Carfilzomib (20/70mg/m^2 Once weekly) Dexamethasone (Kd) therapy - 28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Carfilzomib[i] In combination with dexamethasone is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy	C90	00595a	ODMS 01/11/2021

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

- Carfilzomib is administered once a week for three weeks (days 1, 8, 15) followed by a 13-day rest period (days 16 to 28) as shown in table 1
- Each 28-day period is considered one treatment cycle.
- Carfilzomib is administered at a starting dose of 20mg/m^2 (maximum dose 44mg) in cycle 1 on day 1
- If tolerated, the dose should be increased on day 8 of cycle 1 to 70mg/m^2 (maximum dose 154mg).
- Dexamethasone is administered as 40mg orally or intravenously on days 1, 8, and 15, for all cycles and day 22 for cycles 1-9 only.
- Treatment may be continued until disease progression or until unacceptable toxicity occurs.

Table 1: Treatment table for carfilzomib and dexamethasone

DRUG	CYCLE 1							
	Week 1		Week 2		Week 3		Week 4	
	Day 1	Days 2-7	Day 8	Days 9-14	Day 15	Days 16-21	Day 22	Days 23-28
Carfilzomib (mg/m^2)[a,b]	20		70		70			
Dexamethasone (mg)[c]	40		40		40		40	
DRUG	**CYCLE 2-9**							
	Week 1		Week 2		Week 3		Week 4	
	Day 1	Days 2-7	Day 8	Days 9-14	Day 15	Days 16-21	Day 22	Days 23-28
Carfilzomib (mg/m^2)[a,b]	70		70		70			
Dexamethasone (mg)[c]	40		40		40		40	
DRUG	**CYCLE 10 onwards**							
	Week 1		Week 2		Week 3		Week 4	
	Day 1	Days 2-7	Day 8	Days 9-14	Day 15	Days 16-21	Days 22-28	
Carfilzomib (mg/m^2)[a,b]	70		70		70			
Dexamethasone (mg)[c]	40		40		40			

[a]Infusion time for first infusion of 20mg/m^2 is 30 minutes and then subsequent infusions of 70mg/m^2 are administered over 30 minutes. See table 2 for details

[b]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 less than or equal to 20%.

[c]Dexamethasone should be administered 30 minutes to four hours before carfilzomib.

Administration guidelines:

Carfilzomib is administered as detailed in table 2 below.

Dexamethasone may be administered orally or intravenously.

Table 2: Administration details for carfilzomib

Cycle	Day	Drug	Dose	Route	Diluent and Rate
1	1	Carfilzomib	[a]20mg/m^2	IV infusion	100ml Glucose 5%[c] over 30mins
1	8 and 15	Carfilzomib	[b]70mg/m^2	IV infusion	100ml Glucose 5%[c] over 30mins
[a]Maximum dose of carfilzomib is 44 mg					
[b]Maximum dose of carfilzomib is 154 mg					
[c]Carfilzomib may be administered in 50-100ml Glucose 5% over 30 mins.					
Carfilzomib is a proteasome inhibitor and is neurotoxic. **Refer to NCCP Guidance on the Safe Use of Neurotoxic drugs (including Vinca Alkaloids) in the treatment of cancer**. (Link).					

ELIGIBILITY:

- Indication as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to carfilzomib or any of the excipients.
- Pregnancy.
- Breastfeeding

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies.

TESTS:

Baseline tests:

- FBC, renal, liver and bone profile
- Blood pressure, blood glucose (patients on oral hypoglycaemics)
- Assessment of peripheral neuropathy status
- Cardiac Assessment as clinically indicated
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), C and HIV
  ***See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation**

Regular tests:

- FBC, renal and liver profile prior to each cycle
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics. (* See Drug Interactions)

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Dose adjustments of carfilzomib do not need to be made for weight changes of less than or equal to 20% subject to local policy.
- Dose level reductions for carfilzomib are summarised in Table 3 below

Table 3: Dose level reductions for carfilzomib

Dose level	Carfilzomib
Starting Dose	**70mg/m^2**
Dose level -1	56mg/m^2
Dose level -2	45mg/m^2
Dose level- 3	36mg/m^2

Haematological:

- Prior to initiating a new cycle of therapy ANC ≥ 1 x 10^9/L and Platelets ≥ 50 x 10^9/L and non-haematological toxicities should have resolved to Grade 1 or baseline

Table 4: Dose Modifications for haematological toxicity

Haematologic toxicity during a cycle	Recommended action[a]
Absolute neutrophil count < 0.5 x 10^9/L	• Withhold dose ○ If recovered to ≥ 0.5 x 10^9/L, continue at 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 carfilzomib
Febrile neutropenia Absolute neutrophil count < 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 absolute neutrophil count returns to baseline grade and fever resolves, resume at the same dose level
Platelet count ≤ 10 x 10^9/L or platelets ≤ 30x10^9/L with evidence of bleeding /bruising	• Withhold dose ○ If recovered to ≥ 10 x 10^9/L and bleeding is controlled continue at 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 carfilzomib
[a]See table 3 for dose level reductions	

Renal and Hepatic Impairment:

Table 6: Dose modification of carfilzomib in renal and hepatic impairment

Renal Impairment	Hepatic Impairment
• No starting dose adjustment for carfilzomib is recommended in patients with baseline mild, moderate, or severe renal impairment or patients on	• No starting dose adjustment is recommended in patients with mild or moderate hepatic

chronic dialysis based on available pharmacokinetic data • Monitor renal function particularly in patients with lower baseline creatinine clearance (CrCL<30 mL/min). • If Serum creatinine ≥2 × baseline or if Creatinine clearance < 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis, stop dose and continue monitoring renal function (serum creatinine or creatinine clearance). ○ Carfilzomib should be resumed when renal function has recovered to within 25% of baseline; consider resuming at 1 dose level reduction. • Since dialysis clearance of carfilzomib concentrations has not been studied, the medicinal product should be administered after the dialysis procedure	impairment based on available pharmacokinetic data. • However, higher subject incidence of hepatic function abnormalities, ≥ grade 3 adverse events and serious adverse events have been reported in patients with mild or moderate baseline hepatic impairment compared with patients with normal hepatic function. • Liver enzymes and bilirubin should be assessed at treatment initiation and monitored monthly during treatment with carfilzomib, regardless of baseline values, and appropriate dose modifications based on toxicity should be made

Management of adverse events:

Table 7: Dose modifications for non-haematological toxicity for carfilzomib

Adverse Event	Dose modification[a]
Non-haematological toxicity **Grade 1 or 2**	Continue at same dose
Grade ≥3	Hold dose until toxicity has resolved to ≤Grade 2 or to baseline grade. Consider restarting the next scheduled treatment at 1 dose level reduction[a]
[a]See table 3 for dose level reductions	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Low **(Refer to local policy)**

PRE-MEDICATIONS:

- Adequate hydration is required before dose administration 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

- Recommended hydration includes both
  - Oral fluids (30mL/kg/day for 48 hours before day 1 of cycle 1) and
  - Intravenous fluids (250mL to 500mL of appropriate intravenous fluid before each dose in cycle 1).
  - Give an additional 250mL to 500mL of intravenous fluids as needed following carfilzomib administration in cycle 1
- Oral and/or intravenous hydration should be continued, as needed, in subsequent cycles.
- Serum potassium levels should be monitored monthly or more frequently during treatment with carfilzomib as clinically indicated. The frequency of assessment will depend on the potassium levels measured before the start of treatment, concomitant therapy used (e.g. medicinal products known to increase the risk of hypokalaemia) and associated comorbidities
- Ensure patient remains well hydrated during treatment

OTHER SUPPORTIVE CARE:

- Antiviral prophylaxis should be considered in patients being treated with carfilzomib to decrease the risk of herpes zoster reactivation **(Refer to local policy)**
- Tumour Lysis Syndrome (TLS) has been reported in patients receiving carfilzomib. As well as adequate prophylaxis, consider prophylactic treatment e.g. allopurinol **(Refer to local policy)**
- In case of neutropenia the consultant may consider the use of filgrastim (G-CSF)
- Bisphosphonates should be considered in all patients with myeloma-related bone disease.
- Consider the use of a H_2 antagonist or proton pump inhibitor if appropriate in patients receiving dexamethasone therapy **(Refer to local policy).**
- Consider requirement for thromboprophylaxis in patients considered at risk **(Refer to local policy)**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.
Carfilzomib is subject to additional monitoring. Healthcare professionals are asked to report any suspected adverse reactions.

Carfilzomib

- **Cardiovascular:** 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. 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.

Stop carfilzomib for grade 3 or 4 cardiac events until recovery and consider whether to restart carfilzomib at 1 dose level reduction based on a benefit/risk assessment. The risk of cardiac failure is increased in elderly patients (≥ 75 years). Patients with signs or symptoms of NYHA Class III or IV cardiac failure, recent history of myocardial infarction (in the last 4 months), and in patients with uncontrolled angina or arrhythmias, should have a comprehensive medical assessment, prior to starting treatment with carfilzomib. This assessment should optimise the patient's status, with particular attention to blood pressure and fluid management. Subsequently 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 with carfilzomib. An effect of carfilzomib on QT interval cannot be excluded.
- **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. Evaluate and stop carfilzomib until resolved and consider whether to restart carfilzomib based on a benefit/risk assessment.
- **Hypertension:** Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with carfilzomib. It is recommended to control hypertension prior to starting treatment. All patients should be routinely evaluated for hypertension while on carfilzomib and treated as needed. If the hypertension cannot be controlled, the carfilzomib dose should be reduced. In case of hypertensive crises, stop carfilzomib until resolved or returned to baseline and consider whether to restart carfilzomib based on a benefit/risk assessment.
- **Infusion reactions:** Infusion reactions, including life-threatening reactions, have been reported in patients who received carfilzomib. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Dexamethasone should be administered prior to carfilzomib to reduce the incidence and severity of reactions.
- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy. (Refer to local infectious disease policy). These patients should be considered for assessment by hepatology.

Dexamethasone

- **Steroid use:** Steroid use is associated with numerous side effects including insomnia, gastric irritation, increased blood sugar levels, mood changes, increased appetite, bruising, skin fragility and osteoporosis (long term use).

DRUG INTERACTIONS:

- Carfilzomib 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.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Moreau et al. Once Weekly Versus Twice Weekly Carfilzomib Dosing in Patients with Relapsed and Refractory Multiple Myeloma (A.R.R.O.W.): Interim Analysis Results of a Randomised Phase 3 Study. Clinical Trial Lancet Oncol, 19 (7), 953-964 Jul 2018
2. Carfilzomib (Kyprolis®) Summary of Product Characteristics EMA. Accessed Feb 2021. Available at https://www.ema.europa.eu/en/documents/product-information/kyprolis-epar-product-information_en.pdf
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	01/11/2021		NCCP Plasma Cell Disorder Clinical Advisory Group

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] 'This is an unlicensed posology for the use of carfilzomib® in Ireland. Patient's should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.'