CARFIZOL®
CARFILZOMIB 60 mg/vial

Lyophilized powder for injection. For intravenous use only
Filed prescription only. Made in Argentina.

COMPOSITION

Each CARFIZOL® vial contains:

Carfilzomib	60 mg
Excipients:	
Sulfobutyl ether beta-cyclodextrin	3000 mg
Citric acid, anhydrous	57.7 mg
Sodium hydroxide	q.s. pH 3.5

THERAPEUTIC ACTION

Pharmacotherapeutic group: antineoplastic agent.

ATC code: L01XX45.

INDICATIONS

CARFIZOL® is indicated:

- for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy for their underlying disease, in combination with:
  - lenalidomide and dexamethasone; or
  - dexamethasone; or
  - daratumumab and dexamethasone.
- as monotherapy in the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy for their underlying disease.

PHARMACOLOGICAL ACTION

Mechanism of action
Carfilzomib is a tetrapeptide with an epoxyketone proteasome inhibitor group that selectively and irreversibly binds to threonine at the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core of the 26S proteasome, and exhibits little to no activity against other types of proteases. In nonclinical models, carfilzomib demonstrated antiproliferative and proapoptotic activity in hematologic tumors. In animals, carfilzomib inhibited proteasome activity in blood and tissues and delayed tumor growth in multiple myeloma models. *In vitro*, carfilzomib showed low neurotoxicity and minimal reaction towards non-proteasomal proteases.

Pharmacodynamic effects
Intravenous administration of carfilzomib resulted in suppression of proteasome chymotrypsin like (CT-L) activity when measured in blood 1 hour after the first dose. Doses ≥15 mg/m² consistently induced ≥80% inhibition of CT-L activity of the proteasome. Furthermore, carfilzomib administration 20 mg/m² resulted in an average inhibition of low molecular mass polypeptide 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) proteasome subunits ranging from 26% to 32% and from 41% to 49%, respectively. Proteasome inhibition was maintained for ≥48 hours after the first dose of carfilzomib in each week of dosing. The combined administration of lenalidomide and dexamethasone did not affect proteasome inhibition. At the highest dose of 56 mg/m², not only was an increase observed in CT-L subunit inhibition (≥90%) compared to doses of 15 to 20 mg/m², but also a greater inhibition of other proteasome subunits (LMP7, MECL1, and LMP2). There was an approximately 8%, 23%, and 34% increase in inhibition of LMP7, MECL1, and LMP2 subunits, respectively, with the 56 mg/m² dose compared to doses of 15 to 20 mg/m². Similar proteasome inhibition was achieved with 2 to 10-minute carfilzomib infusion and 30-minute carfilzomib infusion at the two dose levels (20 and 36 mg/m²) that were analyzed.

PHARMACOKINETICS

Absorption
The C_{max} and AUC after a 2 to 10-minute intravenous infusion of 27 mg/m² were 4,232 ng/ ml and 379 ng•h/ ml/l, respectively. After repeated doses of carfilzomib 15 and 20 mg/m², systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, indicating that there was no systemic carfilzomib accumulation. At doses between 20 and 56 mg/m², it appears that there was a dose-dependent increase in exposure.
A 30-minute infusion showed a similar half-life and AUC, but a C_{max} that was 2 to 3 times lower compared to that observed with a 2 to 10-minute infusion at the same dose.
Following a 30-minute infusion of 56 mg/m² dose, the average AUC of 948 ng•h/ ml was approximately 2.5 times higher than that observed with 27 mg/m² dose, and the C_{max} (2079 ng/ ml) was lower compared to 27 mg/m² dose administered as a 2 to 10-minute infusion.

Distribution
The mean steady-state volume of distribution for a 20 mg/m² dose of carfilzomib was 28 L. When tested *In vitro*, the binding of carfilzomib to human plasma proteins averaged 97% over the strength range of 0.4 to 4 micromolar.

Metabolism
Carfilzomib was rapidly and extensively metabolized. The predominant metabolites identified in human plasma and urine and generated *In vitro* by human hepatocytes, were peptide fragments and the diol of carfilzomib, indicating that peptidase cleavage and epoxide hydrolysis were the main metabolic pathways. Cytochrome P450-mediated mechanisms played a minor role in the overall metabolism of carfilzomib. The biological activity of these metabolites is unknown.

Elimination
After intravenous administration of doses ≥15 mg/m², carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤1 hour on Day 1 of Cycle 1. Systemic clearance ranged from 151 to 263 l/hour and exceeded hepatic blood flow, indicating that carfilzomib was largely cleared extrahepatically. Carfilzomib is mainly cleared through metabolism with subsequent excretion of its metabolites in the urine.

Special populations
Population pharmacokinetic analyses indicate that age, gender, or race have no effects on the pharmacokinetics of carfilzomib.

Hepatic impairment
A pharmacokinetic study assessed patients with advanced neoplasms in relapse or progression, who had normal liver function, mild hepatic impairment or moderate hepatic impairment. The pharmacokinetics of carfilzomib have not been studied in patients with severe hepatic impairment. Carfilzomib was administered as a single agent. The baseline liver function status had no identified effect on the total systemic exposure (final AUC) of carfilzomib following single or repeated doses. However, in patients with mild or moderate baseline hepatic impairment who had solid tumors, there was a higher incidence of subjects with abnormal liver function experiencing ≥ grade 3 or serious adverse events, compared to subjects with normal liver function.

of 27 mg/m² according to BSA) experienced hypotension, increased heart rate, and elevated troponin T serum levels. Repeated intravenous bolus 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 due to toxicities in the cardiovascular (heart 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/m² based on BSA. The highest non-severely toxic dose of 0.5 mg/ kg in monkeys led to interstitial inflammation in the kidney along with mild glomerulopathy and mild cardiac inflammation. These findings were observed at 6 mg/m², which is below the recommended dose in humans of 27 mg/m².
Fertility studies have not been conducted with carfilzomib. No effects on reproductive tissues were observed during toxicity studies in rats and monkeys at repeated doses for 28 days or in 6-month rat and 9-month monkey chronic toxicity studies.
Carfilzomib caused embryofetal toxicity (increased pre-implantation losses, early resorptions, and post-implantation losses, and decreased fetal weight) in pregnant rabbits at doses lower than those received by patients at the recommended dose. Carfilzomib administered to pregnant rats during organogenesis was not teratogenic at doses up to 2 mg/kg/day, which is approximately half the recommended dose in humans of 27 mg/m² based on BSA.

Women of childbearing potential/ male and female contraception
Women of childbearing potential (and/ or their partners) should use effective contraceptive methods during treatment and for up to one month after its completion.
The effectiveness of oral contraceptives may not be guaranteed during treatment with carfilzomib. Furthermore, due to an increased risk of venous thromboembolic events associated with carfilzomib, women should avoid the use of hormonal contraceptives associated with thrombosis risk during CARFIZOL® treatment. If a patient is currently using oral contraceptives or any hormonal contraception method associated with thrombosis risk, the patient should switch to an alternative effective contraceptive method.
Before starting CARFIZOL® treatment, women of childbearing potential should undergo pregnancy tests to rule out pregnancy.
Male patients should use effective contraceptive methods during treatment and for 3 months after its completion if their partner is pregnant or of childbearing age and not using effective contraceptive methods.
Based on its mechanism of action, carfilzomib may affect fertility in both males and females.

Pregnancy
There is no data regarding the use of carfilzomib in pregnant women.
Animal studies have shown reproductive toxicity.
Considering its mechanism of action and findings in animals, carfilzomib may have harmful effects on the fetus if administered to a pregnant woman. CARFIZOL® should not be used during pregnancy unless the potential benefit clearly outweighs the potential risks to the fetus. If CARFIZOL® is used during pregnancy or if the patient becomes pregnant while taking this medication, the patient should be informed of the potential risks to the fetus.
Lenalidomide is structurally similar to thalidomide. Thalidomide is a known teratogenic agent in humans, causing severe and potentially fatal birth defects in newborns. If lenalidomide is used during pregnancy, teratogenic effects of lenalidomide in humans are expected. The conditions of the Pregnancy Prevention Program for lenalidomide must be strictly adhered to unless there is reliable evidence that the patient is not fertile. Please refer to the approved and current lenalidomide package insert for more information.

Lactation
It is unknown whether carfilzomib or its metabolites are excreted in breast milk. Based on its pharmacological properties, the risk to nursing infants cannot be excluded. Therefore, as a precautionary measure, breastfeeding is contraindicated during and for at least 2 days after the completion of treatment with CARFIZOL®.

Effects on the ability to drive and use machines
The influence of carfilzomib on the ability to drive and operate machinery is minor.
Fatigue, dizziness, fainting, blurred vision, drowsiness, and/ or a drop in blood pressure have been observed in clinical studies. Patients treated with CARFIZOL® should be advised not to drive or operate machinery if they experience any of these symptoms.

Special populations
Use in pediatric population
The safety and efficacy of carfilzomib have not been established in pediatric patients. No data are available.

Use in elderly patients
There were no differences in effectiveness with carfilzomib treatment between older and younger patients. Overall, the incidence of some adverse effects (including heart failure) in clinical studies was higher in patients aged ≥75 years than in patients aged <75 years.

Use in renal impairment
No initial dose adjustment of CARFIZOL® is required for patients with mild, moderate, or severe pre-existing renal impairment or patients on chronic dialysis. Since clearance of carfilzomib strengths during dialysis has not been studied, the medication should be administered after the dialysis procedure. In clinical studies, the incidence of adverse effects of acute renal impairment was higher in subjects with lower baseline creatinine clearance compared to those with higher baseline creatinine clearance.
Renal function should be monitored at the beginning of the treatment and then at least monthly or according to the accepted clinical practice guidelines, especially in patients with lower baseline creatinine clearance. Dose adjustments should be made as appropriate based on toxicity (see Table 8). There is limited efficacy and safety data in patients with baseline creatinine clearance <30 ml/ min.

Use in hepatic impairment
For patients with mild hepatic dysfunction (total bilirubin between 1 and 1.5 × ULN and any AST [Aspartate Amino Transferase] value or total bilirubin ≤ ULN and AST > ULN) or moderate hepatic dysfunction (total bilirubin > 1.5 to 3 × ULN and any AST value), reduce the dose of CARFIZOL® by 25%.
Liver enzymes and bilirubin levels should be monitored at the beginning of the treatment and monthly during treatment with CARFIZOL®, regardless of baseline values. Appropriate dose adjustments should be made based on toxicity (see Table 8). Special attention should be paid to patients with moderate and severe hepatic impairment, given the very limited efficacy and safety data in this population.

ADVERSE REACTIONS

Serious adverse reactions that may occur during treatment with CARFIZOL® include heart failure, myocardial infarction, cardiac arrest, myocardial ischemia, interstitial lung disease, pneumonitis, acute respiratory distress syndrome, acute respiratory impairment, pulmonary hypertension, dyspnea, hypertension including hypertensive crises, acute renal impairment, tumor lysis syndrome, infusion reactions, gastrointestinal hemorrhage, intracranial hemorrhage, pulmonary hemorrhage, thrombocytopenia, hepatic impairment, hepatitis B virus reactivation, posterior reversible encephalopathy syndrome (PRES), thrombotic microangiopathy, and TTP/HUS. In clinical studies with carfilzomib, cardiac toxicity and dyspnea generally occurred early in the course of treatment. The most common adverse reactions (occurring in >20% of subjects) were anemia, fatigue, thrombocytopenia, nausea, diarrhea, pyrexia, dyspnea, respiratory tract infections, cough, and neutropenia. Potential dose-related adverse reactions include: heart failure, dyspnea, hypertension, and pulmonary hypertension.
The adverse reactions that occurred during treatment with carfilzomib are listed below, grouped by system organ class and frequency. Frequencies are defined as follows: common (>10%); uncommon (1% to 10%); rare (<1%). Adverse reactions are presented in decreasing order of severity within each frequency interval.

Infections and infestations
Common: pneumonia, respiratory tract infection. *Uncommon:* sepsis, lung infection, influenza, herpes zoster*, urinary tract infection, bronchitis, gastroenteritis, viral infection, nasopharyngitis, rhinitis. *Rare:* Clostridium difficile colitis, cytomegalovirus infection, hepatitis B virus reactivation.
* The frequency is calculated based on data from clinical studies where prophylaxis was administered to many patients.

Immune system disorders
Rare: drug hypersensitivity.

Blood and lymphatic system disorders
Common: thrombocytopenia, neutropenia, anemia, lymphopenia, leukopenia. *Uncommon:* febrile neutropenia. *Rare:* HUS, TTP, thrombotic microangiopathy.

Metabolism and nutrition disorders
Common: hypokalemia, decreased appetite. *Uncommon:* dehydration, hyperkalemia, hypomagnesemia, hyponatremia, hypercalcemia, hypocalcemia, hypophosphatemia, hyperuricemia, hypoalbuminemia, hyperglycemia. *Rare:* tumor lysis syndrome.

Psychiatric disorders
Common: insomnia. *Uncommon:* anxiety, confusional state.
Nervous System disorders. *Common:* dizziness, peripheral neuropathy*, headache. *Uncommon:* paresthesia, hypoesthesia. *Rare:* intracranial hemorrhage, stroke, PRES. Frequency not established: deafness.
* Peripheral neuropathies include peripheral neuropathy, sensory peripheral neuropathy, and motor peripheral neuropathy.

Eye disorders
Uncommon: cataracts, blurred vision.

Ear and labyrinth disorders.
Uncommon: tinnitus.

Cardiac disorders
Uncommon: heart failure, myocardial infarction, atrial fibrillation, tachycardia, reduced ejection fraction, palpitations. *Rare:* cardiac arrest, cardiomyopathy, myocardial ischemia, pericarditis, pericardial effusion, ventricular tachycardia.

Vascular disorders
Common: hypertension. *Uncommon:* deep vein thrombosis, hypotension, flushing. *Rare:* hypertensive crisis, hemorrhage, hypertensive emergency.

Respiratory, thoracic and mediastinal disorders
Common: dyspnea, cough. *Uncommon:* pulmonary embolism, pulmonary edema, epistaxis, oropharyngeal pain, dysphonia, wheezing, pulmonary hypertension. *Rare:* ARDS, acute respiratory impairment, pulmonary hemorrhage, interstitial lung disease, pneumonitis.

Gastrointestinal disorders
Common: vomiting, diarrhea, constipation, abdominal pain, nausea. *Uncommon:* gastrointestinal hemorrhage, dyspepsia, dental pain. *Rare:* gastrointestinal perforation, acute pancreatitis.

Hepatobiliary disorders
Uncommon: increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, hyperbilirubinemia. *Rare:* renal impairment, cholestasis.

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, erythema, hyperhidrosis. *Rare:* angioedema.

Musculoskeletal and connective tissue disorders.
Common: back pain, arthralgia, limb pain, muscle spasms. *Uncommon:* musculoskeletal pain, musculoskeletal chest pain, bone pain, myalgia, muscle weakness.

Renal and urinary disorders
Common: elevated blood creatinine. *Uncommon:* acute renal failure, renal failure, renal impairment, decreased renal creatinine clearance.

General disorders and administration site conditions
Common: pyrexia, peripheral edema, asthenia, fatigue, chills. *Uncommon:* chest pain, pain, infusion site reaction, flu-like illness, malaise. *Rare:* multiorgan failure.

Complementary investigations
Uncommon: elevated C-reactive protein, hyperuricemia.

Injury, poisoning and procedural complications
Uncommon: infusion-related reaction.

Description of selected adverse reactions
Heart failure, myocardial infarction and myocardial ischemia
In clinical studies, heart failure (reported in approximately 5% of subjects – approximately 3% of subjects with grade ≥3 events), myocardial infarction (reported in approximately 1% of subjects – approximately 1% of subjects with grade ≥3 events), and myocardial ischemia (reported in <1% of subjects - <1% of subjects with grade ≥3 events) typically occurred early in carfilzomib treatment (<5 cycles).

Dyspnea
Dyspnea was reported in approximately 24% of subjects in clinical studies with carfilzomib. Most dyspnea adverse events were not severe (<5% of subjects experienced grade ≥3 events), were resolved, rarely led to treatment discontinuation, and occurred early in the study (<3 cycles).

Hypertension including hypertensive crises
Cases of hypertensive crises (hypertensive urgency or hypertensive emergency) have occurred following carfilzomib administration. Some of these events have been fatal. In clinical studies, hypertension adverse events occurred in approximately 21% of subjects, with 8% experiencing grade ≥3 hypertension events, but hypertensive crises occurred in <0.5% of patients. The incidence of hypertension adverse events was similar between those with or without a history of pre-existing hypertension.

Thrombocytopenia
Thrombocytopenia has been reported in approximately 33% of subjects in clinical studies with carfilzomib, with approximately 20% of subjects experiencing grade ≥3 events. Carfilzomib induces thrombocytopenia by inhibiting platelet budding from megakaryocytes, resulting in a classic cyclic thrombocytopenia with platelet nadir around Day 8 or 15 of each 28-day cycle, typically associated with a recovery to baseline levels at the start of the next cycle.

Venous thromboembolic events
Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients receiving carfilzomib. The overall incidence of venous thromboembolic events including grade ≥3 events was higher in carfilzomib-treated groups in pivotal clinical studies.

Hepatic impairment
Cases of hepatic impairment, including fatal cases, have been reported in <1% of subjects in clinical studies with carfilzomib.

Peripheral neuropathy
In an open-label, multicenter, randomized study in patients receiving 20/ 56 mg/m² of carfilzomib as a 30-minute infusion in combination with dexamethasone versus bortezomib plus dexamethasone, grade 2 or higher peripheral neuropathy events were reported in 7% of relapsed multiple myeloma patients in carfilzomib-treated group, compared to 35% in the bortezomib-treated group at the planned overall survival analysis. In another study, grade 2 or higher peripheral neuropathy events were reported in 10.1% of relapsed multiple myeloma patients in the carfilzomib/ dexamethasone/ daratumumab group compared to 3.9% in the carfilzomib/ dexamethasone group.

Infusion reactions
In clinical studies, the risk of infusion reactions was higher when carfilzomib was administered in combination with daratumumab.

Respiratory tract infections
In clinical studies in combination with daratumumab, respiratory tract infections were reported as serious adverse events, with fatal events occurring in 1.3% of patients in the carfilzomib/ dexamethasone/ daratumumab group.

Secondary primary malignancies
In clinical studies in combination with daratumumab and dexamethasone, secondary primary malignancies were reported in both treatment groups (1.9% in the carfilzomib/ dexamethasone/ daratumumab group and 1.3% in the carfilzomib/ dexamethasone group).

Opportunistic infections
In clinical studies in combination with daratumumab and dexamethasone, opportunistic infections were reported in both treatment groups (9.4% in the carfilzomib/ dexamethasone/ daratumumab group and 3.9% in the carfilzomib/ dexamethasone group). Opportunistic infections that were experienced by ≥1% of subjects in the carfilzomib/ dexamethasone/ daratumumab group include herpes zoster, oral candidiasis, oral herpes, and herpes simplex.

Hepatitis B virus reactivation
In clinical studies, the incidence of hepatitis B virus reactivation was 0.6% in the carfilzomib/ dexamethasone/ daratumumab group and 0% in the carfilzomib/ dexamethasone group.

Other special populations
Elderly population (≥75 years)
Overall, in clinical studies with carfilzomib, the incidence of certain adverse events (including cardiac arrhythmias, heart failure, dyspnea, leukopenia, and thrombocytopenia) was higher in patients aged ≥75 years than in patients aged <75 years.
In clinical studies in combination with daratumumab and dexamethasone, adverse events with fatal outcome during treatment occurred in 6% of patients aged <65 years and 14% of patients aged ≥65 years in the carfilzomib/ dexamethasone/ daratumumab group; in the carfilzomib/ dexamethasone group, these events occurred in 8% of patients aged <65 years and 3% of patients aged ≥65 years.

Post-marketing experience
Adverse reactions have been identified during the use of carfilzomib following its approval. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship with drug exposure. These reactions include hemolytic uremic syndrome, hepatitis B reactivation, gastrointestinal perforation, pericarditis, and cytomegalovirus infection, including chorioretinitis, pneumonitis, enterocolitis, viremia, and intestinal obstruction.

Reporting suspected adverse reactions
Following drug authorization, it is important to report suspected adverse drug reactions. This allows for ongoing monitoring of the benefit-risk assessment.
Healthcare professionals are encouraged to report suspected adverse reactions through the National Pharmacovigilance System at the following link: http://sistemas.anmat.gov.ar/aplicaciones_net/fvg_eventos_adversos_nuevo/index.htlm and/ or to the Pharmacovigilance Department of Gador S.A. via e-mail at farmacovigilancia@gador.com or by calling 0800-220-2273 (CARE).

OVERDOSE
Currently, there is not enough information to conclude on the safety of doses higher than those evaluated in clinical studies of carfilzomib. The sudden onset of chills, hypotension, renal impaiment, thrombocytopenia, and lymphopenia has been reported following an accidental dose of 200 mg of carfilzomib.
There is no known specific antidote for carfilzomib overdose. In the event of an overdose, the patient should be monitored specifically for the adverse reactions mentioned in the corresponding section.

"In the event of an overdose, go to the nearest hospital or contact Poison Control Centers:
HOSPITAL DE PEDIATRÍA RICARDO GUTIÉRREZ:
(011) 4962-6666 / 2247
HOSPITAL ALEJANDRO POSADAS:
(011) 4654-6648 / 4658-7777
Alternatively, other Poison Control Centers".

HOW SUPPLIED
CARFIZOL® is supplied in packages containing a single-use vial containing lyophilized powder for injection. Discard the unused portion; for intravenous use only.

STORAGE AND HANDLING
Store in a refrigerator between 2°C and 8°C, in its original package to protect from light. Once reconstituted, the solution remains stable for 24 hours in the refrigerator (between 2°C and 8°C) or for 4 hours at room temperature (15°C-30°C).

"This medication should only be used under medical prescription and supervision and cannot be repeated without a new medical prescription"

This medication is subject to additional monitoring, which will expedite the detection of new safety information.

Patient information

Composition

Each CARFIZOL® vial contains:

Carfilzomib	60 mg
Excipients:	
Sulfobutyl ether beta-cyclodextrin	3000 mg
Citric acid, anhydrous	57.7 mg
Sodium hydroxide	q.s. pH 3.5

CARFIZOL® is subject to additional monitoring, which includes measures to expedite the detection and outreach of new safety information. You can contribute by reporting any adverse events you may experience. In this leaflet, you will find the contact information for reporting any product-related issues.

Please read this entire leaflet carefully before starting to take this medication, and each time it is prescribed to you, as there may be new information. This information does not replace discussing your health status or treatment with your doctor.

- Keep this leaflet, as you may need to read it again.
- If you have any doubts, **ASK YOUR DOCTOR**.
- This medication has been prescribed only for you, and you should not give it to other people even if they have the same symptoms as you, as it may be harmful to them.
- If you experience unwanted effects, **ASK YOUR DOCTOR**, even if they are possible side effects not listed in this leaflet.

Leaflet content

- What CARFIZOL® is and what it is used for
- What you need to know before starting to use CARFIZOL®
- How to use CARFIZOL®
- Possible side effects of CARFIZOL®
- Reminder
- CARFIZOL® Storage
- Package contents and additional information

• What CARFIZOL® is and what it is used for

CARFIZOL® is a medicine that contains the active ingredient carfilzomib.
Carfilzomib works by blocking a system within cells that breaks down proteins when they are damaged or no longer needed, called "proteasome." By preventing the breakdown of proteins in cancer cells (which are more likely to contain an excess of abnormal proteins), CARFIZOL® causes the death of malignant cells.

CARFIZOL® is used to treat adult patients with multiple myeloma who have had at least one prior treatment for this disease. Multiple myeloma is a cancer of plasma cells (a type of white blood cell responsible for producing immunoglobulins or "defense" proteins).
CARFIZOL® can be administered to you alone or in combination with other medicines used to treat multiple myeloma.

• What you need to know before starting to use CARFIZOL®

Your doctor will examine you and review your complete medical history. You will be closely monitored during treatment.
Before starting treatment with CARFIZOL® and during treatment, blood tests will be performed. This is to check that you have enough blood cells and your liver and kidneys are working properly.
Your doctor or nurse will ensure that you receive an adequate amount of fluids.

You should read the leaflet for all the medicines you take in combination with CARFIZOL®, so you can understand the information related to these medicines.

You must not use CARFIZOL®

- If you are allergic to carfilzomib or any of the other components of this medicine.
- If you are breastfeeding.

Warnings and precautions

Talk to your doctor or nurse before using CARFIZOL® if you have any of the conditions listed below. Additional tests may be required to ensure that your heart, kidneys, and liver are working correctly.

- Heart problems, including a history of chest pain (angina pectoris), heart attack, irregular heartbeat, or if you have ever taken a medicine for your heart.
- Lung problems, including a history of shortness of breath at rest or during activities (dyspnea).
- Kidney problems, including kidney failure, or if you have ever received dialysis.
- Liver problems, including a history of hepatitis, fatty liver, or if you have ever been told that your liver is not working properly.
- Unusual bleeding, including easy bruising or bleeding from an injury, such as a cut that takes longer than expected to stop bleeding; or internal bleeding such as coughing up blood, vomiting up blood, black stools, or bright red blood in your stools or brain hemorrhages that causes sudden numbness or paralysis on one side of the face, legs, or arms, severe and sudden headache, or trouble seeing or difficulty speaking or swallowing. This may indicate a low platelet count (cells that aid in the clotting of blood).
- History of blood clots in your veins-
- Leg or arm pain or swelling (which could be symptoms of blood clots in the deep veins of the legs or arms), chest pain, or breathing difficulties (which could be symptoms of blood clots in the lungs).
- Any other significant medical condition for which you were hospitalized or received medication.

Symptoms to be alert to

You must look out for certain symptoms while taking CARFIZOL® to reduce the risk of problems. CARFIZOL® can worsen some symptoms or cause serious adverse events that could even be life-threatening, such as heart, lung, and kidney problems, tumor lysis syndrome (a potentially life-threatening condition that occurs when cancer cells break down and release their contents into the blood), infusion reactions, unusual bruising or bleeding (including internal bleeding), blood clots in your veins, liver problems, certain blood disorders, or a neurological syndrome known as "Posterior Reversible Encephalopathy Syndrome." *Please carefully read the section* **Possible Side Effects of CARFIZOL®**.
Inform your doctor if you have ever had or might now have a hepatitis B virus infection. The reason is that this medication could cause the hepatitis B virus to become reactivated. Your doctor will examine you for signs of this infection before, during, and for some time after completing treatment with this medication. Tell your doctor immediately if you experience worsening fatigue or yellowing of your skin or white part of your eyes.
At any time during the treatment or after its completion, tell your doctor immediately if you experience blurred vision, loss of vision or double vision, difficulty speaking, weakness in an arm or leg, a change in your gait or balance, persistent numbness, decreased sensation or loss of sensation, or memory loss or confusion. These all may be symptoms of a potentially life-threatening brain disorder known as progressive multifocal leukoencephalopathy (PML). If you had these symptoms before starting treatment with carfilzomib, inform your doctor about any changes you experience in these symptoms.

Use of CARFIZOL® with other medicines

Inform your doctor if you are taking, have recently taken, or might need to take any other medicines, including any medicines obtained without a prescription, such as vitamins or herbal remedies.
Tell your doctor or nurse if you are taking medications used to prevent pregnancy, such as oral contraceptives or other hormonal contraceptives, as these may not be suitable for use with CARFIZOL®.

Pregnancy and lactation

For women taking CARFIZOL®
Do not take CARFIZOL® if you are pregnant, think you might be pregnant, or are planning to get pregnant. Treatment with carfilzomib has not been evaluated in pregnant women. While taking CARFIZOL®, and for 30 days after stopping treatment, you should use an appropriate contraceptive method to ensure that you do not become pregnant. Ask your doctor about suitable contraception methods.
If you become pregnant while receiving CARFIZOL®, inform your doctor immediately.
Do not take CARFIZOL® if you are breastfeeding. It is unknown whether carfilzomib is excreted in breast milk.
Lenalidomide is expected to be harmful to the fetus. If CARFIZOL® is administered in combination with lenalidomide, you must follow the Pregnancy Prevention Program (ASK YOUR DOCTOR).

For men taking CARFIZOL®
While taking CARFIZOL® and up to 90 days after discontinuing treatment, you should use a condom to ensure that your partner does not become pregnant, even if your partner is already pregnant.
If your partner becomes pregnant while you are receiving CARFIZOL® or up to 90 days after discontinuing treatment, inform your doctor immediately.

Driving and using machines

While receiving treatment with CARFIZOL®, you may experience fatigue, dizziness, fainting, and/ or a drop in blood pressure. This may affect your ability to drive or operate machinery. Do not drive or operate machinery if you have these symptoms.

CARFIZOL® contains sodium

This medicine contains 0.3 mmol of sodium (equivalent to 7 mg of sodium) per milliliter of reconstituted solution. This should be taken into account if you require a low-sodium diet.

CARFIZOL® contains cyclodextrin

This medicine contains 3000 mg of cyclodextrin (sulfobutyl ether beta cyclodextrin) per 60 mg vial, equivalent to 88 mg/kg for a 70 kg adult.

• How to use CARFIZOL®

CARFIZOL® will be given to you by a doctor or nurse. The dose will be calculated based on your height and weight (body surface area). Your doctor will determine the CARFIZOL® dose you should receive.
CARFIZOL® will be given as infusion into a vein. Depending on the prescribed regimen, the infusion will last approximately 10 minutes or 30 minutes. CARFIZOL® is typically administered on 1 day or 2 consecutive days weekly for 3 weeks, followed by one week without treatment, depending on your treatment schedule.
Each 28-day period is a treatment cycle. This means that you will receive CARFIZOL® on Days 1, 2, 8, 9, 15, and 16, or on Days 1, 8, and 15 in each 28-day cycle. In certain dosing regimens, doses on Days 8 and 9 of each cycle will not be administered as from cycle 13.
Most patients will receive treatment as long as their disease improves or remains stable. However, CARFIZOL® treatment may also be discontinued if you experience side effects that cannot be managed.
You may also receive other medications as part of your treatment regimen.

If you take more CARFIZOL® than you should

This medication will be administered by a doctor or nurse, so it is unlikely that you will receive more than the prescribed amount. However, if you are given more CARFIZOL® than you should, your doctor will monitor you for any undesirable effects.
If you have any doubts about the use of this medicine, ask your doctor.

"In the event of an overdose, go to the nearest hospital or contact the Poison Control Centers:

HOSPITAL DE PEDIATRÍA RICARDO GUTIÉRREZ:
(011) 4962-6666/2247
HOSPITAL ALEJANDRO POSADAS:
(011) 4654-6648/4658-7777

Alternatively, you can contact other Poison Control Centers".

• Possible side effects of CARFIZOL®

Like all medicines, CARFIZOL® can cause side effects, although not everyone gets them.

Signs and symptoms to be alert to
Some side effects can be significant. Tell your doctor straight away if you experience any of the following symptoms:

- Chest pain, breathing difficulties, or swelling of your feet, which may be symptoms of heart problems.
- Breathing difficulties, including breathing difficulties at rest or with activity, or cough (dyspnea), rapid breathing, a feeling of not being able to breathe when there is enough oxygen, wheezing (breathing noises), or cough, which may be signs of pulmonary toxicity.
- Very high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or anxiety attacks, which may be signs of a condition known as hypertensive crisis.
- Breathing difficulties in daily activities or at rest, irregular heartbeat, racing pulse, tiredness, dizziness, and fainting, which may be signs of a condition known as pulmonary hypertension.
- Swollen ankles, feet, or hands, loss of appetite, decreased urine output, or abnormal blood test results, which may be symptoms of kidney problems or renal impairment.
- An adverse effect called Tumor Lysis Syndrome, which can result from the rapid breakdown of tumor cells and can cause irregular heartbeats, renal impairment, or abnormal blood test results.
- Fever, chills or shivering, joint pain, muscle pain, facial congestion or swelling of the face, lips, tongue, and/or throat that can cause difficulty breathing or swallowing (angioedema), weakness, breathing difficulties, low blood pressure, fainting, slow heart rate, chest tightness, or chest pain can occur as a reaction to infusion.
- Unusual bruising or bleeding, such as a cut taking longer than usual to stop bleeding; or internal bleeding like coughing up blood, vomiting up blood, black stools, or bright red blood in your stools; or brain bleeding that causes sudden numbness or paralysis on one side of the face, legs, or arms, severe and sudden headache, or difficulty in vision, speech, or swallowing.
- Leg or arm pain or swelling (which could be symptoms of blood clots in deep veins of the legs or arms), chest pain or breathing difficulties (which could be symptoms of blood clots in the lungs).
- Yellowing of your skin and eyes (jaundice), abdominal pain or swelling, nausea or vomiting, which could be symptoms of liver problems, including hepatic impairment. If you have ever had a hepatitis B virus infection, treatment with this medication may cause a reactivation of the hepatitis B virus infection.
- Bleeding, bruising, weakness, confusion, fever, nausea, vomiting, diarrhea, and acute renal impairment, which could be signs of a blood disorder known as thrombotic microangiopathy.
- Headaches, confusion, seizures (convulsions), visual loss, and high blood pressure (hypertension), which could be symptoms of a neurological disorder called posterior reversible encephalopathy syndrome (PRES).

Other possible adverse events
Frequent adverse events (which may affect more than 1 in 10 people):

- Severe lung infection (pneumonia).
- Respiratory tract infection (infection of the airways).
- Low platelet counts, which can cause bruising or bleeding (thrombocytopenia).
- Low white blood cell count, which can decrease your ability to fight infections and may be associated with fever.
- Low red blood cell count (anemia), which can cause tiredness and fatigue.
- Changes in blood tests (decreased blood levels of potassium, increased blood levels of sugar and/ or creatinine).
- Decreased appetite.
- Difficulty sleeping (insomnia).
- Headache.
- Numbness, tingling, or decreased sensation in hands and/or feet.
- Dizziness.
- High blood pressure (hypertension).
- Breathing difficulties.
- Cough.
- Diarrhea.
- Nausea.
- Constipation.
- Vomiting.
- Stomach pain.
- Back pain.
- Joint pain.
- Pain in limbs, hands, or feet.
- Muscle spasms.
- Fever.
- Chills.
- Swelling of hands, feet, or ankles.
- Weakness.
- Tiredness (Fatigue).

Uncommon adverse events (which may affect up to 1 in 10 people)

- Infusion reactions.
- Heart failure and heart problems including fast, strong, or irregular heartbeats.
- Heart attack.
- Kidney problems, including renal impairment.
- Blood clots in the veins (deep vein thrombosis).
- Hot flashes.
- Blood clots in the lungs.
- Fluid in the lungs.
- Wheezing (noises when breathing).
- Severe infection, including bloodstream infection (sepsis).
- Lung infection.
- Liver problems, including increased liver enzymes in the blood.
- Flu-like symptoms (influenza).
- Reactivation of the chicken pox virus that can cause a rash and pain (herpes zoster).
- Urinary tract infection (infection of the structures that transport urine).
- Cough that may include chest tightness or pain, nasal congestion (bronchitis).
- Sore throat.
- Inflammation of the nose and throat.
- Runny nose, nasal congestion, or sneezing.
- Viral infection.
- Stomach and intestinal infection (gastroenteritis).
- Changes in blood tests (decreased blood levels of sodium, magnesium, proteins, calcium, or phosphate, increased blood levels of calcium, uric acid, potassium, bilirubin, C-reactive protein, or sugar).
- Dehydration.
- Anxiety.
- Feeling confused.
- Blurred vision.
- Cataracts.
- Low blood pressure (hypotension).
- Nosebleed.
- Changes in voice or hoarseness.
- Indigestion.
- Toothache.
- Skin rash.
- Bone pain, muscle pain, and chest pain.
- Muscle weakness.
- Aching muscles.
- Itchy skin.
- Skin redness.
- Increased sweating.
- Pain.
- Pain, swelling, irritation, or discomfort at the site of intravenous injection.
- Ringing in the ears (tinnitus).
- Feeling sick or general malaise.

Rare adverse events (which may affect up to 1 in 100 people)

- Bleeding in the lungs.
- Inflammation of the colon caused by the bacterium Clostridium difficile.
- Allergic reaction to CARFIZOL®.
- Multiorgan failure.
- Reduced blood flow to the heart.
- Brain hemorrhage.
- Cerebral infarction.
- Difficulty breathing, rapid breathing, and/or slightly blue fingertips and lips (acute respiratory distress syndrome).
- Swelling of the lining of the heart (pericarditis), symptoms include pain behind the breastbone, sometimes spreading to the neck and shoulders, sometimes with fever.
- Fluid build-up between the lining of the heart and your heart (pericardial effusion), symptoms include chest pain or pressure and breathing difficulties.
- Obstruction of bile flow from the liver (cholestasis), which can cause itchy skin, yellow skin, very dark urine, and very pale stools.
- Perforation of the digestive system.
- Cytomegalovirus infection.
- Reactivated hepatitis B virus infection (viral inflammation of the liver).
- Pancreatitis.

Reporting adverse events

If you experience any type of undesirable effects, ask your doctor, even if they are possible side effects not listed in this leaflet.
You can also contact the Gador S.A. Pharmacovigilance Department at farmacovigilancia@gador.com.ar or at 0800-220-2273 (CARE).
"In case of any inconvenience with the product, you can fill out the form on the ANMAT Website: http://www.anmat.gov.ar/farmacovigilancia/Notificar.asp, or call ANMAT Responde Program at 0800-333-1234".
By reporting undesirable effects, you can contribute to providing more information about the safety of this medication.

Reminder

"This medication has been prescribed only for your current medical condition. Do not recommend it to others".

• CARFIZOL® storage

Store in a refrigerator between 2°C and 8°C, in its original package to protect from light. The reconstituted solution remains stable for 24 hours in the refrigerator (between 2°C and 8°C) or for 4 hours at room temperature (between 15°C and 30°C).
The reconstituted product should be a clear and colorless solution, and it should not be administered if any discoloration or particulate matter is observed.
CARFIZOL® is intended for single use only. Disposal of unused medication and all materials derived from its use should be done in accordance with local regulations.
Do not use this medicine if the package is damaged.
You can use CARFIZOL® until the last day of the month indicated on the package. Do not take CARFIZOL® after the expiration date.

• Package contents and additional information

CARFIZOL® composition
The active ingredient is carfilzomib. Each vial contains 60 mg of carfilzomib. After reconstitution, 1 ml of solution contains 2 mg of carfilzomib.
The other components are: sulfobutylether beta cyclodextrin, citric acid anhydrous, sodium hydroxide.

How-supplied

CARFIZOL® is available in packages containing a single-use vial with lyophilized powder for injection. Dispose the unused portion. For intravenous use only.

"This medication should be used exclusively under medical prescription and supervision and should not be repeated without a new medical prescription"

"KEEP ALL THE MEDICINES OUT OF THE REACH OF CHILDREN"

For more information about our products

visit our site: **www.gador.com/productos**

or send us your query to: **info@gador.com**

Gador s.A. Darwin 429, C1414CUI, C.A.B.A. Tel: 4858-9000.
Manufactured by IMA S.A.I.C Palpa 2862, CABA, Argentina, for Gador S.A.
Last Revision Date: Jan-2022

G00000000-00

Recyclable Materials

Gador

Renal impairment
The pharmacokinetics of carfilzomib were studied in two specific renal impairment trials. In one study involving patients with multiple myeloma and normal renal function, mild, moderate or severe renal impairment, or on chronic dialysis, carfilzomib as a single agent was administered intravenously over 2 to 10 minutes at doses up to 20 mg/m². Another study was conducted in relapsed multiple myeloma patients with creatinine clearance ≥ 75 ml/ min and in patients with end-stage renal disease (ESRD) requiring dialysis. The results of both studies showed that the renal function status had no noticeable effect on the exposure to carfilzomib following single or repeated doses. Serious adverse events related to worsening of renal function were more frequent in patients with pre-existing renal dysfunction.

DOSAGE AND ANDMINISTRATION

Treatment with CARFIZOL® should be supervised by a physician experienced in the use of chemotherapy.

Dosage
The CARFIZOL® dose is calculated based on the patient's baseline body surface area (BSA). Patients with a BSA greater than 2.2 m² should receive a dose based on a BSA of 2.2 m². Dose adjustments are not necessary for weight variations of less than or equal to 20%.

• CARFIZOL® in combination with lenalidomide and dexamethasone
In the combination regimen with lenalidomide and dexamethasone, CARFIZOL® should be administered intravenously as a 10-minute infusion on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered a treatment cycle.
CARFIZOL® is administered at an initial dose of 20 mg/m² (maximum dose 44 mg) on Days 1 and 2 of Cycle 1. If tolerated, the dose should be increased to 27 mg/m² (maximum dose 60 mg) on Day 8 of Cycle 1. As from Cycle 13, CARFIZOL® doses on Days 8 and 9 are omitted. Treatment may continue until disease progression or the appearance of unacceptable toxicity occurs. The treatment with CARFIZOL® in combination with lenalidomide and dexamethasone for more than 18 Cycles should be based on an individual assessment of the benefit-risk balance, as data on tolerability and toxicity of carfilzomib beyond 18 cycles are limited.
Lenalidomide, in combination with CARFIZOL®, is administered at a dose of 25 mg orally on Days 1-21, and dexamethasone is administered at a dose of 40 mg orally or intravenously on Days 1, 8, 15, and 22 of 28-day cycles. Appropriate reduction of the initial lenalidomide dose should be considered in accordance with the current product package insert recommendations. Dexamethasone should be administered between 30 minutes and 4 hours before CARFIZOL®. Please refer to the prescribing information for lenalidomide and dexamethasone for other concomitant medications that may be necessary with these agents, such as the use of anticoagulants and antacid prophylaxis. **(Table 1).**

• CARFIZOL® in combination with dexamethasone

<u>20/ 56 mg/m² regimen twice a week by a 30-minute infusion</u>
CARFIZOL® should be administered intravenously as a 30-minute infusion on two consecutive days, every week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered a treatment cycle.
CARFIZOL® is administered by infusion over 30 minutes at an initial dose of 20 mg/m² (maximum dose 44 mg) in Cycle 1, on Days 1 and 2. If tolerated, dose should be increased to 56 mg/m² (maximum dose 123 mg) on Day 8 of Cycle 1.
Dexamethasone is administered at a dose of 20 mg orally or intravenously on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28-day cycle. Dexamethasone should be administered between 30 minutes and 4 hours before CARFIZOL®. Treatment may continue until disease progression or the appearance of unacceptable toxicity occurs. Please refer to the prescribing information for dexamethasone for other concomitant medications that may be necessary. **(Table 2).**

<u>20/ 70 mg/m² regimen once a week by a 30-minute infusion</u>
CARFIZOL® should be administered intravenously as a 30-minute infusion on Days 1, 8, and 15 of each cycle, followed by a 13-day rest period (Days 16 to 28). Each 28-day period is considered a treatment cycle.
CARFIZOL® is administered by infusion over 30 minutes at an initial dose of 20 mg/m² (maximum dose 44 mg) in Cycle 1, on Day 1. If tolerated, dose should be increased to 70 mg/m² on Day 8 of Cycle 1.
Dexamethasone is administered at a dose of 40 mg orally or intravenously on Days 1, 8, 15, and 22 of each 28-day cycle up to Cycle 9, and as from Cycle 10, on Days 1, 8, and 15 of each 28-day cycle. Dexamethasone should be administered between 30 minutes and 4 hours before CARFIZOL®.
Treatment may continue until disease progression or the appearance of unacceptable toxicity occurs. Please refer to the prescribing information for dexamethasone for other concomitant medications that may be necessary. **(Table 3).**

• CARFIZOL® in combination with intravenous dexamethasone and daratumumab

<u>20/ 56 mg/m² regimen twice a week by a 30-minute infusion</u>
Administer CARFIZOL® intravenously as a 30-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with intravenous dexamethasone and daratumumab until disease progression or unacceptable toxicity occurs, as outlined in Table 4. The recommended starting dose of CARFIZOL® is 20 mg/m² (maximum dose 44 mg) in Cycle 1, on Days 1 and 2. If tolerated, increase the dose to 56 mg/m² (maximum dose 123 mg) in Cycle 1, on Day 8, and subsequently.
Dexamethasone is administered at a dose of 20 mg orally or intravenously on Days 1, 2, 8, 9, 15, and 16, and at a dose of 40 mg orally or intravenously on Day 22 of each 28-day Ccycle. For patients > 75 years old, administer 20 mg of dexamethasone orally or intravenously weekly after the first week.
Daratumumab is administered intravenously at a dose of 16 mg/ kg body weight, with a split dose of 8 mg/ kg in Cycle 1 on Days 1 and 2. Subsequently, daratumumab is administered at a dose of 16 mg/ kg once weekly on Days 8, 15, and 22 of Cycle 1 and on Days 1, 8, 15, and 22 of Cycle 2, followed by every 2 weeks for 4 cycles (Cycles 3 to 6), and then every 4 weeks in the remaining cycles or until disease progression. On days when more than one of these medications are administered, the recommended order is the following: dexamethasone, medication pre-infusion of daratumumab, carfilzomib, daratumumab, and medication post-infusion of daratumumab.
Administer dexamethasone between 30 minutes and 4 hours before CARFIZOL® and between 1 and 3 hours before intravenous daratumumab, taking into consideration the specified doses in Table 4.
Please refer to the prescribing information for intravenous dexamethasone and daratumumab for additional dosing information. **(Table 4).**

<u>20/ 70 mg/m² regimen once a week by a 30-minute infusion</u>
Administer CARFIZOL® intravenously as a 30-minute infusion on Days 1, 8, and 15 of each 28-day cycle in combination with intravenous dexamethasone and daratumumab until disease progression or unacceptable toxicity occurs, as outlined in Table 5. The recommended starting dose of CARFIZOL® is 20 mg/m² in Cycle 1, on Day 1. If tolerated, increase the dose to 70 mg/m² in Cycle 1, on Day 8, and subsequently. Administer dexamethasone between 30 minutes and 4 hours before CARFIZOL® and between 1 and 3 hours before intravenous daratumumab, taking into consideration the doses specified in Table 5. Please refer to the prescribing information for intravenous dexamethasone and daratumumab for additional dosing information. **(Table 5).**

• CARFIZOL® as monotherapy
When CARFIZOL® is used as monotherapy, it should be administered intravenously as a 10 or 30-minute infusion, depending on the selected regimen, as described below.

<u>20/ 27 mg/m² regimen twice a week by a 10-minute infusion</u>
For monotherapy with CARFIZOL® using the 20/ 27 mg/m² regimen, it should be administered intravenously as a 10-minute infusion. In Cycles 1 to 12, administer CARFIZOL® on two consecutive days, every week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered a treatment cycle. As from Cycle 13, the doses on Days 8 and 9 of CARFIZOL® are omitted.
Premedicate with 4 mg of dexamethasone orally or intravenously, 30 minutes to 4 hours before each dose of CARFIZOL® in Cycle 1, and then as needed to help prevent infusion-related reactions.
CARFIZOL® is administered at an initial dose of 20 mg/m² in Cycle 1, on Days 1 and 2. If tolerated, dose should be increased to 27 mg/ m² on Day 8 of Cycle 1, and subsequently. Treatment may continue until disease progression or the appearance of unacceptable toxicity occurs. **(Table 6).**

<u>20/ 56 mg/m² regimen twice a week by a 30-minute infusion</u>
For monotherapy with CARFIZOL® using the 20/ 56 mg/m² regimen, it should be administered intravenously as a 30-minute infusion. In Cycles 1 to 12, administer CARFIZOL® on two consecutive days, every week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered a treatment cycle. As from Cycle 13, the doses on Days 8 and 9 of CARFIZOL® are omitted.
Premedicate with 8 mg of dexamethasone orally or intravenously, 30 minutes to 4 hours before each dose of CARFIZOL® in Cycle 1, and then as needed to help prevent infusion-related reactions.
CARFIZOL® is administered at an initial dose of 20 mg/m² in Cycle 1, on Days 1 and 2. If tolerated, dose should be increased to 56 mg/m² on Day 8 of Cycle 1. Treatment may continue until disease progression or the appearance of unacceptable toxicity occurs. **(Table 7)**

Concomitant medication
- To reduce the risk of herpes zoster reactivation in patients treated with CARFIZOL® prophylaxis should be considered.
- Patients receiving CARFIZOL® treatment in combination with other therapies are recommended to undergo thromboprophylactic measures, in accordance with the assessment of underlying risks and the clinical status of the patients. For other concomitant medications that may be necessary, such as the use of antacid prophylaxis, please refer to the current package inserts for lenalidomide and dexamethasone.
- Premedicate with the recommended dose of dexamethasone for CARFIZOL® monotherapy or the recommended dose of dexamethasone in the case of combination therapy. Administer dexamethasone orally or intravenously at least 30 minutes but no more than 4 hours before all doses of CARFIZOL® during Cycle 1 to reduce the incidence and severity of infusion-related reactions. Reinitiate dexamethasone premedication if these symptoms occur in subsequent cycles.
- Patients treated with CARFIZOL® in combination with daratumumab and dexamethasone should receive pre-infusion medication to reduce the risk of daratumumab infusion-related reactions. Please refer to current daratumumab package insert for additional information on concomitant medication, including pre- and post-infusion medication.

Hydration, fluid and electrolyte monitoring
Adequate hydration is required before dose administration in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity. All patients should be monitored for signs of volume overload, and fluid needs should be tailored to individual patient requirements. The total fluid volume should be adjusted as clinically indicated in patients with pre-existing heart failure or those at risk of heart failure.
Recommended hydration includes both oral fluids (30 ml/ kg/ day for 48 hours before Day 1 of Cycle 1) and intravenous fluids (250 ml to 500 ml of appropriate intravenous fluids before each dose in Cycle 1). Administer additional 250 ml to 500 ml of intravenous fluids if needed after the administration of CARFIZOL® in Cycle 1. Oral and/ or intravenous hydration should be continued as needed in subsequent Cycles. When administered in combination with intravenous daratumumab, oral and/ or intravenous hydration is not necessary on days when daratumumab infusion is given.
Serum potassium levels should be monitored monthly or more frequently during CARFIZOL® treatment, as clinically indicated, depending on potassium levels measured before treatment initiation, concomitant treatment used (e.g., medications known to increase the risk of hypokalemia), and associated comorbidities.

Recommended dose adjustments
CARFIZOL® dose adjustments should be based on toxicity. Recommended actions and dose adjustments are shown in Table 8. The dose reduction levels are shown in Table 9. Please refer to the information provided in the respective approved and current package inserts for lenalidomide, intravenous daratumumab, and dexamethasone. **(Table 8).**

Table 1. CARFIZOL® (10-minute infusion) in combination with lenalidomide and dexamethasone

	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
Cycle 1	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/m²)	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide (mg)	25/ day, Days 1 to 21										
Cycles 2-12	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/m²)	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide (mg)	25/ day, Days 1 to 21										
Cycles 13 and beyond	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/m²)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide (mg)	25/ Day, Days 1 to 21										

Table 2. CARFIZOL® 20/56 mg/m² twice a week (30-minute infusion) in combination with dexamethasone

	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
Cycle 1	Week 1			Week 2			Week 3			Week 4		
CARFIZOL® (mg/m²)	20	20	-	56	56	-	56	56	-	-	-	
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	
Cycles 2 and beyond	Week 1			Week 2			Week 3			Week 4		
CARFIZOL® (mg/m²)	56	56	-	56	56	-	56	56	-	-	-	
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	

Table 3. CARFIZOL® 20/ 70 mg/m² once a week (30-minute infusion) in combination with dexamethasone.

	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
Cycle 1	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/m²)	20	-	-	70	-	-	70	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Cycles 2-9	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/ m²)	70	-	-	70	-	-	70	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Cycles 10 and beyond	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/ m²)	70	-	-	70	-	-	70	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	-	-

Table 4: CARFIZOL® 20/ 56 mg/m² twice a week (30-minute infusion) in combination with intravenous dexamethasone and daratumumab.

	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
Cycle 1	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/ m²)	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	
CARFIZOL® (mg/ m²)	56	56	-	56	56	-	56	56	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	40	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	
Cycles 3-6	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/ m²)	56	56	-	56	56	-	56	56	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	40	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-	-	-
Cycles 7 and beyond	Week 1			Week 2			Week 3			Week 4	
CARFIZOL® (mg/ m²)	56	56	-	56	56	-	56	56	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	40	
Daratumumab (mg/kg)	16	-	-	-	-	-	-	-	-	-	-

* Administer 20 mg of dexamethasone orally or intravenously weekly after the first week to patients over 75 years.

Table 5: CARFIZOL® 20/70 mg/m² once a week (30-minute infusion) in combination with intravenous dexamethasone and daratumumab.

	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
Cycle 1	Week 1			Week 2			Week 3			Week 4		
CARFIZOL® (mg/m²)	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		
CARFIZOL® (mg/m²)	70	-	-	70	-	-	70	-	-	-		-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
Cycles 3-6	Week 1			Week 2			Week 3			Week 4		
CARFIZOL® (mg/m²)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	20	20	-	40	-	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
Cycles 7 and beyond	Week 1			Week 2			Week 3			Week 4		
CARFIZOL®(mg/m²)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	20	20	-	40	-	-	40	-	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-

* Administer 20 mg of dexamethasone orally or intravenously weekly after the first week to patients over 75 years.

Table 6. CARFIZOL® as monotherapy, 20/ 27 mg/m² twice a week (10-minute infusion).

	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
Cycle 1	Week 1			Week 2			Week 3			Week 4
CARFIZOL® (mg/m²)[a]	20	20	-	27	27	-	27	27	-	-
Cycles 2-12	Week 1			Week 2			Week 3			Week 4
CARFIZOL® (mg/m²)	27	27	-	27	27	-	27	27	-	-
Cycles 13 and beyond	Week 1			Week 2			Week 3			Week 4
CARFIZOL® (mg/m²)	27	27	-	-	-	-	27	27	-	-

[a] For each dose of CARFIZOL® in Cycle 1 premedication with dexamethasone is required.

Table 7. CARFIZOL® as monotherapy, 20/ 56 mg/m² twice a week (30-minute infusion)

	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Days 22-28
Cycle 1	Week 1			Week 2			Week 3			Week 4
CARFIZOL® (mg/ m²)[a]	20	20	-	56	56	-	56	56	-	-
Cycles 2-12	Week 1			Week 2			Week 3			Week 4
CARFIZOL® (mg/ m²)	56	56	-	56	56	-	56	56	-	-
Cycles 13 and beyond	Week 1			Week 2			Week 3			Week 4
CARFIZOL® (mg/ m²)	56	56	-	-	-	-	56	56	-	-

[a] For each dose of CARFIZOL® in Cycle 1 premedication with dexamethasone is required.

Table 8. Dose adjustments during CARFIZOL® treatment

Hematologic toxicity	Recommended measure
• Absolute Neutrophil Count <0.5 x 10⁹/ l	• Withhold dose - If it recovers up to ≥0.5 x 10⁹/ l, continue at the same dose level • For subsequent decreases up to <0.5 x 10⁹/ l, follow the above-mentioned recommendations and consider reducing 1 dose level when restarting CARFIZOL®[a]
• Febrile neutropenia Absolute neutrophil count <0.5 x 10⁹/ l and an oral temperature >38.5ºC or two consecutive readings >38ºC over 2 hours	• Withhold dose - If the absolute neutrophil count returns to baseline and the fever is resolved, resume at the same dose level
• Platelet count <10 x 10⁹/ l or signs of bleeding with thrombocytopenia	• Withhold dose - If it recovered up to ≥10 x 10⁹/ l and/ or bleeding is controlled, continue at the same dose level • For subsequent decreases up to <10 x 10⁹/ l, follow the same recommendations mentioned above and consider a dose level reduction when restarting CARFIZOL®[a]
Non-hematological (renal) toxicity	**Recommended measure**
• Serum creatinine of 2 times or higher than baseline; or • Creatinine clearance less than <15 ml/ min, or a decrease in creatinine clearance to ≤50% from baseline, or the need for dialysis	• Withhold the dose and continue monitoring renal function (serum creatinine or creatinine clearance) - If attributable to CARFIZOL®, it should be resumed when renal function has been resolved within 25% from baseline; consider resuming with a one dose level reduction[a] - If not attributable to CARFIZOL®, it can be resumed at the discretion of the treating physician. • For patients on dialysis receiving CARFIZOL®, the dose should be administered after the dialysis procedure.
Other non-hematological toxicity	**Recommended measure**
• All other grade 3 or 4, severe or life-threatening non-hematological toxicities	• Withhold until it resolved or returned to baseline • Consider restarting the next scheduled treatment with a one dose level reduction[a]

[a] See Table 9 for dose level reductions

Table 9. CARFIZOL® dose level reduction

Regimen	Dose	First dose reduction	Second dose reduction	Third dose reduction
CARFIZOL® / Dexamethasone, or CARFIZOL® / daratumumab/ Dexamethasone (once a week)	70 mg/m²	56 mg/m²	45 mg/m²	36 mg/m²
CARFIZOL® / lenalidomide/ Dexamethasone, or CARFIZOL® monotherapy (20/ 27 mg/ m²) (twice a week)	27 mg/m²	20 mg/m²	15 mg/m²[a]	-
CARFIZOL® / Dexamethasone, or CARFIZOL® / daratumumab/ Dexamethasone, or CARFIZOL® ® monotherapy (20/ 56 mg/ m²) (twice a week)	56 mg/m²	45 mg/m²	36 mg/m²	27 mg/m²[a]

Note: infusion times are not modified with dose reduction.
[a] If toxicity persists, discontinue CARFIZOL® treatment.

Special populations
<u>Renal impairment</u>
Patients with moderate or severe renal impairment were excluded from clinical studies of carfilzomib in combination with lenalidomide. Adequate initial dose reduction of lenalidomide should be considered in patients with pre-existing renal impairment, in accordance with the recommendations in the current lenalidomide package insert.
No initial dose adjustment of CARFIZOL® is required for patients with pre-existing mild, moderate or severe renal impairment or for patients on chronic dialysis. Since clearance of carfilzomib strengths during dialysis has not been studied, it should be administered after the dialysis procedure. In clinical studies, the incidence of adverse effects of acute renal impairment was higher in subjects with lower baseline creatinine clearance than in subjects with higher baseline creatinine clearance.
Renal function should be monitored at the beginning of treatment and then at least monthly or in accordance with accepted clinical practice guidelines, especially in patients with lower baseline creatinine clearance. Based on toxicity, appropriate dosing adjustments should be made (see Table 8). There is limited efficacy and safety data in patients with baseline creatinine clearance <30 ml/ min.

<u>Hepatic impairment</u>
The pharmacokinetics of carfilzomib have not been evaluated in patients with severe hepatic impairment. Based on available pharmacokinetic data, no initial dose adjustment is recommended for patients with mild or moderate hepatic impairment. However, a higher incidence of subjects with abnormalities in liver function, adverse events ≥ Grade 3, or serious adverse events has been reported in patients with prior mild or moderate hepatic impairment compared to patients with normal liver function.
Liver enzymes and bilirubin should be monitored at the beginning of treatment and monthly during treatment with CARFIZOL®, regardless of baseline values. Appropriate dose adjustments should be made based on toxicity (see Table 8). Special attention should be paid to patients with moderate and severe hepatic impairment due to very limited efficacy and safety data for this population.

<u>Elderly population</u>
Overall, the incidence of certain adverse effects (including heart failure) in clinical studies was higher in patients aged ≥75 years compared to those aged <75 years.

<u>Pediatric population</u>
The safety and efficacy of carfilzomib have not been established in pediatric patients. No data are available.

Mode of administration
CARFIZOL® is administered intravenously as an infusion over 10 or 30 minutes, depending on the corresponding dosing regimen. CARFIZOL® should not be given as a bolus.
The intravenous catheter should be flushed with normal saline solution or 5% dextrose solution for injection immediately before and after CARFIZOL® administration. CARFIZOL® should not be co-administered or mix with other drugs.
Before administering CARFIZOL®, please refer to the reconstitution instructions provided below.

Reconstitution and Preparation for Intravenous Administration
CARFIZOL® vials do not contain antimicrobial preservatives and they are intended for single use. Proper aseptic technique must be observed.
The reconstituted solution contains carfilzomib at a 2 mg/ ml strength. The amount of CARFIZOL® contained in each vial (60 mg carfilzomib) may exceed the required dose; exercise caution when calculating the amount to be administered to prevent overdosage. Please read the complete preparation instructions before reconstitution.
1. Remove the vial from refrigerator immediately before use.
2. Calculate the dose (mg/m²) and the number of CARFIZOL® vials needed, taking into account the patient's baseline BSA. Patients with a BSA greater than 2.2 m² should receive a dose based on a body surface of 2.2 m². No dose adjustments are necessary for weight changes of less than or equal to 20%.
3. Aseptically reconstitute each vial by slowly injecting 29 ml of sterile water for injection through the stopper, using a 21G needle or larger (outer diameter of the needle 0.8 mm or smaller), and directing the solution onto the INNER WALL OF THE VIAL to minimize foaming.

4. Gently swirl and/ or invert the vial for approximately one minute or until complete dissolution. DO NOT SHAKE. If foaming occurs, allow the solution to settle in the vial until the foaming decreases (approximately 5 minutes) and the solution becomes clear.
5. Visually inspect for particles and any color changes before 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 remaining in the vial. DO NOT pool unused portions from other vials. DO NOT administer more than one dose per vial.
7. CARFIZOL® can be administered directly by intravenous infusion or optionally in an intravenous bag containing 50 to 100 ml of **5% dextrose solution for injection**. Do not administer as an intravenous injection or bolus.
8. When administering in an intravenous bag, use a 21 G or larger needle (outer diameter of the needle 0.8 mm or smaller) to withdraw the calculated dose from the vial and **dilute into 50 ml or 100 ml intravenous bag with 5% dextrose solution for injection** (based on the total calculated dose and infusion time).

The stability of reconstituted CARFIZOL® under different temperatures and packaging conditions is shown in Table 10.

Table 10. Stability of reconstituted CARFIZOL®

Storage conditions for reconstituted CARFIZOL®	Stability[a] according to the container: Vial	Syringe	Intravenous bag (D5W[b])
Refrigerated (2°C to 8°C)	24 hours	24 hours	24 hours
Room temperature (15°C to 30°C)	4 hours	4 hours	4 hours

[a] Total time between reconstitution and administration should not exceed 24 hours.
[b] 5% Glucose solution for injection.

CONTRAINDICATIONS

CARFIZOL® is contraindicated in:
- Patients with hypersensitivity to the active substance or any of the excipients of this product.
- Breastfeeding women.

Since CARFIZOL® can be administered in combination with other medications, please refer to the respective current package inserts for additional contraindications.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Since CARFIZOL® can be administered in combination with other medications, it is necessary to consult the respective current package inserts before starting treatment with CARFIZOL®. Since lenalidomide can be used in combination with CARFIZOL®, special attention should be paid to lenalidomide requirements for pregnancy tests and prevention.

<u>Heart Disorders</u>
Following carfilzomib administration, worsening or new onset of heart failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathies, myocardial ischemias, and myocardial infarctions have occurred. Some events occurred in patients with normal baseline ventricular function. Deaths due to cardiac arrest have occurred within one day after carfilzomib administration, and fatal cases of heart failure and myocardial infarction have been reported.
Adequate hydration is required before Cycle 1 dose, and all patients should be monitored for signs of volume overload, especially in patients at risk of heart failure. The total fluid volume should be adjusted as clinically indicated in patients with prior heart failure or at risk of heart failure.
Patients should be monitored for signs or symptoms of heart failure or myocardial ischemia. CARFIZOL® should be withheld in the event of grade 3 or 4 cardiac events until recovery, and restarting CARFIZOL® with one dose level reduction based on the benefit-risk assessment should be considered.
The risk of heart failure is increased in elderly patients (≥75 years).
The risk of heart failure is also increased in Asian patients.
A thorough evaluation of cardiovascular risk factors is recommended before initiating treatment with CARFIZOL®.
Patients with heart failure and greater functional decline, recent myocardial infarction (within the last 4 months), and angina or heart block not controlled with medication may have a higher risk of developing cardiac complications; these patients should undergo a comprehensive cardiological evaluation before starting treatment with CARFIZOL®. This evaluation should enhance the patient's condition, paying particular attention to blood pressure and fluid management. Subsequently, these patients should be treated with caution and remain under close monitoring.

<u>Changes in Electrocardiogram</u>
Cases of QT interval prolongation have been reported in clinical studies with carfilzomib, and its effect on the QT interval cannot be ruled out. Cases of ventricular tachycardia have been reported in patients receiving carfilzomib.

<u>Lung Toxicity</u>
Patients receiving carfilzomib have developed acute respiratory distress syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative lung disease such as pneumonitis and interstitial lung disease. Some of these events have been fatal.
CARFIZOL® should be assessed and withheld until these events have been resolved, and CARFIZOL® restarting based on a risk-benefit assessment should be considered.

<u>Pulmonary Hypertension</u>
Pulmonary hypertension has been reported in patients treated with carfilzomib. Some of these events have been fatal. Appropriate additional tests should be conducted if pulmonary hypertension is suspected.
CARFIZOL® should be withheld in cases of pulmonary hypertension until resolution or recovery to baseline values, and restarting based on a risk-benefit assessment should be considered.

<u>Dyspnea</u>
Dyspnea has been frequently reported in patients treated with carfilzomib. Evaluate dyspnea to exclude cardiopulmonary conditions, including heart failure and pulmonary syndromes.
CARFIZOL® should be withheld in cases of grade 3 and 4 dyspnea until resolution or recovery to baseline values, and restarting based on a risk-benefit assessment should be considered.

<u>Hypertension</u>
Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with carfilzomib. Some of these events have been fatal. Cases of hypertension were reported more frequently in patients who received carfilzomib in combination with daratumumab in clinical studies.
Blood pressure monitoring before starting CARFIZOL® treatment and during treatment is recommended. Blood pressure should be regularly monitored, and all patients should be routinely evaluated for hypertension and treated as necessary. If hypertension cannot be controlled, CARFIZOL® dose should be reduced. In cases of hypertensive crises, CARFIZOL® should be withheld until resolution or recovery to baseline values occurs, and restarting based on a risk-benefit assessment should be considered.

<u>Acute renal impairment</u>
Cases of acute renal impairment have been reported in patients receiving carfilzomib. Some of these events have been fatal. Cases of acute renal impairment occurred more frequently in patients with advanced relapsed and refractory multiple myeloma who received carfilzomib as monotherapy. In clinical studies performed with carfilzomib, the incidence of adverse events of acute renal impairment was higher in subjects with lower baseline creatinine clearance than in those with higher baseline creatinine clearance. Creatinine clearance remained stable over time for most patients. Renal function should be regularly monitored, at least monthly or in accordance with accepted clinical practice guidelines, especially in patients with lower baseline creatinine clearance. CARFIZOL® dose should be reduced or withheld as appropriate.

<u>Tumor Lysis Syndrome</u>
Cases of tumor lysis syndrome (TLS), including fatal cases, have been reported in patients receiving carfilzomib. Patients with multiple myeloma and a high tumor burden are at higher risk of TLS.
Patients should be adequately hydrated before CARFIZOL® administration in Cycle 1 and subsequent cycles as needed. Medications that decrease uric acid levels should be considered for patients at high risk of TLS. Signs of TLS should be monitored during treatment, including regular monitoring of serum electrolytes, and treated promptly. CARFIZOL® treatment should be withheld until TLS is resolved.

<u>Infusion reactions</u>
Cases of infusion reactions, including potentially fatal reactions, have been reported in patients receiving carfilzomib. Symptoms may include fever, chills, arthralgia, myalgia, facial congestion, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness or angina pectoris. These reactions can occur immediately or up to 24 hours after CARFIZOL® administration. Dexamethasone should be administered before CARFIZOL® to reduce reaction incidence and severity. Patients should be informed about associated risks and symptoms and the need to promptly contact a physician if any infusion-related manifestations occurs.

<u>Bleeding and Thrombocytopenia</u>
Cases of bleeding (e.g., gastrointestinal, pulmonary, and intracranial bleeding) often associated with thrombocytopenia have been reported in patients treated with carfilzomib. Some of these events have been fatal.
Carfilzomib induces thrombocytopenia, with platelet nadir typically occurring between Days 8 and 15 of each 28-day cycle, followed by recovery to baseline platelet counts at the start of the new cycle.
Platelet counts should be monitored frequently during CARFIZOL® treatment, and the dose should be reduced or withheld as appropriate.

<u>Hepatic toxicity and hepatic impairment</u>
Cases of hepatic impairment, including fatal cases, have been reported during carfilzomib treatment. Carfilzomib can cause elevations in serum transaminases. The CARFIZOL® dose should be reduced or withheld as appropriate. Liver enzymes and bilirubin levels should be regularly monitored at the beginning of the treatment and monthly during treatment, regardless of baseline values.

<u>Venous thromboembolic events</u>
Venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been observed in patients receiving carfilzomib.
Close monitoring for patients with known risk factors for thromboembolism, including previous thrombosis, is recommended. Measures should be taken to reduce all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidemia). Attention should be paid to 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 encouraged to pay special attention to the occurrence of signs and symptoms of thromboembolism. Patients should be instructed on how to seek medical help if they develop symptoms such as shortness of breath, chest pain, hemoptysis, pain or swelling in legs or arms.
Antithrombotic prophylaxis measures should be based on an individual risk-benefit assessment. The antithrombotic prophylaxis regimen should be based on the patient's risk factors.
Patients using oral contraceptives or hormonal contraception methods associated with thrombosis risk should consider alternative effective contraception methods during CARFIZOL® treatment in combination with dexamethasone or lenalidomide and dexamethasone.

<u>Thrombotic microangiopathy</u>
Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP/HUS), have been reported in patients receiving carfilzomib. Some of these events have been fatal. Signs and symptoms of TTP/HUS should be monitored. If TTP/HUS is suspected, CARFIZOL® should be withheld, and patients with suspected TTP/HUS should be evaluated. If the diagnosis of TTP/HUS is ruled out, CARFIZOL® can be resumed. The safety of restarting carfilzomib treatment in patients who previously experienced TTP/HUS is unknown.

<u>Posterior reversible encephalopathy syndrome</u>
Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving carfilzomib. PRES is a rare neurological disorder that can present with seizures, headaches, lethargy, confusional states, blindness, visual and neurological disturbances, along with hypertension, and is diagnosed through neuroradiological imaging.
If PRES is suspected, CARFIZOL® should be withheld, and patients should be adequately evaluated. The safety of resuming carfilzomib treatment in patients who previously experienced PRES is unknown.

<u>Reactivation of hepatitis B virus (HBV)</u>
Cases of reactivation of hepatitis B virus (HBV) have been reported in patients who received carfilzomib.
All patients should undergo screening for HBV before starting CARFIZOL® treatment. For patients with positive HBV serology, antiviral prophylaxis should be considered. These patients should be monitored for clinical and laboratory signs of HBV reactivation during and after treatment.
When necessary, consultation with specialists in HBV treatment is recommended.
It is unknown whether it is safe to resume carfilzomib treatment after adequately controlling HBV reactivation. Therefore, the decision to resume treatment should be made in consultation with experts in HBV treatment.

<u>Progressive multifocal leukoencephalopathy</u>
Cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients who received carfilzomib and had previously received or concomitantly received immunosuppressive treatment.
As part of the differential diagnosis of CNS disorders, patients receiving carfilzomib should be monitored for any new onset or worsening of neurological, cognitive, or behavioral signs and symptoms that may be indicative of PML.
If PML is suspected, treatment administration should be temporarily withheld until a specialist rules out PML using the appropriate diagnostic test. If PML is confirmed, carfilzomib treatment should be permanently discontinued.

<u>Embryofetal toxicity and contraception</u>
Carfilzomib can cause fetal harm if administered to pregnant women, based on its mechanism of action and observations in animals. There are no adequate and well-controlled studies of carfilzomib use in pregnant women.
Women of childbearing potential (and/ or their partners) should use effective contraception during and for at least 1 month after completing treatment. Male patients should use effective contraception during and for up to 3 months after completing treatment if their partner is pregnant or of childbearing potential and not using effective contraception.
CARFIZOL® may reduce the effectiveness of oral contraceptives.

<u>Increased fatal or severe toxicities in combination with melphalan and prednisone in newly diagnosed transplant-ineligible patients</u>
In a clinical study in patients with transplant-ineligible newly diagnosed multiple myeloma randomized to receive carfilzomib, melphalan, and prednisone or bortezomib, melphalan, and prednisone, a higher incidence of fatal adverse reactions (7% vs. 4%) and serious adverse reactions (50% vs. 42%) was observed in the group that included carfilzomib in the treatment regimen compared to patients in the bortezomib group. Patients in the first group had a higher incidence of all-grade adverse reactions, including heart failure (11% vs. 4%), hypertension (25% vs. 8%), acute renal impairment (14% vs. 6%), and dyspnea (18% vs. 9%).
CARFIZOL® in combination with melphalan and prednisone is not indicated for patients with transplant-ineligible newly diagnosed multiple myeloma.

<u>Sodium content</u>
This medication contains 0.3 mmol (7 mg) of sodium per milliliter of reconstituted solution, which should be taken into account in patients on low-sodium diets.

<u>Cyclodextrin content</u>
Each 60 mg vial contains 3,000 mg of cyclodextrin (sulfobutyl ether beta-cyclodextrin) equivalent to 88 mg/kg for a 70 kg adult.

Drug interactions and other forms of interaction
Carfilzomib is primarily metabolized through peptidase pathway and epoxide hydrolase, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors or inducers. *In vitro* studies have shown that carfilzomib did not induce CYP3A4 in cultured human hepatocytes. In a clinical study using oral midazolam as a CYP3A probe, conducted with carfilzomib dose of 27 mg/m² (2-10 minute infusion), it was demonstrated that the pharmacokinetics of midazolam were not affected by concomitant administration of carfilzomib, indicating that carfilzomib is not expected to inhibit the metabolism of CYP3A4/ 5 substrate and is not an inducer of CYP3A4 in humans. No clinical study was conducted with doses of 56 mg/m².
While carfilzomib is not expected to influence the exposure to other drugs, it is unknown whether carfilzomib induces CYP1A2, 2C8, 2C9, 2C19, and 2B6 with therapeutic strengths. Therefore, caution should be exercised when carfilzomib is combined with medications that are substrates of these enzymes, such as oral contraceptives. Effective measures should be taken to prevent pregnancy by using an alternative method of effective contraception if the patient is taking oral contraceptive.
Since carfilzomib does not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 *In vitro*, it is not expected to affect the exposure of drugs that are substrates of these enzymes as a result of inhibition.
Carfilzomib is a substrate of P-glycoprotein (P-gp) but not of BCRP. However, carfilzomib is administered intravenously and undergoes extensive metabolism, so its pharmacokinetic profile is unlikely to be affected by inhibitors or inducers of P-gp or BCRP. *In vitro*, at strengths (3 µM) lower than those expected at therapeutic doses, carfilzomib inhibits the transport of digoxin, a P-gp substrate, by 25%. Caution should be exercised when carfilzomib is combined with P-gp substrates (e.g., digoxin, colchicine).
Carfilzomib inhibits OATP1B1 *In vitro* with an IC50 of 2.01 µM, while it is unknown whether carfilzomib can inhibit other OATP1B3, OAT1, OAT3, OCT2, and BSEP transporters systemically. Carfilzomib does not inhibit human UGT2B7 but inhibits human UGT1A1 with an IC50 of 5.5 µM. However, considering the rapid elimination of carfilzomib, which shows a notable rapid decrease in the systemic strength 5 minutes after the end of the infusion, the risk of clinically relevant interactions with OATP1B1 and UGT1A1 substrates is likely low.

Incompatibilities
In the absence of compatibility studies, this medication should not be mixed with others.
CARFIZOL® powder for solution for infusion should not be mixed with sodium chloride 9 mg/ mL (0.9%) solution for injection.

Special precautions for disposal and handling
Carfilzomib is a cytotoxic agent. Therefore, CARFIZOL® should be handled and prepared with caution. The use of gloves and other protective equipment is recommended. Disposal of unused medication and all materials that have come into contact with it should be done in accordance with local regulations.

Carcinogenesis, mutagenesis, impairment of fertility and nonclinical safety data
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 it was not clastogenic in the *in vivo* micronucleus assay in mouse bone marrow.
Monkeys given a single intravenous bolus dose of carfilzomib at 3 mg/kg (equivalent to 36 mg/m² and similar to the recommended human dose