For use in India only

To be sold by retail on the prescription of an Oncologist only.

PRESCRIBING INFORMATION

1. GENERIC NAME

Carfilzomib For Injection 10 mg/Vial

Kyfil

कायफिल

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains

Carfilzomib-------------10 mg

3. DOSAGE FORM AND STRENGTH

Carfilzomib for Injection 10mg/vial

4. CLINICAL PARTICULARS

4.1. Indications

Carfilzomib is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

Carfilzomib is indicated as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

4.2. Posology and Method of Administration

Hydration

Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high-risk of tumor lysis syndrome (TLS) or renal toxicity. Consider hydration with both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, give an additional 250 mL to 500 mL of intravenous fluids following Carfilzomib administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles.

Monitor patients for evidence of volume overload and adjust hydration to individual patient needs, especially in patients with or at risk for cardiac failure.

Electrolyte Monitoring

Monitor serum potassium levels regularly during treatment with Carfilzomib.

Premedications and Concomitant Medications

Premedicate with the recommended dose of dexamethasone for monotherapy or dexamethasone administered as part of the combination therapy.

Administration

Administer dexamethasone orally or intravenously at least 30 minutes but no more than 4 hours prior to all doses of Carfilzomib during Cycle 1 to reduce the incidence and severity of infusion-related reactions. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.

Provide thromboprophylaxis for patients being treated with Carfilzomib in combination with other therapies.

Consider antiviral prophylaxis to decrease the risk of herpes zoster reactivation.

Dose Calculation

For patients with body surface area (BSA) of 2.2 m^2 or less, calculate the Carfilzomib dose using actual BSA. Dose adjustments do not need to be made for weight changes of 20% or less. For patients with a BSA greater than 2.2 m^2, calculate the Carfilzomib dose using a BSA of 2.2 m^2.

Recommended Dosage

Carfilzomib in Combination with Lenalidomide and Dexamethasone

Administer Carfilzomib 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. The recommended starting dose of Carfilzomib 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 Carfilzomib on Days 1, 2, 15, 16 until Cycle 18. Discontinue Carfilzomib after 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.

Table 1: Carfilzomib 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 23-28
Carfilzomib (mg/m^2)	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycle 2to 12										
	Week 1			Week 2			Week 3			Week 4	
	Day 1	Day 2	Day 3–7	Day 8	Day 9	Day 10-14	Day 15	Day 16	Day 17-21	Day 22	Day 23-28
Carfilzomib (mg/m^2)	27	27	-	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	Day 3–7	Day 8	Day 9	Day 10-14	Day 15	Day 16	Day 17-21	D a y 22	Day 23 Day 24-28
Carfilzomib (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	-	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 13 and later[a]										
	Week 1			Week 2			Week 3			Week 4	
	1	2	3-7	8	9	10-14	15	16	17-21	22	23-28
Carfilzomib (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-

[a]Carfilzomib is administered through Cycle 18; lenalidomide and dexamethasone continue thereafter.

Carfilzomib in Combination with Dexamethasone

Administer Carfilzomib intravenously as a 30-minute infusion on Days 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 Carfilzomib 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 Carfilzomib.

Table 2: Carfilzomib 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	Days 2	Days 3–7	Day 8	Day 9	Day 10–14	Day 15	Day 16	Day 17–21	Day 22	Day 23	Day 24-28
Carfilzomib (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	Day 10–14	Day 15	Day 16	Day 17–21	Day 22	Day 23	Day 24-28
Carfilzomib (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

Administer Carfilzomib 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 Carfilzomib is 20 mg/m^2 on Cycle 1, 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 Carfilzomib. Refer to Prescribing Information for dexamethasone for additional dosage information.

Table 3: Carfilzomib 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
Carfilzomib (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
Carfilzomib (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
Carfilzomib (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	-	-	-

Carfilzomib Monotherapy

20/27 mg/m2 twice weekly regimen by 10-minute infusion

Administer Carfilzomib intravenously as a 10-minute infusion. In Cycles 1 through 12, administer Carfilzomib on Days 1, 2, 8, 9, 15 and 16 of each 28-day cycle. From Cycle 13, administer Carfilzomib on Days 1, 2, 15 and 16 of each 28- day cycle. Premedicate with dexamethasone 4 mg orally or intravenously 30 minutes to 4 hours before each Carfilzomib dose in Cycle 1, then as needed to minimize infusion-related reactions. The recommended starting dose of Carfilzomib is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 27 mg/m2 on Day 8 of Cycle 1 and thereafter. Continue Carfilzomib until disease progression or unacceptable toxicity.

Table 4: Carfilzomib Monotherapy 20/27 mg/m2 Twice Weekly (10-Minute Infusion)

	Cycle 1									
	Week 1			Week 2			Week 3			Week 4
Carfilzomib (mg/ m^2)[a]	20	20	-	27	27	-	27	27	-	-
	Cycles 2 to 12									
	Week 1			Week 2			Week 3			Week 4
Carfilzomib (mg/m^2)	27	27	-	27	27	-	27	27	-	-
	Cycles 13 and later									
	Week 1			Week 2			Week 3			Week 4
Carfilzomib (mg/m^2)	27	27	-	-	-	-	27	27	-	-

[a] Dexamethasone premedication is required for each Carfilzomib dose in Cycle 1.

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

Administer Carfilzomib intravenously as a 30-minute infusion. In Cycles 1 through 12, administer Carfilzomib on Days 1, 2, 8, 9, 15 and 16 of each 28-day cycle. From Cycle 13, administer Carfilzomib on Days 1, 2, 15 and 16 of each 28- day cycle. Premedicate with dexamethasone 8 mg orally or intravenously 30 minutes to 4 hours before each Carfilzomib dose in Cycle 1, then as needed to minimize infusion-related reactions. The recommended starting dose of Carfilzomib is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m2 on Day 8 of Cycle 1. Continue Carfilzomib until disease progression or unacceptable toxicity.

Table 5: Carfilzomib Monotherapy 20/56 mg/m^2 Twice Weekly (30-Minute Infusion)

	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	Days 22-28
Carfilzomib (mg/ m^2)[a]	20	20	-	56	56	-	56	56	-	-
	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	Days 22–28
Carfilzomib (mg/m^2)	56	56	-	56	56	-	56	56	-	-
	Cycles 13 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	Days 22-28
Carfilzomib (mg/m^2)	56	56	-	-	-	-	56	56	-	-

[a] Dexamethasone premedication is required for each Carfilzomib dose in Cycle 1.

Dosage Modifications for Adverse Reactions

See the Lenalidomide and dexamethasone prescribing information respectively for recommended dosage modifications associated with each product.

Table 6: Dosage Modifications for Adverse Reactions[a]

Hematologic Toxicity	Recommended Action
• ANC less than 0.5 × 10^9/L	• Withhold dose • If recovered to greater than or equal to 0.5 × 10^9/L, continue at the same dose level • For subsequent drops to less than 0.5 × 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilzomib[a]
• Febrile neutropenia: ANC less than 0.5×10^9/Landanoraltemperaturemorethan38.5°Cortwoconsecutive 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 × 10^9/L or evidence of bleeding with thrombocytopenia	• Withhold dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level
Renal Toxicity	**Recommended Action**
• Serum creatinine greater than or equal to 2 × baseline, or • Creatinine clearance 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 Carfilzomib, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction If not attributable to Carfilzomib, dosing may be resumed at the discretion of the healthcare provider • For patients on hemodialysis receiving Carfilzomib, the dose is to be administered after the hemodialysis procedure
Other Non-hematologic Toxicity	**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 below table for dose level reductions.

b Grade 3 and 4.

Table 6: Dose Level Reductions for Adverse Reactions

Regimen	Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
Carfilzomib and Dexamethasone	70 mg/m^2	56 mg/ m^2	45 mg/m^2	36 mg/ m^2
Carfilzomib and Dexamethasone OR Carfilzomib Monotherapy (twice weekly)	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2[a]
Carfilzomib, Lenalidomide, and Dexamethasone OR Carfilzomib Monotherapy (twice weekly)	27 mg/m^2	20 mg/m^2	15 mg/m^2	—

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

a If toxicity persists, discontinue Carfilzomib 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 Carfilzomib by 25%.

Recommended Dosage for End Stage Renal Disease

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

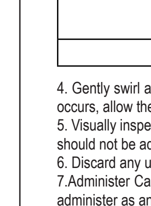
Preparation and Administration

Carfilzomib vials contain no antimicrobial preservatives and are intended for single-dose only. 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 discoloration prior to administration, whenever solution and container permit.

Reconstitution/Preparation Steps:

1. Remove vial from refrigerator just prior to use.
2. Calculate the dose (mg/m^2) and number of vials of Carfilzomib required using the patient's BSA at baseline.
3. Aseptically reconstitute each Carfilzomib vial only with Sterile Water for Injection, USP using the volumes described in Table 10. Use a 21-gauge or larger needle (0.8 mm or smaller external diameter needle) to reconstitute each vial by slowly injecting Sterile Water for Injection, USP through the stopper and directing the Sterile Water for Injection, USP onto the INSIDE WALL OF THE VIAL to minimize foaming. **There is no data to support the use of closed system transfer devices with Carfilzomib.**



Reconstitution Volumes

Table 7:

Strength	Amount of Sterile Water for Injection, USP required for reconstitution
10 mg vial	5 mL

4. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear.
5. Visually inspect for particulate matter and discoloration prior to administration. The reconstituted product should be a clear, colorless solution and should not be administered if any discoloration 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.Administer Carfilzomib directly by intravenous infusion or in a 50 mL to 100 mL intravenous bag containing 5% Dextrose Injection, USP. Do not administer as an intravenous push or bolus.
8.When administering in an intravenous bag, use 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 50 mL or 100 mL intravenous bag containing only 5% Dextrose Injection, USP (based on the calculated total dose and infusion time).
9.Flush the intravenous administration line with normal saline or 5% Dextrose Injection, USP immediately before and after Carfilzomib administration.
10.Do not mix Carfilzomib with or administer as an infusion with other medicinal products.

Table 7: Stability of Reconstituted Carfilzomib

Storage Conditions of Reconstituted Carfilzomib	Stability[a] per Container		
	Vial	Syringe	Intravenous Bag (D5W[b])
Refrigerated 2°C to 8°C (36°F to 46°F)	24 hours	24 hours	24 hours
Room Temperature 15°C to 30°C (59°F to 86°F)	4 hours	4 hours	4 hours

a Total time from reconstitution to administration should not exceed 24 hours.

b 5% Dextrose Injection, USP.

4.3. Contraindications

Carfilzomib is contraindicated in patients who are

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

4.4. Special Warnings and Precautions for Use

Cardiac Toxicities

New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Carfilzomib. Some events occurred in patients with normal baseline ventricular function.

Death due to cardiac arrest has occurred within one day of Carfilzomib administration. In randomized, open-label, multicenter trials for combination therapies, the incidence of cardiac failure events was 8% and that of arrythmias was 8% (majority of which were atrial fibrillation and sinus tachycardia).

Monitor patients for clinical signs or symptoms of cardiac failure or cardiac ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold Carfilzomib for Grade 3 or 4 cardiac adverse reactions until recovery and consider whether to restart Carfilzomib at 1 dose level reduction based on a benefit/risk assessment.

While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure.

In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to younger patients. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, may be at greater risk for cardiac complications; for these patients, complete a comprehensive medical assessment (including blood pressure control and fluid management) prior to starting treatment with Carfilzomib and remain under close follow-up.

Acute Renal Failure

Cases of acute renal failure have occurred in patients receiving Carfilzomib. Some of these events have been fatal. Renal insufficiency (including renal failure) has occurred in approximately 9% of patients who received Carfilzomib. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Carfilzomib monotherapy. The risk of fatal renal failure was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft-Gault equation).

Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome

Cases of TLS, including fatal outcomes, have been reported in patients who received Carfilzomib. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS.

Administer oral and intravenous fluids before administration of Carfilzomib in Cycle 1 and in subsequent cycles as needed. Consider uric acid-lowering drugs in patients at risk for TLS. Monitor for TLS during treatment and manage promptly, including interruption of Carfilzomib until TLS is resolved.

Pulmonary Toxicity

Acute Respiratory Distress Syndrome (ARDS) and acute respiratory failure have occurred in approximately 2% of patients who received Carfilzomib. In addition, acute diffuse infiltrative pulmonary disease, such as pneumonitis and interstitial lung disease, occurred in approximately 2% of patients who received Carfilzomib. Some events were fatal.

In the event of drug-induced pulmonary toxicity, discontinue Carfilzomib.

Pulmonary Hypertension

Pulmonary arterial hypertension was reported in approximately 2% of patients who received Carfilzomib, with Grade 3 or greater in less than 1%. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Carfilzomib for pulmonary hypertension until resolved or returned to baseline and consider whether to restart Carfilzomib based on a benefit/risk assessment.

Dyspnea

Dyspnea was reported in 25% of patients treated with Carfilzomib, with Grade 3 or greater in 4%.

Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Carfilzomib for Grade 3 or 4 dyspnea until resolved or returned to baseline. 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.

Optimize blood pressure prior to starting Carfilzomib. Monitor blood pressure regularly in all patients while on Carfilzomib. If hypertension cannot be adequately controlled, withhold Carfilzomib and evaluate. Consider whether to restart Carfilzomib based on a benefit/risk assessment.

Venous Thrombosis

Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Carfilzomib.

Provide thromboprophylaxis for patients being treated with Carfilzomib in combination with lenalidomide and dexamethasone; with dexamethasone. Select the thromboprophylaxis regimen based on the patient's underlying risks.

For patients using oral contraceptives or hormonal contraception associated with a risk of thrombosis, consider non-hormonal contraception during treatment when Carfilzomib is administered in combination.

Infusion-Related Reactions

Infusion-related reactions, including life-threatening reactions, have occurred in patients receiving Carfilzomib. Signs and symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, laryngeal edema, 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 Carfilzomib.

Administer dexamethasone prior to Carfilzomib to reduce the incidence and severity of infusion- related reactions.

Hemorrhage

Fatal or serious cases of hemorrhage have been reported in patients treated with Carfilzomib. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. The bleeding can be spontaneous and intracranial hemorrhage has occurred without trauma. Hemorrhage has been reported in patients having either low or normal platelet counts. Hemorrhage has also been reported in patients who were not on antiplatelet therapy or anticoagulation. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

Thrombocytopenia

Carfilzomib causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle. Hemorrhage may occur.

Monitor platelet counts frequently during treatment with Carfilzomib. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure

Cases of hepatic failure, including fatal cases, have been reported (2%) during treatment with Carfilzomib. Carfilzomib can cause increased serum transaminases.

Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Carfilzomib. Some of these events have been fatal.

Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Carfilzomib and evaluate. If the diagnosis of TTP/HUS is excluded, Carfilzomib may 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 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 (MRI).

Discontinue Carfilzomib if PRES is suspected and evaluate. The safety of reinitiating Carfilzomib therapy in patients previously experiencing PRES is not known.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML), which can be fatal, has been reported with Carfilzomib. In addition to Carfilzomib, other possible contributary factors include prior or concurrent immunosuppressive therapy that may cause immunosuppression.

Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, discontinue Carfilzomib and initiate evaluation for PML including neurology consultation.

Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients

Carfilzomib in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

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/m^2 based on BSA caused post-implantation loss and a decrease in fetal weight.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Carfilzomib and for 6 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Carfilzomib and for 3 months following the final dose.

4.5. Drug Interactions

Carfilzomib is primarily metabolised via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of Carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers.

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

Carfilzomib is a P-glycoprotein (P-gp) but not a BCRP substrate. However, given that Carfilzomib 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. Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Carfilzomib can cause fetal harm based on findings from animal studies and its mechanism of action. There are no available data on Carfilzomib use in pregnant women to evaluate for drug-associated risks. Carfilzomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose. Advise pregnant women of the potential risk to the fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Lactation

There are no data on the presence of Carfilzomib in human milk, the effects on the breastfed child, or the effects of the drug on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with Carfilzomib and for 2 weeks after treatment.

Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, Carfilzomib can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing

Conduct pregnancy testing on females of reproductive potential prior to initiating Carfilzomib treatment.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Carfilzomib and for at least 6 months following the final dose.

Males

Advise males with female sexual partners of reproductive potential to use effective contraception during treatment with Carfilzomib and for at least 3 months following the final dose.

Infertility

Based on the mechanism of action, Carfilzomib may have an effect on either male or female fertility. There are no data on the effect of Carfilzomib on human fertility.

Pediatric Use

The safety and effectiveness of Carfilzomib in pediatric patients have not been established.

Geriatric Use

No overall differences in effectiveness were observed between older and younger patients.

Hepatic Impairment

Reduce the dose of Carfilzomib by 25% in 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. A recommended dosage of Carfilzomib has not been established for patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST). The incidence of serious adverse reactions was higher in patients with mild, moderate, and severe hepatic impairment combined (22/35 or 63%) than in patients with normal hepatic function (3/11 or 27%).

4.7. Effects on Ability to Drive and Use Machines

Carfilzomib 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. Patients being treated with Carfilzomib should be advised not to drive or operate machines in the event that they experience any of these symptoms.

4.8. Undesirable Effects

The following clinically significant adverse reactions are described elsewhere in the labelling:

- Cardiac Toxicities
- Acute Renal Failure
- Tumor Lysis Syndrome
- Pulmonary Toxicity
- Pulmonary Hypertension
- Dyspnea
- Hypertension
- Venous Thrombosis
- Infusion-Related Reactions
- Hemorrhage
- Thrombocytopenia
- Hepatic Toxicity and Hepatic Failure
- Thrombotic Microangiopathy
- Posterior Reversible Encephalopathy Syndrome
- Progressive Multifocal Leukoencephalopathy

Adverse reactions are presented below by system organ class and frequency category:

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Infections and infestations	Pneumonia Respiratory tract infection	Sepsis Lung infection Influenza Herpes zoster Urinary tract infection Bronchitis Gastroenteritis Viral infection Nasopharyngitis Rhinitis	Clostridium difficile colitis Cytomegalovirus infection Hepatitis B virus reactivation	
Immune system disorders			Drug hypersensitivity	
Blood and lymphatic system disorders	Thrombocytopenia Neutropenia Anaemia Lymphopenia Leukopenia	Febrile neutropenia	HUS TTP	Thrombotic microangiopathy
Metabolism and nutrition disorders	Hypokalaemia Decreased appetite	Dehydration Hyperkalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia Hypocalcaemia Hypophosphataemia Hyperuricaemia Hypoalbuminaemia Hyperglycaemia	Tumour lysis syndrome	
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	
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		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 Creative protein Increased blood uric acid		
Injury, poisoning and procedural complications		Infusion related reaction		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9. Overdose

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia were few events due to over dose of Carfilzomib.

There is no known specific antidote for Carfilzomib overdosage. In the event of overdose, monitor patients for adverse reactions and provide supportive care as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities *in vitro* in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic, and solid tumors.

5.2 Pharmacodynamic Properties

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 carfilzomib ≥ 15 mg/m^2 with or without lenalidomide and dexamethasone induced a ≥ 80% inhibition of the CT-L activity of the proteasome. In addition, carfilzomib, 20 mg/m^2 intravenously as a single agent, resulted in a mean inhibition of the low molecular mass polypeptide 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the proteasome ranging from 26% to 32% and 41% to 49%, respectively. Proteasome inhibition was maintained for ≥ 48 hours following the first dose of carfilzomib for each week of dosing.

5.3 Pharmacokinetic Properties

Carfilzomib at doses between 20 mg/m^2 and 70 mg/m^2 administered as a 30-minute infusion resulted in dose-dependent increases in maximum plasma concentrations (C_{max}) and area under the curve over time to infinity (AUC_{0-INF}) in patients with multiple myeloma. A dose-dependent increase in C_{max} and AUC_{0-INF} was also observed between Carfilzomib 20 mg/m^2 and 56 mg/m^2 as a 2- to 10-minute infusion in patients with relapsed or refractory multiple myeloma. A 30-minute infusion resulted in a similar AUC_{0-INF}, but 2- to 3-fold lower C_{max} than that observed with a 2- to 10-minute infusion at the same dose. There was no evidence of Carfilzomib accumulation following repeated administration of Carfilzomib 70 mg/m^2 as a 30-minute once weekly infusion or 15 and 20 mg/m^2 as a 2- to 10-minute twice weekly infusion. Below table lists the estimated mean average daily area under the curve in the first cycle ($AUC_{C1,avg}$), average daily area under the curve at steady-state (AUC_{ss}) and C_{max} at the highest dose in the first cycle ($C_{max,C1}$) for the different dosing regimens.

Carfilzomib Exposure Parameters for Different Dosing Regimens

Estimated Parameters (%CV)	20/27 mg/m^2 twice weekly with 2- to 10- minute infusion	20/56 mg/m^2 twice weekly with 30- minute infusion	20/70 mg/m^2 once weekly with 30- minute infusion
AUCC1,avg (ng•hr/mL)	95 (40)	170 (35)	114 (36)
AUCss (ng•hr/mL)	111 (34)	228 (28)	150 (35)
Cmax,C1 (ng/mL)	1282 (17)	1166 (29)	1595 (36)

CV = Coefficient of variation

Distribution

The mean steady-state volume of distribution of a 20 mg/m^2 dose of Carfilzomib was 28 L. Carfilzomib is 97% bound to human plasma proteins over the concentration range of 0.4 to 4 micromolar *in vitro*.

Elimination

Carfilzomib has a half-life of ≤ 1 hour on Day 1 of Cycle 1 following intravenous doses ≥ 15 mg/m^2. The half-life was similar when administered either as a 30-minute infusion or a 2- to 10-minute infusion. The systemic clearance ranged from 151 to 263 L/hour.

Metabolism

Carfilzomib is rapidly metabolized. Peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450 (CYP)-mediated mechanisms contribute a minor role in overall Carfilzomib metabolism.

Excretion

Approximately 25% of the administered dose of Carfilzomib was excreted in urine as metabolites in 24 hours. Urinary and fecal excretion of the parent compound was negligible (0.3% of total dose).

Specific Populations

Age (35-89 years), sex, race or ethnicity (80% White, 11% Black, 6% Asians, 3% Hispanics), and mild to severe renal impairment (creatinine clearance 15-89 mL/min) did not have clinically meaningful effects on the pharmacokinetics of Carfilzomib.

Patients with 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).

Patients with Renal Impairment

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

Drug Interaction Studies

Clinical Studies

Effect of Carfilzomib on Sensitive CYP3A Substrate: Midazolam (a sensitive CYP3A substrate) pharmacokinetics was not affected by concomitant administration of carfilzomib.

In Vitro Studies

Effect of Carfilzomib on Cytochrome P450 (CYP) Enzymes: Carfilzomib showed direct and time-dependent inhibition of CYP3A but did not induce CYP1A2 and CYP3A4 *in vitro*. Effect of Transporters on Carfilzomib: Carfilzomib is a P-glycoprotein (P-gp) substrate *in vitro*.

Effect of Carfilzomib on Transporters: Carfilzomib inhibits P-gp *in vitro*. However, given that Carfilzomib is administered intravenously and is extensively metabolized, the pharmacokinetics of Carfilzomib is unlikely to be affected by P-gp inhibitors or inducers.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with carfilzomib.

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.

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.

6.2 Animal Toxicology or Pharmacology

Cardiovascular Toxicity

Monkeys administered a single bolus intravenous dose of Carfilzomib at 3 mg/kg (approximately 1.3 times recommended dose in humans of 27 mg/m^2 based on BSA) experienced hypotension, increased heart rate, and increased serum levels of troponin-T.

Chronic Administration

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 hemorrhage/degeneration), gastrointestinal (necrosis/hemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (hemorrhage/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 dose of 2 mg/kg/dose in monkeys is approximately equivalent to the recommended dose in humans based on BSA.

7. PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities

None

7.2 Packing Information

Carfilzomib 10 mg----10 ml clear tubular vial

7.3 Storage and Handling Instructions

Unopened vials should be stored refrigerated 2°C to 8°C (36°F to 46°F). Retain in original package to protect from light.

8. PATIENT COUNSELLING INFORMATION

Advise patient or medical professional to read package insert. Discuss the following with patients prior to treatment with Carfilzomib:

Cardiac Toxicities: Advise patients of the risks and symptoms of cardiac failure and ischemia.

Dehydration: Counsel patients to avoid dehydration, since patients receiving Carfilzomib therapy may experience vomiting and/or diarrhea. Instruct patients to seek medical advice if they experience symptoms of dehydration.

Respiratory: Advise patients that they may experience cough or shortness of breath (dyspnea) during treatment with Carfilzomib. This most commonly occurs within a day of dosing. Advise patients to contact their healthcare provider if they experience shortness of breath.

Venous Thrombosis: Inform patients of the risk of venous thromboembolism and discuss the options for prophylaxis. Advise patients to seek immediate medical attention for symptoms of venous thrombosis or embolism.

Infusion-Related Reactions: Advise patients of the risk of infusion-related reactions and discuss the common signs and symptoms of infusion-related reactions with the patients.

Bleeding: Inform patients that they may bruise or bleed more easily or that it may take longer to stop bleeding and to report to their healthcare provider any prolonged, unusual or excessive bleeding. Instruct patients on the signs of occult bleeding.

Hepatic: Inform patients of the risk of developing hepatic failure. Advise patients to contact their healthcare provider for symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes.

Other: Inform patients to contact their healthcare provider if they experience neurologic symptoms such as headaches, confusion, dizziness or loss of balance, difficulty talking or walking, decreased strength or weakness on one side of the body, seizures, or visual loss.

Driving/Operating Machines: Advise patients that Carfilzomib 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.

Embryo-Fetal Toxicity: Advise females of the potential risk to the fetus. Advise females of reproductive potential to inform their healthcare provider immediately of a known or suspected pregnancy. Advise female patients to use effective contraceptive during treatment with Carfilzomib and for 6 months following the final dose. Advise male patients with female sexual partners of reproductive potential to use effective contraception during treatment with Carfilzomib and for 3 months following the final dose.

Lactation: Advise patients to avoid breastfeeding while receiving Carfilzomib and for 2 weeks after the final dose.

Concomitant Medications: Advise patients to discuss with their healthcare provider any medication they are currently taking prior to starting treatment with Carfilzomib, or prior to starting any new medication(s) during treatment with Carfilzomib.

9. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,
Formulation Division,
Unit-II, Sy.No. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

M.L.No.: 5/MN/TS/2014/F/G

11. DATE OF REVISION

July-2021

C030471-00