carfilzomib over dosage. In the event of overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE:

Advise patients that Carfilnat may cause fatigue, dizziness, fainting, and/or drop in blood pressure. Advise patients not to drive or operate machinery if they experience any of these symptoms.

INSTRUCTIONS FOR USE:

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

Reconstitution and preparation for intravenous administration

Carfilnat vials contain no antimicrobial preservatives and are intended for single use only. Unopened vials of Carfilnat are stable until the date indicated on the package when stored in the original package at 2-8°C. 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. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permits.

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 $\leq$ 20%.
3. Use only a 21-gauge or larger gauge needle (0.8 mm or smaller external diameter needle) to aseptically reconstitute each vial by slowly injecting 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, color less solution and free from extraneous visible matter and should not be administered if any discolouration or particulate matter is observed.
6. Discard any unused portion left in the vial. Do not pool unused portions from the vials. Do not administer more than one dose from a vial.
7. Carfilnat can be administered directly by intravenous infusion or optionally, administered in a 50ml intravenous bag containing 5% Dextrose Injection USP. 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 50mL intravenous bag containing 5% Dextrose Injection, USP for injection based on the calculated total dose and infusion time.

Disposal

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

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.

STORAGE CONDITIONS:

Unopen vial

Store in a refrigerator at 2°C – 8°C. Store in carton to protect from light. Keep out of reach of children.

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.

SHELF LIFE:

Please refer to outer package for details.

PACK SIZES:

A single use 50ml Type 1 clear glass tubular lyo vial with a 20mm double slotted rubber stopper and sealed with 20mm flip off seal ivory colour packed in an individual outer carton box together with a package insert

Pack of 1 unit vial/ box

MANUFACTURER:

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

PRODUCT REGISTRATION HOLDER:

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