

Carfilez

Carfilzomib INN

COMPOSITION

Carfilez 10 Injection: Each vial contains Carfilzomib INN 10 mg (as lyophilized powder).

Carfilez 30 Injection: Each vial contains Carfilzomib INN 30 mg (as lyophilized powder).

Carfilez 60 Injection: Each vial contains Carfilzomib INN 60 mg (as lyophilized powder).

CLINICAL PHARMACOLOGY

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.

PHARMACODYNAMICS

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/m² with or without lenalidomide and dexamethasone induced a $\geq 80\%$ inhibition of the CT-L activity of the proteasome. In addition, carfilzomib, 20 mg/m² 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.

PHARMACOKINETICS

Carfilzomib at doses between 20 mg/m² and 70 mg/m² 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/m² and 56 mg/m² 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/m² as a 30-minute once weekly infusion or 15 and 20 mg/m² as a 2- to 10-minute twice weekly infusion.

Distribution: The mean steady-state volume of distribution of a 20 mg/m² 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/m². 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 by 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).

INDICATIONS AND USAGE

Relapsed or Refractory Multiple Myeloma

DOSAGE AND ADMINISTRATION

Carfilzomib can be administered in a 50 mL or 100 mL intravenous bag of 5% Dextrose Injection, USP. Infuse over 10 or 30 minutes depending on the Carfilzomib dose regimen. Administer as an intravenous infusion. Flush the intravenous administration line with normal saline or 5% Dextrose Injection, USP immediately before and after Carfilzomib administration. Do not mix Carfilzomib with or administer as an infusion with other medicinal products.

Regimen	Dose	Infusion time
Carfilzomib plus Dexamethasone	20/70 mg/m ² once weekly	30 minutes
Carfilzomib plus Dexamethasone or Monotherapy	20/56 mg/m ² twice weekly	30 minutes
Carfilzomib, Lenalidomide, and Dexamethasone, or Monotherapy	20/27 mg/m ² twice weekly	10 minutes

Reconstitution/Preparation Steps:

1. Remove vial from refrigerator just prior to use.
2. Calculate the dose (mg/m²) and number of vials of Carfilzomib required using the patient's BSA at baseline. Patients with a BSA greater than 2.2 m² should receive a dose based upon a BSA of 2.2 m². Dose adjustments do not need to be made for weight changes of less than or equal to 20%.
3. Aseptically reconstitute each Carfilzomib vial only with Sterile Water for Injection, USP using the volumes described in following Table 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

Strength	Amount of Sterile Water for Injection, USP required for reconstitution
10 mg Vial	5 mL
30 mg Vial	15 mL
60 mg Vial	29 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 to slightly yellow solution and should not be administered if any discoloration or particulate matter is observed.

6. Discard any unused portion left in the vial. DO NOT pool unused portions from the vials. DO NOT administer more than one dose from a vial.

7. Carfilzomib can be administered directly by intravenous infusion or optionally, administered 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).

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Cardiac Toxicities
- Acute Renal Failure
- Tumor Lysis Syndrome
- Pulmonary Toxicity
- Pulmonary Hypertension
- Dyspnea
- Hypertension
- Venous Thrombosis
- Infusion Reactions
- Hemorrhage
- Thrombocytopenia
- Hepatic Toxicity and Hepatic Failure
- Thrombotic Microangiopathy
- Posterior Reversible Encephalopathy Syndrome
- Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients
- Embryo-Fetal Toxicity

ADVERSE REACTIONS

The most common adverse reactions occurring in at least 20% of patients treated with Carfilzomib in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, dyspnea, diarrhea, headache, cough, edema peripheral.

The most common adverse reactions occurring in at least 20% of patients treated with Carfilzomib in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia.

DRUG INTERACTION

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.

OVERDOSAGE

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 overdosage. In the event of overdosage, the patient should be monitored, specifically for the side effects and/or adverse reactions

STORAGE CONDITIONS

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

PRESENTATION AND PACKAGING

Carfilez 10 Injection: Each box contains 1 Vial of Carfilzomib INN 10 mg (as lyophilized powder) and 1 Ampoule of 5 mL Sterile Water for Injection, USP.

Carfilez 30 Injection: Each box contains 1 Vial of Carfilzomib INN 30 mg (as lyophilized powder) and 3 Ampoule of 5 mL Sterile Water for Injection, USP.

Carfilez 60 Injection: Each box contains 1 Vial of Carfilzomib INN 60 mg (as lyophilized powder) and 3 Ampoule of 10 mL Sterile Water for Injection, USP.

Manufactured By

Beacon Pharmaceuticals PLC

Bhaluka, Mymensingh, Bangladesh