APPROVED PROFESSIONAL INFORMATION
DR. REDDY'S LABORATORIES (PTY) LTD
KARPILRED
(carfilzomib)
powder for solution for infusion

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

KARPILRED powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use 50 ml vial contains 60 mg of carfilzomib.

After reconstitution, 1 ml contains 2 mg of carfilzomib.

Excipients with known effect:

Each vial contains 216 mg sodium

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off-white lyophilised cake or powder.

The reconstituted product should be a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

KARPILRED in combination with either dexamethasone and daratumumab, lenalidomide and dexamethasone or

with dexamethasone alone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy (see section 5.1).

KARPILRED, as a single medicine is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies that included bortezomib and an immunomodulatory therapy (see section 5.1).

4.2 Posology and method of administration

KARPILRED treatment should be supervised by a healthcare professional experienced in the use of anti-cancer therapy.

Posology

KARPILRED is an intravenous (IV) infusion that can be administered once or twice weekly based on the selected regimen. (see Table 1). Treatment may be continued until disease progression or until unacceptable toxicity occurs.

Table 1: Dosing Information

Regimen	**KARPILRED Starting Dose**	**If Tolerated, Increase KARPILRED on Day 8 of Cycle 1 to**	**KARPILRED Infusion Time[a]**
KARPILRED Monotherapy	20 mg/m^2	27 mg/m^2 twice weekly	10 minutes
KARPILRED, Lenalidomide, and Dexamethasone	20 mg/m^2	27 mg/m^2 twice weekly	10 minutes
KARPILRED plus Dexamethasone	20 mg/m^2	56 mg/m^2 twice weekly	30 minutes

	20 mg/m^2	70 mg/m^2 once weekly	30 minutes
KARPILRED Dexamethasone and Daratumumab	20 mg/m^2	56 mg/m^2 twice weekly	30 minutes
		70 mg/m^2 once weekly	30 minutes

[a] Infusion time remains consistent throughout each regimen.

The dose is calculated using the patient's baseline body surface area (BSA).

Patients with a BSA greater than 2,2 m^2 should receive a dose based upon a body surface area of 2,2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20 %.

KARPILRED Monotherapy

Twice weekly (27 mg/m^2)

KARPILRED is administered at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, the dose should be increased to 27 mg/m^2 on Day 8 of Cycle 1. KARPILRED is omitted on Days 8 and 9 of Cycles 13 and higher. KARPILRED 20/27 mg/m^2 is administered IV 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 one treatment cycle.

Table 2: Monotherapy 20/27 mg/m² Twice Weekly (10-Minute Infusion)

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

[a] Dexamethasone premedication is required for each KARPILRED dose in Cycle 1, (See section 4.2 Dexamethasone Premedication for KARPILRED Monotherapy).

KARPILRED as monotherapy in Combination with Lenalidomide and Dexamethasone

KARPILRED is administered at a starting dose of 20 mg/m² in Cycle 1 on Days 1 and 2. If tolerated, the dose should be increased to 27 mg/m² on

Day 8 of Cycle 1. KARPILRED is omitted on Days 8 and 9 of Cycles 13 and higher.

KARPILRED 27 mg/m^2 is administered IV 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 one treatment cycle.

If administered in combination with lenalidomide and dexamethasone, Lenalidomide is administered as 25 mg orally on Days 1 to 21 and dexamethasone is administered as 40 mg orally or IV on Days 1, 8, 15, and 22 of the 28-day cycles. Appropriate dose reduction for the starting dose of lenalidomide should be considered according to the recommendations in the lenalidomide Prescribing Information, for example, for patients with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before KARPILRED.

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

	Day 1	Day 2	Days 3 to 7	Day 8	Day 9	Days 10 to 14	Day 15	Day 16	Days 17 to 21	Day 22	Days 23 to 28
KARPILRED (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1 to 21									-	-

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

KARPILRED in Combination with Dexamethasone

Twice Weekly Dosing (56 mg/m^2)

KARPILRED is administered at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, the dose should be increased to 56 mg/m^2 on Day 8 of Cycle 1. KARPILRED 20/56 mg/m^2 is administered IV 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 one treatment cycle. Dexamethasone is administered as 20 mg orally or IV on Days 1, 2, 8, 9, 15, 16, 22, and 23 of the 28-day cycles. Dexamethasone should be administered 30 minutes to 4 hours before KARPILRED.

Table 4: KARPILRED 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 to 7	Day 8	Day 9	Days 10 to 14	Day 15	Day 16	Days 17 to 21	Day 22	Day 23	Days 24 to 28
KARPILRED (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 to 7	Day 8	Day 9	Days 10 to 14	Day 15	Day 16	Days 17 to 21	Day 22	Day 23	Days 24 to 28

KARPILRED (mg/m²)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

Once Weekly Dosing (70 mg/m²)

KARPILRED is administered at a starting dose of 20 mg/m² in Cycle 1 on Day 1.

If tolerated, the dose should be increased to 20/70 mg/m² on Day 8 of Cycle 1. KARPILRED 70 mg/m² is administered IV once weekly for three weeks (Days 1, 8, and 15, followed by a 13-day rest period (Days 16 to 28). Each 28-day period is considered one treatment cycle. Dexamethasone is administered as 40 mg orally or IV on Days 1, 8, and 15 of all cycles and on Day 22 of Cycles 1 to 9.

Dexamethasone should be administered 30 minutes to 4 hours before KARPILRED.

Table 5: KARPILRED 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 to 7	Day 8	Day 9	Days 10 to 14	Day 15	Day 16	Days 17 to 21	Day 22	Day 23	Days 24 to 28
KARPILRED (mg/m²)	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 to 7	Day 8	Day 9	Days 10 to 14	Day 15	Day 16	Days 17 to 21	Day 22	Day 23	Days 24 to 28
KARPILRED (mg/m²)	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 to 7	Day 8	Day 9	Days 10 to 14	Day 15	Day 16	Days 17 to 21	Day 22	Day 23	Days 24 to 28
KARPILRED (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	-	-	-

KARPILRED in Combination with Dexamethasone plus Daratumumab

For the combination regimen with dexamethasone plus daratumumab, administer KARPILRED intravenously once weekly or twice weekly as a 30-minute infusion as described in Table 6 & 7 below.

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

KARPILRED is administered intravenously as a 30-minute infusion each week for three weeks followed by a 13-day rest period as shown in Table 6. Each 28-day period is considered one treatment cycle. Administer KARPILRED at a starting dose of 20 mg/m^2 in Cycle 1 on Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Day 8 of Cycle 1 and thereafter. Dexamethasone is administered orally or intravenously at a dose of 20 mg in Cycle 1 and 2 on Days 1, 2, 8, 9, 15, 16, 22 and 23. In cycles 3 to 6, Dexamethasone is taken at a dose of 20 mg on Days 1, 2, 15 and 16 and at a dose of 40 mg on Day 8 and 22. In cycles 7 and thereafter, Dexamethasone is administered at a dose of 20 mg on Days 1 and 2 and at a dose of 40 mg on Days 8, 15, and 22.

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

Administer dexamethasone 30 minutes to 4 hours before KARPILRED. Daratumumab is administered intravenously at a dose of 16 mg/kg actual body weight; with a split dose of 8 mg/kg in Cycle 1 on Days 1 and 2.

Administer 16 mg/kg once weekly on Days 8, 15 and 22 of Cycle 1 and Days 1, 8 and 15 and 22 of Cycle 2, then every 2 weeks for 4 cycles (cycles 3 to 6) and then every 4 weeks for the remaining cycles or until disease progression.

Table 6: KARPILRED Once Weekly (30-Minute IV Infusion) in Combination with Dexamethasone plus Daratumumab

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

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

Treatment may be continued until disease progression or unacceptable toxicity occurs.

Refer to the dexamethasone and daratumumab Prescribing Information for other information on that product.

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

KARPILRED is administered intravenously as a 30-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 7. Each 28-day period is considered one treatment cycle. Administer KARPILRED at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1 and thereafter. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 8, 9, 15 and 16 and 40 mg by mouth or intravenously on Day 22 of each 28-day cycle. Administer dexamethasone 30 minutes to 4 hours before KARPILRED.

Daratumumab is administered intravenously at a dose of 16 mg/kg actual body weight; with a split dose of 8 mg/kg in Cycle 1 on Days 1 and 2. Administer 16 mg/kg once weekly on Days 8, 15 and 22 of Cycle 1 and Days 1, 8 and 15 and 22 of Cycle 2, then every 2 weeks for 4 cycles (cycles 3 to 6) and then every 4 weeks for the remaining cycles or until disease progression.

Table 7: KARPILRED Twice Weekly (30-Minute Infusion) in Combination with Dexamethasone and Daratumumab

	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
KARPILRED (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-

	Cycle 2											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	Day 2	Days 3 to 7	Day 8	Day 9	Days 10 to 14	Day 15	Day 16	Days 17 to 21	Day 22	Day 23	Days 24 to 28
KARPILRED (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
	Cycles 3 to 6											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	Day 2	Days 3 to 7	Day 8	Day 9	Days 10 to 14	Day 15	Day 16	Days 17 to 21	Day 22	Day 23	Days 24 to 28
KARPILRED (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-		-	-
*For patients > 75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week.												

Refer to the daratumumab and dexamethasone Prescribing Information for additional details on administration and concomitant medications.

Dexamethasone pre-medication prior to KARPILRED

When KARPILRED is administered as monotherapy, pre-medicate with dexamethasone 4 mg orally or intravenously at least 30 minutes but no more than 4 hours prior to all doses of KARPILRED during Cycle 1 to reduce the incidence and severity of infusion reactions (see section 4.4). Reinstate dexamethasone co-medication if these symptoms develop or reappear during subsequent cycles.

Concomitant medicine

Consider antiviral prophylaxis in patients being treated with KARPILRED to decrease the risk of herpes zoster reactivation (see section 4.8).

Refer to the lenalidomide and dexamethasone professional information for other concomitant medications such as the use of antacid prophylaxis, refer to the current lenalidomide and dexamethasone summary of product characteristics.

Thromboprophylaxis is recommended in patients being treated with KARPILRED in combination With daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone and should be based on an assessment of the patient's underlying risks and clinical status.

In patients treated with KARPILRED in combination with daratumumab and dexamethasone, Pre-infusion medications should be administered to reduce the risk of infusion-related reactions with daratumumab.

Hydration, fluid and electrolyte monitoring

Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumour lysis syndrome or renal toxicity. All patients should be monitored for evidence of volume overload and fluid requirements should be tailored to individual patient needs.

The total volume of fluids may be adjusted as clinically indicated in patients with baseline cardiac failure or who are at risk for cardiac failure (see section 4.4). Recommended hydration includes both oral fluids (30 ml/kg/day for 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). Give an additional 250 ml to 500 ml of intravenous fluids as needed following KARPILRED administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor serum potassium levels regularly during treatment with KARPILRED.

When given in combination with IV daratumumab, oral and/or intravenous hydration is not required on days when

IV daratumumab is dosed.

Recommended dose modifications

Modify dosing based on toxicity. Recommended actions and dose modifications are presented in Table 8.

Dose level reductions are presented in Table 9.

Table 8: Dose Modifications during KARPILRED Treatment

Haematologic Toxicity	**Recommended Action**
Absolute Neutrophil Count (ANC) < 0,5 x 10^9/l (see section 4.4).	• Stop dose • If recovered to ≥ 0,5 x 10^9/l, continue at the same dose level • For subsequent drops to < 0,5 x 10^9/l, follow the same recommendations as above and consider 1 dose level reduction when restarting KARPILRED [a]
Febrile neutropenia ANC < 0,5 x 10^9/l and an oral temperature > 38,5 °C or two consecutive readings	• Stop dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level.
Platelets < 10 x 10^9/l or evidence of bleeding with Thrombocytopenia (see section 4.4).	• Stop dose • If recovered to ≥ 10 x 10^9/l and/or bleeding is controlled, continue at the same dose level • For subsequent drops to < 10 x 10^9/l, follow the same recommendations as above and consider 1 dose level reduction when restarting KARPILRED [a]
Non-Haematologic Toxicity (Renal)	**Recommended Action**

Serum creatinine equal to or greater than 2 × baseline, or Creatinine clearance < 15 ml/min (or creatinine clearance decreases to ≤ 50 % of	• Stop dose and continue monitoring renal function (serum creatinine or creatinine clearance) • If attributable to KARPILRED, resume when renal function has recovered to within 25 % of baseline; start at 1 dose level reduction[a] • If not attributable to KARPILRED, dosing may
Other Non-haematologic Toxicity	**Recommended Action**
All other Grade 3 or 4 non-haematological toxicities (see section 4.4).	• Stop KARPILRED until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction[a] • If tolerated, the reduced dose may be increased to the previous dose at the discretion of the physician
ANC = absolute neutrophil count [a]see Table 9 for dose level reductions.	

Table 9: Dose Level Reductions for KARPILRED

Regimen	**Dose**	**First Dose Reduction**	**Second Dose Reduction**	**Third Dose Reduction**
Monotherapy	27 mg/m^2	20 mg/m^2	15 mg/$^{m^{2a}}$	-
KARPILRED, lenalidomide, and dexamethasone	27 mg/m^2	20 mg/m^2	15 mg/m^{2a}	-
KARPILRED, Dexamethasone, and Daratumumab	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^{2a}
	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^{2a}
KARPILRED plus dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2
	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2
Note: Infusion times remain unchanged during dose reduction(s). [a]If symptoms do not resolve, discontinue KARPILRED treatment.				

Special Populations

Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis (see section 5.2). Since dialysis clearance of KARPILRED concentrations has not been studied, the medicine should be administered after the dialysis procedure.

Cardiac Impairment

Patients with New York Heart Association Class III and IV heart failure were excluded from clinical trials. Safety and efficacy in this population have not been evaluated.

Hepatic Impairment

No starting dose adjustment is required in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The pharmacokinetics of KARPILRED has not been evaluated in patients with severe (Child-Pugh class C) hepatic impairment (see section 5.2).

Elderly Population

Overall, the subject incidence of certain adverse events (including cardiac failure) in clinical trials was higher for patients who were ≥ 75 years of age compared to patients who were < 75 years of age (see section 4.4).

Paediatric Population

The safety and efficacy of KARPILRED have not yet been established in paediatric population.

Method of administration

Administer intravenously as a 10 minute or 30-minute infusion, depending on the KARPILRED dose regimen (see Table 1).

KARPILRED should not be administered as a bolus. The intravenous administration line should be flushed with normal saline or 5 % dextrose injection immediately before and after KARPILRED administration.

Do not mix KARPILRED with or administer as an infusion with other medicines.

Reconstituted KARPILRED for injection should not be diluted into a 0,9 % sodium chloride IV bag for IV administration only.

KARPILRED vials contain no antimicrobial preservatives and are intended for single use Proper aseptic technique must be observed.

Any unused medicine or waste material should be disposed of.

For instructions on reconstitution of KARPILRED before administration, see section 6.6.

4.3 Contraindications

KARPILRED is contraindicated in:

- Hypersensitivity to the active substance (carfilzomib) or to any of the excipients listed in section 6.1.
- Women who are breast feeding (see section 4.6).

As KARPILRED is administered in combination with other medicines refer to their professional information for additional contraindications.

4.4 Special warnings and precautions for use

As KARPILRED is administered in combination with other medicines, the professional information of these other medicines must be consulted prior to initiation of treatment with KARPILRED. As lenalidomide may be used in combination with KARPILRED, particular attention to the lenalidomide pregnancy testing and prevention requirements is needed (see section 4.6).

Cardiac disorders

New or worsening cardiac failure (e.g., congestive cardiac failure, pulmonary oedema) decreased ejection fraction)

myocardial ischaemia and infarction have occurred following administration of carfilzomib.

Death due to cardiac arrest has occurred within a day of carfilzomib administration and fatal outcomes have been reported with cardiac failure and myocardial infarction. While adequate hydration is required prior to dosing in Cycle 1, all patients should be monitored for evidence of volume overload, especially patients at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in patients with baseline cardiac failure or who are at risk for cardiac failure (see section 4.2).

Stop KARPILRED for Grade 3 or 4 cardiac events until recovery and consider whether to restart KARPILRED at 1 dose level reduction based on a benefit/risk assessment (see section 4.2).

The risk of cardiac failure is increased in elderly patients (≥ 75 years). The risk of cardiac failure is also increased in Asian patients. It should be noted that patients with New York Heart Association (NYHA) Class III and IV heart failure, recent myocardial infarction, cardiac conduction abnormalities, angina pectoris or dysrhythmias uncontrolled by medications were excluded from the clinical trials.

These patients may be at greater risk for cardiac complications and should have a comprehensive cardiological assessment (particularly, blood pressure control and volume of fluids management) prior to starting treatment with KARPILRED. Subsequently these patients should be treated with caution and remain under close follow up.

Electrocardiographic changes

There have been cases of QT interval prolongation reported in clinical studies and post-marketing. Cases of ventricular tachycardia have been reported in patients receiving carfilzomib.

Pulmonary toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving carfilzomib.

Some of these events have been fatal. KARPILRED should be discontinued in these cases (see section 4.2).

Pulmonary hypertension

Pulmonary hypertension has been reported commonly in patients treated with carfilzomib.

Some of these events have been fatal. Evaluate as appropriate. Stop KARPILRED for pulmonary hypertension until resolved or returned to baseline and consider whether to restart KARPILRED based on a benefit/risk assessment (see section 4.2).

Dyspnoea

Dyspnoea was reported very commonly in patients treated with carfilzomib.

Evaluate dyspnoea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KARPILRED for Grade 3 and 4 dyspnoea until resolved or returned to baseline and consider whether to restart KARPILRED based on a benefit/risk assessment (see sections 4.2 and 4.8)

Hypertension

Hypertension occurred very commonly and included cases of hypertensive crisis and hypertensive emergency. Some of these events have been fatal. Hypertension was reported more frequently in patients who received carfilzomib in combination with daratumumab.

It is recommended to control hypertension prior to starting KARPILRED. All patients should be routinely evaluated for hypertension while on KARPILRED and treated as needed. If the hypertension cannot be controlled, KARPILRED dose should be discontinued until resolved. In case of hypertensive crisis, KARPILRED should be discontinued (see section 4.2).

Acute renal failure

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

Some of these events have been fatal. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KARPILRED monotherapy.

This incidence was increased in patients with a lower baseline creatinine clearance, than among subjects with higher baseline creatinine clearance. Renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance should be monitored.

Reduce or stop KARPILRED as appropriate (see section 4.2).

Tumour lysis syndrome

Cases of tumour lysis syndrome (TLS), including fatal outcome, have been reported in patients who received carfilzomib. Patients with a high tumour burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of carfilzomib in Cycle 1, and in subsequent cycles as needed. Uric acid lowering medicines should be considered in patients at high risk for TLS. Monitor for evidence of TLS during treatment including regular measurement of serum electrolytes, and manage promptly. Interrupt KARPILRED until TLS is resolved (see section 4.2).

Infusion reactions

Infusion reactions, including life-threatening reactions, have been reported in patients who received carfilzomib. Signs and symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, laryngeal oedema, vomiting, weakness, shortness of breath, hypotension, syncope, bradycardia, chest tightness, or angina pectoris. These reactions can occur immediately following or up to 24 hours after administration of KARPILRED. Dexamethasone should be administered prior to KARPILRED to reduce the incidence and severity of reactions (see section 4.2).

Haemorrhage and Thrombocytopenia

Cases of haemorrhage (e.g., gastrointestinal, pulmonary and intracranial haemorrhage) have been reported in patients treated with carfilzomib, often associated with thrombocytopenia. Some of these events have been fatal (see section 4.8).

Carfilzomib causes thrombocytopenia with platelet nadirs observed on Day 8 or Day 15 of each 28-day cycle usually with recovery to baseline platelet count by the start of the next cycle (see section 4.8). Monitor platelet counts frequently during treatment with KARPILRED. Reduce or stop dose as appropriate (see section 4.2).

Venous thromboembolic events

Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received ccarfilzomib. Patients with known risk factors for thromboembolism, including prior thrombosis, should be closely monitored.

Thromboprophylaxis should be considered based on an individual benefit/risk assessment.

Caution should be used in the concomitant administration of other products that may increase the risk of thrombosis (e.g., erythropoietic medicines or hormone replacement therapy). Patients and medical practitioners are advised to observe for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, haemoptysis, arm or leg swelling or pain.

Hepatic toxicity

Cases of hepatic failure, including fatal cases, have been reported. Carfilzomib can cause elevations of serum transaminases (see section 4.8). Monitor liver enzymes regularly, regardless of baseline values. Reduce or stop dose as appropriate (see section 4.2).

Thrombotic microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic 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 KARPILRED and evaluate patients for possible TTP/HUS.

If the diagnosis of TTP/HUS is excluded, KARPILRED can be restarted. The safety of reinitiating KARPILRED therapy in patients previously experiencing TTP/HUS is not known.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (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.

Cases of PRES have been reported in patients receiving carfilzomib. Discontinue KARPILRED if PRES is suspected. The safety of reinitiating KARPILRED therapy in patients previously experiencing PRES is not known.

Hepatitis B Virus (HBV) Reactivation

Cases of Hepatitis B Virus (HBV) reactivation have been reported in patients receiving carfilzomib. Patients should be tested for HBV infection before initiating treatment. For patients who are carriers of HBV, prophylaxis with antivirals should be considered. Carriers of HBV who require treatment with KARPILRED should be closely monitored for signs and symptoms of active HBV infection throughout and following the end of treatment. Consider consulting a specialist for patients who test positive for HBV infection prior to or during treatment. The safety of resuming KARPILRED after HBV reactivation is adequately controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

Progressive Multifocal Leukoencephalopathy

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients treated with carfilzomib who have had prior or concurrent immunosuppressive therapy. The causal relationship with carfilzomib is unknown. Patients should be monitored for any new or worsening neurologic, cognitive or behavioural signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders. If PML is suspected, further KARPILRED administration must be suspended and the patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue KARPILRED if PML diagnosis is confirmed.

Increased Incidence of Fatal and Serious Adverse Events in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Multiple Myeloma Patients

In a clinical trial of 955 transplant ineligible patients with newly diagnosed multiple myeloma randomised to carfilzomib (20/36 mg/m^2 by 30 minute infusion twice weekly for four weeks of each six-week cycle), melphalan and 8,5 %) prednisone (KMP) or bortezomib, melphalan and prednisone (VMP), a higher incidence of fatal adverse events, a higher incidence of serious adverse events and a higher incidence of any grade adverse events involving cardiac failure, hypertension, acute renal failure, and dyspnoea were observed in patients in the KMP arm compared to patients in the VMP arm. 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.

Contraception

Females of child bearing potential and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with KARPILRED.

Sodium content

KARPILRED contains 216 mg sodium per 60 mg vial which is equivalent to 11 % of The WHO recommended maximum daily intake of 2 g sodium for an adult

Cyclodextrin content

KARPILRED contains 3 000 mg of cyclodextrin (Betadex sulfobutyl ether sodium) per 60 mg vial which is equivalent to 88 mg/lg for a 70 kg adult.

4.5 Interaction with other medicines and other forms of interaction

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

Carfilzomib is not expected to influence exposure of other medicines (see section 5.2).

Based on *in vitro* and *in vivo* data, carfilzomib is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates. A clinical trial using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration.

Carfilzomib is a P-glycoprotein (P-gp) substrate but not a BCRP substrate. However, given that carfilzomib is administrated intravenously and is extensively metabolised, the pharmacokinetic profile of carfilzomib is unlikely to be affected by P-gp or BCRP inhibitors or inducers.

In vitro, at concentrations (3 µM) lower than those expected at therapeutic doses,

carfilzomib inhibits the efflux transport of digoxin, a P-gp substrate, by 25 %. Caution should be observed when carfilzomib is combined with substrates of P-gp (e.g., digoxin, colchicine).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Females and males of reproductive potential should be advised to avoid conceiving/fathering a child while being treated with carfilzomib. Female patients of child bearing potential treated with KARPILRED and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with KARPILRED.

If pregnancy occurs during this time, patients should be apprised of the potential hazard to the foetus. It is not known if KARPILRED will reduce the efficacy of oral contraceptives.

Due to an increased risk of venous thrombosis associated with carfilzomib, patients currently using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception (see sections 4.4 and 4.8).

Male patients treated with KARPILRED and/or their female partners (if of childbearing potential) should use effective contraceptive methods or abstain from sexual activity while treated with KARPILRED and for 90 days after treatment.

Pregnancy

There are no data on the use of carfilzomib in pregnant women.

Studies in animals have shown reproductive toxicity.

Based on its mechanism of action and findings in animals, carfilzomib can cause foetal harm when administered to a pregnant woman. KARPILRED should not be used during pregnancy.

Breast-feeding

Mothers should not breastfeed their infants as KARPILRED is present in human breast milk.

Fertility

No fertility studies have been performed.

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 and/or a drop in blood pressure have been observed in clinical trials. Patients being treated with KARPILRED should, therefore, be advised not to drive or operate machinery if they experience any of these symptoms.

4.8 Undesirable effects

Summary of safety profile

Serious adverse reactions that may occur during KARPILRED treatment include: cardiac failure, myocardial infarction, cardiac arrest, myocardial ischemia, interstitial lung disease, pneumonitis, acute respiratory distress syndrome, acute respiratory failure, pulmonary hypertension, dyspnoea, hypertension including hypertensive crisis, acute kidney injury, tumour lysis syndrome, infusion related reaction, gastrointestinal haemorrhage, intracranial haemorrhage, pulmonary haemorrhage, thrombocytopenia, hepatic failure, hepatitis B virus reactivation, PRES and thrombotic microangiopathy.

The most frequent adverse reactions were: anaemia, thrombocytopenia, neutropenia, nausea diarrhoea, fatigue, pyrexia, respiratory tract infection, dyspnoea, and cough.

Tabulated list of adverse reactions

System Organ Class	Frequent	Less frequent
Infections and Infestations	Respiratory tract, infection[a], Pneumonia, Nasopharyngitis, Bronchitis, Urinary tract infection, Influenza, Herpes zoster,	Septic shock, *Clostridium difficil*e colitis, Hepatitis B Virus, reactivation[a], Cytomegalovirus Chorioretinitis

	Rhinitis, Viral infection, Sepsis, Gastroenteritis, Lung infection.	
Blood and Lymphatic System Disorders	Anaemia[a], Thrombocytopaenia[a] Neutropaenia[a] Lymphopenia[a] Leukopaenia[a] Febrile neutropaenia.	Thrombotic microangiopathy, Thrombotic Thrombocytopenic Purpura, Haemolytic Uraemic Syndrome.
Immune System Disorders		Drug hypersensitivity.
Metabolism and Nutrition Disorders	Decreased appetite, Hypokalaemia, Hyperglycaemia, Hypocalcaemia, Hypophosphataemia, Hypomagnaesemia, Hyponatraemia, Hyperuricaemia, Hyperkalaemia, Hypercalcaemia, Hypoalbuminaemia, Dehydration.	Tumour lysis syndrome.
Psychiatric Disorders	Insomnia, Anxiety, Confusional state.	
Nervous System Disorders	Headache, Dizziness, Peripheral neuropathy[a], Paraesthesia, Hypoesthesia.	Cerebrovascular accident, Intracranial haemorrhage[a], Posterior Reversible

		Encephalopathy Syndrome.
Eye disorders	Blurred vision, Cataract.	
Ear and labyrinth disorders	Tinnitus.	
Cardiac disorders	Cardiac failure[a], Tachycardia, Palpitations, Atrial fibrillation, Ejection fraction decreased, Myocardial infarction[a].	Cardiac arrest, Cardiomyopathy, Myocardial ischaemia, Pericardial effusion, Pericarditis, Ventricular tachycardia.
Vascular Disorders	Hypertension, Hypotension, Deep vein thrombosis, Flushing.	Hypertensive crisis, Haemorrhage, Hypertensive Emergency.
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnoea, Cough[a], Epistaxis, Oropharyngeal pain, Wheezing, Dysphonia, Pulmonary embolism, Pulmonary oedema, Pulmonary hypertension.	Pulmonary haemorrhage[a], Pneumonitis, Acute respiratory distress syndrome, Acute respiratory failure, Interstitial lung disease, Laryngeal oedema.
Gastro intestinal disorders	Nausea, Diarrhoea, Vomiting, Constipation, Abdominal pain[a], Dyspepsia, Toothache.	Gastrointestinal haemorrhage[a], Pancreatitis acute[a], Intestinal obstruction, Gastrointestinal perforation.
Hepatobiliary	Increased alanine	Hepatic failure,

Disorders	aminotransferase, Increased aspartate aminotransferase, Gammaglutamyltransferase increased, Hyperbilirubinemia.	Cholestasis.
Skin and Subcutaneous Tissue Disorders	Rash, Pruritus, Erythema, Hyperhidrosis.	Angioedema.
Musculoskeletal and Connective Tissue Disorders	Back pain, Muscle spasms, Arthralgia, Pain in extremity, Musculoskeletal chest pain, Musculoskeletal pain, Bone pain, Muscular weakness, Myalgia.	
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, Pain,	Multi-organ dysfunction syndrome.

	Chest pain, Infusion site reactions[a], Malaise, Influenza-like illness.	
Investigations	Increased c-reactive protein, Increased blood uric acid.	
Injury, Poisoning and Procedural Complications	Infusion related reaction.	

Foot notes:

a

- 'Anaemia' includes Anaemia, Haematocrit decreased and Haemoglobin decreased
- 'Thrombocytopenia' includes Platelet count decreased and Thrombocytopenia
- 'Neutropenia' includes Neutrophil count decreased and Neutropenia
- 'Pancreatitis acute' includes Pancreatitis and Acute Pancreatitis
- 'Lymphopenia' includes Lymphocyte count decreased and Lymphopenia
- 'Leukopenia' includes Leukopenia and White blood cell count decreased
- 'Cardiac failure' includes Cardiac failure and Congestive Cardiac failure
- 'Myocardial infarction' includes Myocardial infarction and Acute myocardial infarction
- 'Abdominal pain' includes Abdominal pain and Abdominal pain upper
- 'Gastrointestinal haemorrhage' includes Gastrointestinal haemorrhage, Gastric haemorrhage, Upper gastrointestinal haemorrhage, and Lower gastrointestinal haemorrhage.
- 'Infusion site reactions' includes Infusion site inflammation, Infusion site erythema, Infusion site reaction, and Infusion site pain
- 'Respiratory tract infection' includes Respiratory tract infection, Lower respiratory tract infection, Upper

respiratory tract infection, and Viral upper respiratory tract infection

- 'Hepatitis B Reactivation' includes Acute Hepatitis B PT, Hepatitis Acute PT, Hepatitis B PT, Hepatitis B DNA Assay Positive PT, Hepatitis B DNA Increased PT, Hepatitis B Reactivation PT, Hepatitis Viral PT
- 'Peripheral neuropathy' includes Peripheral sensory neuropathy and Neuropathy peripheral
- 'Intracranial haemorrhage' includes Haemorrhage intracranial, Cerebral haemorrhage, Subarachnoid haemorrhage and Subdural hematoma
- 'Cough' includes Productive cough and Dry cough
- 'Pulmonary haemorrhage' includes Pulmonary haemorrhage, Pulmonary alveolar haemorrhage, and Haemoptysis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

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

There is no known specific antidote for carfilzomib overdose. In the event of an overdose, the patient should be monitored, specifically for the side effects and/or adverse medicine reactions (see section 4.8).

5 PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XG02

5.1 Pharmacodynamic properties

Mechanism of action

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that selectively and irreversibly binds to the N terminal threonine containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome and displays little or no activity against other protease classes. Carfilzomib had antiproliferative and proapoptotic activities in preclinical models in solid and haematologic tumours.

Pharmacodynamic Effects

Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like (CT L) activity when measured in blood 1 hour after the first dose. Doses of ≥ 15 mg/m^2 consistently induced an (≥ 80 %) inhibition of the CT-L activity of the proteasome.

In addition, carfilzomib administration at 20 mg/m^2 resulted in inhibition of the low molecular mass polypeptide 2 (LMP2) and multi-catalytic endopeptidase complex-like immunoproteasome ranging from 26 % to 32 % and 41 % to 49 %, respectively. 1 (MECL1) subunits of the Proteasome inhibition was maintained for ≥ 48 hours following the first dose of carfilzomib for each week of dosing. Combination dosing with lenalidomide and dexamethasone did not affect proteasome inhibition.

5.2 Pharmacokinetics properties

Absorption:

At doses between 20 and 70 mg/m^2, carfilzomib administered as a 30-minute infusion resulted in dose-dependent increases in maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC). Following repeated administration of carfilzomib 70 mg/m^2, systemic exposure (AUC) and half-life were similar on day 15 of cycles 1 and 2, suggesting there was no systemic carfilzomib accumulation.

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 in urine.

Special populations

Hepatic Impairment

The pharmacokinetics of carfilzomib was studied in patients with relapsed or progressive advanced malignancies with mild or moderate chronic hepatic impairment relative to those with normal hepatic function.

No marked differences in exposures (AUC and C_{max}) were observed between patients with normal hepatic function and those with mild or moderate hepatic impairment. The pharmacokinetics of carfilzomib has not been studied in patients with severe hepatic impairment (see section 4.2).

Renal Impairment

The pharmacokinetics of carfilzomib was studied in relapsed multiple myeloma patients with normal renal function; mild, moderate or severe renal impairment; and patients with end-stage renal disease requiring haemodialysis. Exposures of carfilzomib (AUC and C_{max}) in patients with renal impairment were highly variable, with mean values similar to those with normal renal function. No starting dose adjustment is required in patients with baseline renal impairment (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous citric acid

Betadex sulfobutyl ether sodium (Sulfobutylether beta-cyclodextrin)

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines. Normal saline should not be used for reconstitution of KARPILRED.

Reconstituted KARPILRED for injection should not be diluted into a 0,9 % sodium chloride IV bag for IV administration.

6.3 Shelf life

Vial (unopened):

24 months.

Reconstituted Solution:

Chemical and physical in-use stability of reconstituted solutions in the vial, syringe or intravenous bag has been demonstrated for 24 hours at 2 °C to 8 °C or for 4 hours at room temperature (15 °C to 30 °C).

The elapsed time from reconstitution to administration should not exceed 24 hours.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions and the responsibility of the user and should not be longer than 24 hours at 2 °C to 8 °C.

6.4 Special precautions for storage

Unopened vials should be stored refrigerated (between 2 °C to 8 °C).

Do not freeze.

Retain in original package to protect from light.

For storage conditions after reconstitution of KARPILRED, see section 6.3.

Keep out of reach of children.

6.5 Nature and contents of container

KARPILRED is supplied as a pack size of one sterile vial packed in a carton.

The single-use 50 ml tubular, Type I, clear glass vial with 20 mm neck

finish is closed with a grey 20 mm chloro butyl rubber stopper with Fluorotec on plug and a brown flip-off seal.

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

Reconstitution and preparation for intravenous administration

The reconstituted solution contains carfilzomib at a concentration of 2 mg/ml. Read the complete preparation instructions prior to reconstitution.

1. Remove vial from refrigerator just prior to use.

2. Calculate the dose (mg/m^2) and number of vials of KARPILRED required using

the patient's body surface area (BSA) at baseline. Patients with a BSA greater than 2,2 m^2 should receive a dose based upon a BSA of 2,2 m^2. Dose adjustments do not need to be made for weight changes of ≤ 20 %.

3. Use only a 21-gauge or larger gauge needle (0,8 mm or smaller external diameter needle) to aseptically reconstitute each vial by slowly injecting 29 ml sterile water for injection through the stopper and directing the

solution onto the INSIDE WALL OF THE VIAL to minimise foaming. Do not reconstitute KARPILRED with normal saline.

4. Gently swirl and/or invert the vial slowly for approximately 1 minute, or until complete dissolution. DO NOT SHAKE. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear.

5. Visually inspect for particulate matter and discolouration prior to administration. The reconstituted product should be a clear, colourless solution and should not be administered if any discolouration or particulate matter is observed.

6. Discard any unused portion left in the vial.

7. KARPILRED can be administered directly by IV infusion or optionally, administered in an IV bag. Do not administer as an IV push or bolus.

8. When administering in an IV bag, use only a 21-gauge or larger gauge needle 0,8 mm or smaller (external diameter needle) to withdraw the calculated dose from the vial and dilute into a 50 or 100 ml IV bag containing 5 % dextrose injection (D5W). Do not dilute KARPILRED into normal saline.

Disposal

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

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54 Maxwell Drive

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8 REGISTRATION NUMBER

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