SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

FILOKYP (Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FILOKYP: Each vial contains 60 mg of carfilzomib.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile Lyophilized Powder for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FILOKYP, 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

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

Posology:

FILOKYP 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: FILOKYP Dosing Information

Regimen	Starting Dose	If Tolerated, Increase FILOKYP Dose on Day 8 of Cycle 1	FILOKYP Infusion Time[a]
FILOKYP Monotherapy	20 mg/m^2	27 mg/m^2 twice weekly	10 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 %.

FILOKYP Monotherapy

Twice weekly (27 mg/m^2)

FILOKYP 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. **FILOKYP** is omitted on Days 8 and 9 of Cycles 13 and higher. **FILOKYP** 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: FILOKYP Monotherapy 20/27 mg/m^2 Twice Weekly (10-Minute Infusion)

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

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

Concomitant medicine

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

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 **FILOKYP** administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor serum potassium levels regularly during treatment with **FILOKYP**.

Recommended dose modifications

Modify dosing based on toxicity. Recommended actions and dose modifications are presented in Table 3.

Dose level reductions are presented in Table 4.

Table 3: Dose Modifications during FILOKYP 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 **FILOKYP**[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	• 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 **FILOKYP**[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 baseline) or need for dialysis (see section 4.4).	• Stop dose and continue monitoring renal function (serum creatinine or creatinine clearance) • If attributable to **FILOKYP**, resume when renal function has recovered to within 25 % of baseline; start at 1 dose level reduction[a] • If not attributable to **FILOKYP**, dosing may be resumed at the discretion of the physician • If tolerated, the reduced dose may be increased to the previous dose at the discretion of the physician • For patients on dialysis receiving **FILOKYP**, the dose is to be administered after the dialysis procedure
Other Non-haematologic Toxicity	**Recommended Action**
All other Grade 3 or 4 non-haematological toxicities (see section 4.4).	Stop **FILOKYP** 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 4 for dose level reductions.	

Table 4: Dose Level Reductions for FILOKYP

Regimen	**Dose**	**First Dose Reduction**	**Second Dose Reduction**	**Third Dose Reduction**
Monotherapy	27 mg/m^2	20 mg/m^2	15 mg/m^2	-
Note: Infusion times remain unchanged during dose reduction(s). [a]If symptoms do not resolve, discontinue **FILOKYP** 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 **FILOKYP** 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 **FILOKYP** has not been evaluated in patients with severe (Child-Pugh class C) hepatic impairment (see section 5.2).

Elderly Patients

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 **FILOKYP** have not yet been established in paediatric population.

Method of administration:

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

FILOKYP 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 **FILOKYP** administration.

Do not mix **FILOKYP** with or administer as an infusion with other medicinal products. Reconstituted **FILOKYP** for injection should not be diluted into a 0,9 % sodium chloride IV bag for IV administration only.

FILOKYP vials contain no antimicrobial preservatives and are intended for single use.

Proper aseptic technique must be observed.

Any unused medicinal product or waste material should be disposed of.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 **FILOKYP** for Grade 3 or 4 cardiac events until recovery and consider whether to restart **FILOKYP** 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 **FILOKYP**. 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. **FILOKYP** 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 **FILOKYP** for pulmonary hypertension until resolved or returned to baseline and consider whether to restart **FILOKYP** 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 **FILOKYP** for Grade 3 and 4 dyspnoea until resolved or returned to baseline and consider whether to restart **FILOKYP** 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.

It is recommended to control hypertension prior to starting **FILOKYP**.

All patients should be routinely evaluated for hypertension while on **FILOKYP** and treated as needed.

If the hypertension cannot be controlled, **FILOKYP** dose should be discontinued until resolved.

In case of hypertensive crisis, **FILOKYP** 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 carfilzomib 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 **FILOKYP** 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 **FILOKYP** 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 **FILOKYP** 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 carfilzomib.

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).

FILOKYP 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 **FILOKYP**. 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 out-comes, have been reported in patients who received carfilzomib. 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 physicians 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. **FILOKYP** 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 **FILOKYP** and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, **FILOKYP** can be restarted. The safety of reinitiating **FILOKYP** 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 **FILOKYP** if PRES is suspected. The safety of reinitiating **FILOKYP** 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 **FILOKYP** 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 **FILOKYP** 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 **FILOKYP** 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 **FILOKYP** administration must be suspended and the patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue **FILOKYP** 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 randomized 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 (6.5 % versus 4.3 %), a higher incidence of serious adverse events (49.6 % versus 42.1 %) and a higher incidence of any grade adverse events involving cardiac failure (10.8 % versus 4.3 %), hypertension (24.7 % versus 8.1 %), acute renal failure (13.9 % versus 6.2 %), and dyspnoea (18.1 % versus 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. **FILOKYP** 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 **FILOKYP**.

Sodium content

FILOKYP 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

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

4.5 Interaction with other medicines and other forms of interaction

Carfilzomib, as found in **FILOKYP**, 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 **FILOKYP**. Females patients of child bearing potential treated with **FILOKYP** and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with **FILOKYP** (see section 5).

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

If pregnancy occurs during this time, patients should be apprised of the potential hazard to the foetus.

It is not known if **FILOKYP** will reduce the efficacy of oral contraceptives.

Due to an increased risk of venous thrombosis associated with **FILOKYP**, 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).

Pregnancy:

There are no data on the use of **FILOKYP** in pregnant women. **FILOKYP** caused embryo-foetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose.

FILOKYP should only be used during pregnancy if the potential benefits to the mother outweigh the potential risks to the foetus.

Breastfeeding:

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

Fertility:

No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

No studies on the effects of **FILOKYP** on the ability to drive or use machines have been performed.

Fatigue, dizziness, fainting and/or a drop in blood pressure have been observed in clinical trials.

Patients being treated with **FILOKYP** should, therefore, be advised not to drive or operate machinery if they experience any of these symptoms.

4.8 Undesirable effects

a. Summary of the safety profile

Serious adverse reactions that may occur during **FILOKYP** 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.

b. Tabulated summary of adverse reactions

System Organ Class	**Adverse Reaction Preferred Term**	**Frequency**
Blood and Lymphatic System Disorders	Anaemia, Thrombocytopenia, Neutropenia, Lymphopenia, Leukopenia, Febrile neutropenia	Frequent
	Thrombotic microangiopathy, Thrombotic thrombocytopenic purpura	Less frequent
Cardiac Disorders	Cardiac failure, Tachycardia Palpitations, Atrial fibrillation, Myocardial infarction	Frequent
	Cardiac arrest, Cardiomyopathy, Myocardial ischaemia, Pericardial effusion	Less frequent
Ear and labyrinth disorders	Tinnitus	Frequent

Eye Disorders	Blurred vision, Cataract	Frequent
Gastrointestinal Disorders	Nausea, Diarrhoea, Vomiting, Constipation, Abdominal pain, Dyspepsia, Toothache	Frequent
	Gastrointestinal haemorrhage, Pancreatitis acute, Intestinal obstruction	Less frequent
General Disorders and Administration Site Conditions	Fatigue, Pyrexia, Oedema peripheral, Asthenia, Chills, Pain Chest pain, Infusion site reactions, Malaise, Influenza like illness	Frequent
	Multi-organ dysfunction syndrome	Less frequent
Hepatobiliary Disorders	Hyperbilirubinemia	Frequent
	Hepatic failure, Cholestasis	Less frequent
Immune System Disorders	Drug hypersensitivity	Less frequent
Infections and Infestations	Respiratory tract infection, Pneumonia, Nasopharyngitis, Bronchitis, Urinary tract infection, Influenza, Rhinitis Viral infection, Sepsis, Gastroenteritis, Lung infection	Frequent
	Septic shock, Clostridium difficile colitis, Hepatitis B Virus Reactivation, Cytomegalovirus infection	Less frequent
Injury, Poisoning and Procedural Complications	Infusion related reaction	Frequent

Investigations	Serum creatinine increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Creatinine clearance decreased, Serum uric acid increased, Gamma- glutamyltransferase increased C-reactive protein increased	Frequent
	Cardiac ejection fraction decreased	Less frequent
Metabolism and Nutrition Disorders	Decreased appetite, Hypokalaemia, Hyperglycaemia Hypocalcaemia, Hypophosphatemia, Hypomagnesemia, Hyponatremia, Hyperuricemia Hyperkalaemia, Hypercalcemia Dehydration, Hypoalbuminemia	Frequent
	Tumour lysis syndrome	Less frequent
Musculoskeletal and Connective Tissue Disorders	Back pain, Muscle spasms, Arthralgia, Pain in extremity, Musculoskeletal chest pain, Musculoskeletal pain, Bone pain, Muscular weakness, Myalgia	Frequent
Nervous System Disorders	Headache, Dizziness, Peripheral neuropathy, Paraesthesia, Hypoesthesia	Frequent
	Cerebrovascular accident, Intracranial haemorrhage, PRES	Less frequent

Psychiatric Disorders	Insomnia, Anxiety	Frequent
Renal and Urinary Disorders	Acute kidney injury, Renal failure, Renal impairment	Frequent
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnoea, Cough, Epistaxis Oropharyngeal pain, Wheezing Dysphonia, Pulmonary embolism, Pulmonary oedema, Pulmonary hypertension	Frequent
	Pulmonary haemorrhage, Pneumonitis, Acute respiratory distress syndrome, Acute respiratory failure, Interstitial lung disease	Less frequent
Skin and Subcutaneous Tissue Disorders	Rash, Pruritus, Erythema, Hyperhidrosis	Frequent
Vascular Disorders	Hypertension, Hypotension, Deep vein thrombosis, Flushing	Frequent
	Hypertensive crisis, Haemorrhage, Hypertensive emergency	Less frequent

Post Marketing Experience

System Organ Class	**Preferred Term**
Blood and Lymphatic System Disorders	Haemolytic Uraemic Syndrome
Cardiac Disorders	Pericarditis
Gastrointestinal Disorders	Gastrointestinal Perforation
Infections and Infestations	Cytomegalovirus Chorioretinitis
Respiratory, Thoracic and Mediastinal Disorders	Laryngeal Oedema

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug 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

5.1 Pharmacodynamic properties

Pharmacological classifications: A26 Cytostatic Agent

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

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 tumours. proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities in preclinical models in solid and haematologic tumours. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumour growth in models of multiple myeloma. *In vitro*, carfilzomib was found to have minimal neurotoxicity and minimal reaction to non-proteasomal proteases.

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 multicatalytic 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.

5.2 Pharmacokinetic 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.

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

Sulfobutyl-ether-β-cyclodextrin sodium (Betadex Sulfobutyl Ether Sodium), Anhydrous citric acid, Sodium hydroxide (1N solution), 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 **FILOKYP**.

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

6.3 Shelf life

Unopened vials – 24 months

Reconstituted solution in the vial, syringe, or infusion bag under refrigeration (2 °C to 8 °C) for up to 18 hours or at room temperature (15 °C to 25 °C) for up to 4 hours.

6.4 Special precautions for storage

Unopened vials to be stored refrigerated at 2 °C to 8 °C. Store in carton to protect from light.

Store the reconstituted solution in the vial, syringe, or infusion bag under refrigeration (2 °C to 8 °C) for up to 18 hours or at room temperature (15 °C to 25 °C) for up to 4 hours.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

An individually packaged single-dose 50ml Clear Tubular Vial Type I containing 60 mg carfilzomib as a white to off-white lyophilized powder with Chlorobutyl Prewash West Rubber Stopper Slotted and Alu flip-off seal.

6.6 Special precautions for disposal and other handling

<u>Reconstitution and preparation for intravenous administration</u>

The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. Read the complete preparation instructions before reconstitution.

1. Remove the vial from the refrigerator immediately before use.

2. Calculate the dose (mg/m^2) and number of vials of carfilzomib lyophilized powder for injection needed using the patient's baseline BSA. Patients with an AUC greater than 2,2 m^2 should receive a dose based on the AUC of 2,2 m^2. Dose adjustments do not need to be made for weight changes ≤ 20%.

3. Use only 21-gauge needles or of larger gauge (0,8 mm or smaller outer needle diameter) to aseptically reconstitute each vial by slowly injecting 29 mL of sterile water (for 60 mg vial) through the cap and directing the solution for the INNER WALL OF THE VIAL, to minimize the formation of bubbles. Do not reconstitute carfilzomib lyophilized powder for injection with normal saline.

4. Move in circles or slowly invert the vial for approximately 1 minute, or until completely dissolved. DO NOT SHAKE. If bubbles appear, let the solution sit in the vial until the bubbles disappear (approximately 5 minutes) and the solution is clear.

5. Visually inspect for particulate matter or colour changes prior to administration. The reconstituted product should be a clear, transparent to slightly yellowish solution and should not be administered if particles or changes in colour are observed.

6. Discard any material left in the vial.

7. Carfilzomib lyophilized powder for injection can be administered directly by IV infusion or choose to administer in an IV infusion bag. Do not administer as an IV bolus.

8. When administering via an IV infusion bag, use only a 21-gauge or larger needle (0.8 mm or smaller outer needle diameter) to withdraw the calculated dose from the vial and dilute into an IV infusion bag of 50 or 100 mL containing 5% glucose for injection. Do not dilute carfilzomib lyophilized powder for injection in normal saline.

Any unused medicine should be returned to the pharmacy to be correctly disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Glenmark Pharmaceuticals South Africa (Pty) Ltd

2nd Floor, Block D, Stoneridge Office Park

8 Greenstone Place, Greenstone, Edenvale, Gauteng

1609

8. REGISTRATION NUMBER(S)

58/26/0172

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

30 September 2025

10. DATE OF REVISION OF TEXT

15 May 2025