PRESCRIBING INFORMATION

1. NAME OF THE MEDICAL PRODUCT
XOMICIB 60 (Carfilzomib lyophilized powder for solution for infusion 60 mg/vial)

2. QUALITATIVE & QUANTITATIVE COMPOSITION
Each Vial Contains: Carfilzomib 60mg

Excipients with known effect:
Each vial contains 36.44 mg sodium.
Each vial contains 3,000 mg of cyclodextrin (betadex sulfobutyl ether sodium).

After reconstitution, 1 mL of solution contains 2 mg of carfilzomib.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Lyophilized powder for solution for infusion.

Before Reconstitution: White to off-white Lyophilized cake or powder in 50 mL USP type-I clear moulded glass vial with 20 mm igloo Bromobutyl rubber stopper and sealed with 20 mm aluminium seal having polypropylene disc.
Diluent: Sterile water for injection USP

After Reconstitution & further dilution: A clear and colorless solution free from visible particulate matter

4. CLINICAL INFORMATION
4.1 Therapeutic indications
Relapsed or Refractory Multiple Myeloma
XOMICIB 60 is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy in combination with:
- Lenalidomide and dexamethasone; or
- Dexamethasone; or
- Daratumumab and dexamethasone.

4.2 Posology and method of administration

ADMINISTRATION PRECAUTIONS

Hydration
Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome (TLS) or renal toxicity. Consider hydration with both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, give an additional 250 mL to 500 mL of intravenous fluids following XOMICIB 60 administration.
Continue oral and/or intravenous hydration, as needed, in subsequent cycles.

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

Electrolyte Monitoring
Monitor serum potassium levels regularly during treatment with XOMICIB 60

Premedications and Concomitant Medications
Premedicate with dexamethasone administered as part of the combination therapy. Administer dexamethasone orally or intravenously at least 30 minutes but no more than 4 hours prior to all doses of XOMICIB 60 during Cycle 1 to reduce the incidence and severity of infusion-related reactions. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.

Provide thromboprophylaxis for patients being treated with XOMICIB 60 in combination with other therapies.
Consider antiviral prophylaxis to decrease the risk of herpes zoster reactivation.

Dose Calculation

For patients with body surface area (BSA) of 2.2 m^2 or less, calculate the XOMICIB 60 dose using actual BSA. Dose adjustments do not need to be made for weight changes of 20% or less. For patients with a BSA greater than 2.2 m^2, calculate the XOMICIB 60 dose using a BSA of 2.2 m^2.

POSOLOGY

Carfilzomib in combination with lenalidomide and dexamethasone

Administer XOMICIB 60 intravenously as a 10-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with lenalidomide and dexamethasone until Cycle 12 as shown in Table 1. The recommended starting dose of XOMICIB 60 is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 27 mg/m^2 on Cycle 1, Day 8. From Cycle 13, administer XOMICIB 60 on Days 1, 2, 15, 16 until Cycle 18. Discontinue XOMICIB 60 after Cycle 18. Continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity occurs. Refer to the Prescribing Information for lenalidomide and dexamethasone for additional dosage information.

Table 1: XOMICIB 60 20/27 mg/m^2 Twice Weekly (10-Minute Infusion) in Combination with Lenalidomide and Dexamethasone

	Cycle 1										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
Carfilzomib (mg/m^2)	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1–21									-	-
	Cycles 2 to12										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
Carfilzomib (mg/m^2)	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1–21									-	-
	Cycles 13 and later[a]										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23-28**
Carfilzomib (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1–21									-	-

a. XOMICIB 60 is administered through Cycle 18, lenalidomide and dexamethasone continue thereafter

Carfilzomib in combination with dexamethasone

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

Administer XOMICIB 60 intravenously as a 30-minute infusion on Days 1, 8, and 15 of each 28- day cycle in combination with dexamethasone until disease progression or unacceptable toxicity as shown in Table 2. The recommended starting dose of XOMICIB 60 is 20 mg/m^2 on Cycle 1, Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Cycle 1, Day 8. Administer dexamethasone 30 minutes to 4 hours before XOMICIB 60. Refer to Prescribing Information for dexamethasone for additional dosage information.

Table 2: XOMICIB 60 20/70 mg/m^2 Once Weekly (30-Minute Infusion) in Combination with Dexamethasone

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

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

Administer XOMICIB 60 intravenously as a 30-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle in combination with dexamethasone until disease progression or unacceptable toxicity as shown in Table 3. The recommended starting dose of XOMICIB 60 is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Cycle 1, Day 8. Administer dexamethasone 30 minutes to 4 hours before XOMICIB 60. Refer to the Prescribing Information for dexamethasone for additional dosage information.

Table 3: XOMICIB 60 20/56 mg/m^2 Twice Weekly (30-Minute Infusion) in Combination with Dexamethasone

	Cycle 1											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
	Cycles 2 and later											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**

Carfilzomib (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

XOMICIB 60 in Combination with Daratumumab and Dexamethasone

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

Administer XOMICIB 60 intravenously as a 30-minute infusion on Days 1, 2, 8, 9, 15 and 16 of each 28-day cycle in combination with Daratumumab and dexamethasone until disease progression or unacceptable toxicity as shown in Table 4. The recommended starting dose of XOMICIB 60 is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Cycle 1, Day 8 and thereafter. Administer dexamethasone 30 minutes to 4 hours before XOMICIB 60 and 1 to 3 hours before Daratumumab. Refer to the Prescribing Information for Daratumumab and dexamethasone for additional dosage information.

Table 4: XOMICIB 60 20/56 mg/m^2 Twice Weekly (30-Minute Infusion) in Combination with Daratumumab and Dexamethasone

	Cycle 1											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg) *	20	20	-	20	20	-	20	20	-	20	20	-
with intravenous daratumumab												
Daratumumab Intravenous (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
OR with subcutaneous daratumumab												
Daratumumab subcutaneous (mg)	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-
	Cycle 2											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg) *	20	20	-	20	20	-	20	20	-	20	20	-
with intravenous daratumumab												
Daratumumab intravenous (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
OR with subcutaneous daratumumab												
Daratumumab subcutaneous (mg)	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-
	Cycles 3 to 6											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg) *	20	20	-	20	20	-	20	20	-	40	-	-
with intravenous daratumumab												

Daratumumab intravenous (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
OR with subcutaneous daratumumab												
Daratumumab subcutaneous (mg)	**1,800**	-	-	-	-	-	**1,800**	-	-	-	-	-
	Cycles 7 and onwards											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
with intravenous daratumumab												
Daratumumab intravenous (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-
OR with subcutaneous daratumumab												
Daratumumab subcutaneous (mg)	**1,800**	-	-	-	-	-	-	-	-	-	-	-

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

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

Administer XOMICIB 60 intravenously as a 30-minute infusion on Days 1, 8 and 15 of each 28-day cycle in combination with Daratumumab and dexamethasone until disease progression or unacceptable toxicity as shown in Table 5. The recommended starting dose of XOMICIB 60 is 20 mg/m^2 on Cycle 1, Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Cycle 1, Day 8 and thereafter. Administer dexamethasone 30 minutes to 4 hours before XOMICIB 60 and 1 to 3 hours before Daratumumab. Refer to the Prescribing Information for Daratumumab and dexamethasone for additional dosage information.

Table 5: XOMICIB 60 20/70 mg/m^2 Once Weekly (30-Minute Infusion) in Combination with Daratumumab and Dexamethasone

	Cycle 1											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	20	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg) *	20	20	-	20	20	-	20	20	-	20	20	-
with intravenous daratumumab												
Daratumumab intravenous (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
OR with subcutaneous daratumumab												
Daratumumab subcutaneous (mg)	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-
	Cycle 2											
	Week 1			**Week 2**			**Week 3**			**Week 4**		

	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg) *	20	20	-	20	20	-	20	20	-	20	20	-
with intravenous daratumumab												
Daratumumab intravenous (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
OR with subcutaneous daratumumab												
Daratumumab subcutaneous (mg)	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-	**1,800**	-	-
	Cycles 3 to 6											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg) *	20	20	-	40	-	-	20	20	-	40	-	-
with intravenous daratumumab												
Daratumumab intravenous (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
OR with subcutaneous daratumumab												
Daratumumab subcutaneous (mg)	**1,800**	-	-	-	-	-	**1,800**	-	-	-	-	-
	Cycles 7 and onwards											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
Carfilzomib (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	40	-	-	40	-	-	40	-	-
with intravenous daratumumab												
Daratumumab intravenous (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-
OR with subcutaneous daratumumab												
Daratumumab subcutaneous (mg)	**1,800**	-	-	-	-	-	-	-	-	-	-	-

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

DOSAGE MODIFICATIONS FOR ADVERSE REACTIONS

Recommended actions and dosage modifications for XOMICIB 60 are presented in Table 6. Dose level reductions are presented in Table 7. See the lenalidomide, intravenous Daratumumab, and dexamethasone Prescribing Information respectively for recommended dosage modifications associated with each product.

Table 6: Dosage Modifications for Adverse Reactions[a]

Haematologic toxicity	**Recommended action**
• ANC < 0.5 x 10^9/L	• Withhold dose - If recovered to greater than or equal to 0.5 ×10^9/L, continue at the same dose level • For subsequent drops to less than 0.5 ×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting XOMICIB 60[a]
• Febrile neutropenia ANC < 0.5 x 10^9/L and an oral temperature > 38.5°C or two consecutive readings of > 38.0°C for 2 hours	• Withhold dose - If ANC returns to baseline grade and fever resolves, resume at the same dose level
• Platelet count < 10 x 10^9/L or evidence of bleeding with thrombocytopenia	• Withhold dose - If recovered to greater than or equal to 10 ×10^9/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to less than 10 ×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting XOMICIB 60[a]
Renal toxicity	**Recommended action**
• Serum creatinine equal to or greater than 2 × baseline; or • Creatinine clearance < 15 mL/min or creatinine clearance decreases to less than or equal to 50% of baseline, or need for hemodialysis.	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance) - If attributable to XOMICIB 60, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction[a] - If not attributable to XOMICIB 60, dosing may be resumed at the discretion of the healthcare provider • For patients on hemodialysis receiving XOMICIB 60, the dose is to be administered after the hemodialysis procedure
Other non-haematologic toxicity	**Recommended action**
• All other severe or life-threatening[b] non-hematological toxicities	• Withhold until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction[a]

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

Table 7. Dose level reductions for Adverse Reactions

Regimen	**Dose**	**First Dose Reduction**	**Second Dose Reduction**	**Third Dose Reduction**
XOMICIB 60 and Dexamethasone OR XOMICIB 60, Daratumumab and Dexamethasone (once weekly)	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^{2a}
XOMICIB 60 and Dexamethasone OR XOMICIB 60, Daratumumab, and Dexamethasone (twice weekly)	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^{2a}
XOMICIB 60, Lenalidomide, and Dexamethasone (twice weekly)	27 mg/m^2	20 mg/m^2	15 mg/m^{2a}	-

Note: Infusion times remain unchanged during dose reduction(s).
[a] If toxicity persists, discontinue XOMICIB 60 treatment.

DOSAGE MODIFICATIONS FOR HEPATIC IMPAIRMENT
For patients with mild (total bilirubin > 1 to 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) or moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment, reduce the dose of XOMICIB 60 by 25%

RECOMMENDED DOSAGE FOR END STAGE RENAL DISEASE
For patients with end stage renal disease who are on hemodialysis, administer XOMICIB 60 after the hemodialysis procedure.

Method of administration
XOMICIB 60 vials contain no antimicrobial preservatives and are intended for single-dose only. The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL.
Read the complete preparation instructions prior to reconstitution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Reconstitution/Preparation Steps:
1. Remove vial from refrigerator just prior to use.
2. Calculate the dose (mg/m^2) and number of vials of XOMICIB 60 required using the patient's BSA at baseline.
3. Aseptically reconstitute each XOMICIB 60 vial only with Sterile Water for Injection, USP using the volumes described in Table 8. 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 XOMICIB 60.

Table 8: Reconstitution Volumes

Strength	Amount of Sterile Water for Injection, USP required for reconstitution
60mg 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 solution and should not be administered if any discoloration or particulate matter is observed.
6. Discard any unused portion left in the vial. DO NOT pool unused portions from the vials. DO NOT administer more than one dose from a vial.
7. Administer XOMICIB 60 directly by intravenous infusion or in a 50 mL to 100 mL intravenous bag containing 5% Dextrose Injection, USP. Do not administer as an intravenous push or bolus.
8. When administering in an intravenous bag, use a 21-gauge or larger gauge needle (0.8 mm or smaller external diameter needle) to withdraw the calculated dose from the vial and dilute into 50 mL or 100 mL intravenous bag containing only 5% Dextrose Injection, USP (based on the calculated total dose and infusion time).
9. Flush the intravenous administration line with normal saline or 5% Dextrose Injection, USP immediately before and after XOMICIB 60 administration.
10. Do not mix XOMICIB 60 with or administer as an infusion with other medicinal products.

The stabilities of reconstituted XOMICIB 60 under various temperature and container conditions are shown in Table 9

Table 9: Stability of Reconstituted XOMICIB 60

Storage Conditions of Reconstituted XOMICIB 60	**Stability[a] per Container**		
	Vial	**Syringe**	**Intravenous Bag (D5W[b])**
Refrigerated 2°C to 8°C	12 hours	12 hours	12 hours

Room Temperature 15°C to 30°C	2 hours	2 hours	2 hours

[a] Total time from reconstitution to administration should not exceed 12 hours.
[b] 5% Dextrose Injection, USP.

4.3 Contraindications

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

As Carfilzomib is administered in combination with other medicinal products, refer to their Prescribing Information for additional contraindications.

4.4 Special warnings and precautions for use

Cardiac Toxicities

New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Carfilzomib. Some events occurred in patients with normal baseline ventricular function. In clinical studies with Carfilzomib, these events occurred throughout the course of Carfilzomib therapy. Death due to cardiac arrest has occurred within one day of Carfilzomib administration. In randomized, open-label, multicenter trials for combination therapies, the incidence of cardiac failure events was 8% and that of arrhythmia was 8% (majority of which were atrial fibrillation and sinus tachycardia)

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

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

In patients ≥ 75 years of age, the risk of cardiac failure is increased compared to younger patients. The risk of cardiac failure is also increased in Asian patients. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities ,angina, or arrhythmias uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications; for these patients, complete a comprehensive medical assessment (including blood pressure control and fluid management) prior to starting treatment with Carfilzomib and remain under close follow-up.

Acute Renal Failure

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

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

Tumor Lysis Syndrome

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

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

Pulmonary Toxicity

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

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

Dyspnea
Dyspnea was reported in 25% of patients treated with Carfilzomib, with Grade 3 or greater in 4%. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Carfilzomib for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart Carfilzomib based on a benefit/risk assessment

Hypertension
Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Carfilzomib. In ASPIRE, the incidence of hypertension events was 17% in the KRd arm *versus* 9% in the Rd arm. In ENDEAVOR, the incidence of hypertension events was 34% in the Kd arm *versus* 11% in the Vd arm. In CANDOR, the incidence of hypertension events was 31% in the DKd arm *versus* 28% in the Kd arm. Some of these events have been fatal.
Optimize blood pressure prior to starting Carfilzomib. Monitor blood pressure regularly in all patients while on Carfilzomib. If hypertension cannot be adequately controlled, withhold Carfilzomib and evaluate. Consider whether to restart Carfilzomib based on a benefit/risk assessment.

Venous Thrombosis
Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Carfilzomib. In ASPIRE, with thromboprophylaxis used in both arms, the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm *versus* 6% in the Rd arm. In ENDEAVOR, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm *versus* 2% in the Vd arm.
Provide thromboprophylaxis for patients being treated with Carfilzomib in combination with lenalidomide and dexamethasone, with dexamethasone; or with Daratumumab and dexamethasone. Select the thromboprophylaxis regimen based on the patient's underlying risks.

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

Infusion-Related Reactions
Infusion-related reactions, including life-threatening reactions, have occurred in patients receiving Carfilzomib. Signs and symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, laryngeal edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of Carfilzomib.
Administer dexamethasone prior to Carfilzomib to reduce the incidence and severity of infusion- related reactions.

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

Thrombocytopenia
Carfilzomib causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in approximately 32% of patients in clinical trials with Carfilzomib. Hemorrhage may occur.
Monitor platelet counts frequently during treatment with Carfilzomib. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure
Cases of hepatic failure, including fatal cases, have been reported (2%) during treatment with Carfilzomib. Carfilzomib can cause increased serum transaminases.
Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy
Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received Carfilzomib. Some of these events have been fatal.
Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Carfilzomib and evaluate. If the diagnosis of TTP/HUS is excluded, Carfilzomib may be restarted. The safety of reinitiating Carfilzomib therapy in patients previously experiencing TTP/HUS is not known.

Posterior Reversible Encephalopathy Syndrome
Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving Carfilzomib. PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI).
Discontinue Carfilzomib if PRES is suspected and evaluate. The safety of reinitiating Carfilzomib therapy in patients previously experiencing PRES is not known.

Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML), which can be fatal, has been reported with Carfilzomib. In addition to Carfilzomib, other possible contributory factors include prior or concurrent immunosuppressive therapy that may cause immunosuppression. Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, discontinue Carfilzomib and initiate evaluation for PML including neurology consultation.

Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients
In CLARION, a clinical trial of 955 transplant-ineligible patients with newly diagnosed multiple myeloma randomized to Carfilzomib (20/36 mg/m^2 by 30-minute infusion twice weekly for four of each six- week cycle), melphalan and prednisone (KMP) or bortezomib, melphalan and prednisone (VMP), a higher incidence of fatal adverse reactions (7% *versus* 4%) and serious adverse reactions (50% *versus* 42%) were observed in the KMP arm compared to patients in the VMP arm, respectively. Patients in the KMP arm were observed to have a higher incidence of any grade adverse reactions involving cardiac failure (11% *versus* 4%), hypertension (25% *versus* 8%), acute renal failure (14% *versus* 6%), and dyspnea (18% *versus* 9%). This study did not meet its primary outcome measure of superiority in progression-free survival (PFS) for the KMP arm. Carfilzomib in combination with melphalan and prednisone is not indicated for transplant- ineligible patients with newly diagnosed multiple myeloma.

Embryo-Fetal Toxicity
Based on the mechanism of action and findings in animals, Carfilzomib can cause fetal harm when administered to a pregnant woman. Carfilzomib administered intravenously to pregnant rabbits during organogenesis at a dose approximately 40% of the clinical dose of 27 mg/m^2 based on BSA caused post-implantation loss and a decrease in fetal weight.
Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Carfilzomib and for 6 months following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Carfilzomib and for 3 months following the last dose.

4.5 Interaction with other medicinal products and other forms of interaction
Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

Carfilzomib can cause fetal harm based on findings from animal studies and its mechanism of action. There are no available data on Carfilzomib use in pregnant women to evaluate for drug-associated risks. Carfilzomib caused embryo-fetal lethality in rabbits at doses lower than the clinical dose (see Data). Advise pregnant women of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the

estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively.

Data

Animal Data

Carfilzomib administered intravenously to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. In rabbits, there was an increase in pre-implantation loss at ≥ 0.4 mg/kg/day and an increase in early resorptions and post-implantation loss and a decrease in fetal weight at the maternally toxic dose of 0.8 mg/kg/day. The doses of 0.4 and 0.8 mg/kg/day in rabbits are approximately 20% and 40%, respectively, of the recommended dose in humans of 27 mg/m^2 based on BSA.

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

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

Pregnancy Testing

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

Contraception

Females

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

Males

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

Infertility

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

4.7 Effects on ability to drive and use machines

Carfilzomib has minor influence on the ability to drive and use machines.
Fatigue, dizziness, fainting, blurred vision, somnolence and/or a drop in blood pressure have been observed. Patients being treated with Carfilzomib should be advised not to drive or operate machines in the event that they experience any of these symptoms.

4.8 Undesirable effects

Summary of safety profile

Serious adverse reactions that may occur during carfilzomib treatment include: cardiac failure, myocardial infarction, cardiac arrest, myocardial ischaemia, interstitial lung disease, pneumonitis, acute respiratory distress syndrome, acute respiratory

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

Tabulated list of adverse reactions

Adverse reactions are presented at Table 10 below by system organ class and frequency category (very common, common, uncommon, rare).

Table 10: Tabulated list of adverse reactions

MedDRA system organ class	**Very common**	**Common**	**Uncommon**	**Rare**
Infections and infestations	Pneumonia Respiratory tract infection	Sepsis Lung infection Influenza Herpes zoster* Urinary tract infection Bronchitis Gastroenteritis Viral infection Nasopharyngitis Rhinitis	Clostridium difficile colitis Cytomegalovirus infection Hepatitis B virus reactivation	
Immune system disorders			Drug hypersensitivity	
Blood and lymphatic system disorders	Thrombocytopenia Neutropenia Anaemia Lymphopenia Leukopenia	Febrile neutropenia	HUS TTP	Thrombotic microangiopathy
Metabolism and nutrition disorders	Hypokalaemia Decreased appetite	Dehydration Hyperkalaemia Hypomagnesaemia Hyponatraemia Hypercalcaemia Hypocalcaemia Hypophosphataemia Hyperuricaemia Hypoalbuminaemia Hyperglycaemia	Tumour lysis syndrome	
Psychiatric disorders	Insomnia	Anxiety Confusional state		
Nervous system disorders	Dizziness Peripheral neuropathy Headache	Paraesthesia Hypoaesthesia	Intracranial haemorrhage Cerebrovascular accident PRES	
Eye disorders		Cataract Blurred vision		

Ear and labyrinth disorders		Tinnitus		
Cardiac disorders		Cardiac failure Myocardial infarction Atrial fibrillation Tachycardia Ejection fraction decreased Palpitations	Cardiac arrest Cardiomyopathy Myocardial ischaemia Pericarditis Pericardial effusion Ventricular tachycardia	
Vascular disorders	Hypertension	Deep vein thrombosis Hypotension Flushing	Hypertensive crisis Haemorrhage	Hypertensive emergency
Respiratory, thoracic, and mediastinal disorders	Dyspnoea Cough	Pulmonary embolism Pulmonary oedema Epistaxis Oropharyngeal pain Dysphonia Wheezing Pulmonary hypertension	ARDS Acute respiratory failure Pulmonary haemorrhage Interstitial lung disease Pneumonitis	
Gastrointestinal disorders	Vomiting Diarrhoea Constipation Abdominal pain Nausea	Gastrointestinal haemorrhage Dyspepsia Toothache	Gastrointestinal perforation Pancreatitis acute	
Hepatobiliary disorders		Increased alanine aminotransferase Increased aspartate aminotransferase Gamma-glutamyltransferase increased Hyperbilirubinaemia	Hepatic failure Cholestasis	
Skin and subcutaneous tissue disorders		Rash Pruritus Erythema Hyperhidrosis		Angioedema
Musculoskeletal and connective tissue disorders	Back pain Arthralgia Pain in extremity Muscle spasms	Musculoskeletal pain Musculoskeletal chest pain Bone pain Myalgia Muscular weakness		
Renal and urinary disorders	Increased blood creatinine	Acute kidney injury Renal failure Renal impairment Decreased creatinine renal clearance		
General disorders and administration site conditions	Pyrexia Peripheral oedema Asthenia Fatigue Chills	Chest pain Pain Infusion site reactions Influenza like illness Malaise	Multi-organ dysfunction syndrome	
Investigations		Increased c-reactive protein Increased blood uric acid		

Injury, poisoning and procedural complications		Infusion related reaction		

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

4.9 Overdose

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of Carfilzomib administered in error.
There is no known specific antidote for Carfilzomib overdosage. In the event of overdose, monitor patients for adverse reactions and provide supportive care as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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

Pharmacodynamic effects

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

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

The Cmax and AUC following a 2-to-10-minute intravenous infusion of 27 mg/m^2 was 4,232 ng/mL and 379 ng•hr/mL, respectively. Following repeated doses of CARFILZOMIB at 15 and 20 mg/m^2, systemic exposure (AUC) and half-life were similar on days 1 and 15 or 16 of cycle 1, suggesting there was no systemic carfilzomib accumulation. At doses between 20 and 56 mg/m^2, there was a dose-dependent increase in exposure.
A 30-minute infusion resulted in a similar half-life and AUC, but 2- to 3-fold lower Cmax compared to that observed with a 2-to-10-minute infusion of the same dose. Following a 30-minute infusion of the 56 mg/m^2 dose, the AUC (948 ng•hr/mL) was approximately 2.5-fold that observed at the 27 mg/m^2 level, and Cmax (2,079 ng/mL) was lower compared to that of 27 mg/m^2 over the 2-to-10-minute infusion.

Distribution

The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib was 28 L. When tested in vitro, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar.

Biotransformation

Carfilzomib was rapidly and extensively metabolised. The predominant metabolites measured in human plasma and urine, and generated in vitro by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450 mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity.

Elimination
Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on day 1 of cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. Carfilzomib is eliminated primarily via metabolism with subsequent excretion of its metabolites in urine.

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

Hepatic impairment
Compared to patients with normal hepatic function, patients with mild (total bilirubin 1 to 1.5 × ULN and any AST or total bilirubin ≤ ULN and AST > ULN) and moderate (total bilirubin > 1.5 to 3 × ULN and any AST) hepatic impairment had approximately 50% higher carfilzomib AUC. The pharmacokinetics of carfilzomib has not been evaluated in patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST).

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Cyclodextrin (betadex sulfobutyl ether sodium)
Anhydrous citric acid
Sodium hydroxide

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
XOMICIB 60 must not be mixed with sodium chloride 9 mg/mL (0.9%) solution for injection

6.3 Shelf Life
Unopened Vial: 2 years

Reconstituted/Diluted Solution: Chemical and physical in-use stability of reconstituted solutions in the vial, syringe or intravenous bag has been demonstrated for 12 hours at 2°C - 8°C or for 2 hours at 25°C. The elapsed time from reconstitution to administration should not exceed 12 hours.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for Storage
Storage condition of unopened vial: Store in refrigerator at 2°C to 8°C. Protect from light

Reconstituted/Diluted Solution: Chemical and physical in-use stability of reconstituted solutions in the vial, syringe or intravenous bag has been demonstrated for 12 hours at 2°C - 8°C or for 2 hours at 25°C. The elapsed time from reconstitution to administration should not exceed 12 hours.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.5 Nature and Contents of container
50 mL USP type-I clear moulded glass vial with 20 mm igloo Bromobutyl rubber stopper and sealed with 20 mm aluminium seal having polypropylene disc. The vial is packed into an outer carton with a pack insert

6.6 Special precautions for disposal and other handling
General precautions
Carfilzomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of XOMICIB

60. Use of gloves and other protective equipment is recommended.

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

7. MANUFACTURER
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8. PRODUCT REGISTRATION HOLDER
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9. DATE OF REVISION
June 2026