Carfilzomib and Dexamethasone (Kd) Therapy - 28 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
In combination with dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy	C90	00566a	ODMS 01/10/2020

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 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) 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 days 1 and 2.
- If tolerated, the dose should be increased on day 8 of cycle 1 to 56mg/m^2 (maximum dose 123mg).
- Dexamethasone is administered as 20mg orally or intravenously on days 1, 2, 8, 9, 15, 16, 22, and 23 of the 28 day cycles.
- Treatment may be continued until disease progression or until unacceptable toxicity occurs.

Table 1: Treatment table for carfilzomib and dexamethasone

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
Carfilzomib (mg/m²)[a,b]	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)[c]	20	20	-	20	20	-	20	20	-	20	20	-
	Cycle 2 and all subsequent cycles											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
Carfilzomib (mg/m²)[a,b]	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)[c]	20	20	-	20	20	-	20	20	-	20	20	

[a]Infusion time is 30 minutes and remains consistent throughout the regimen. See table 2 for further information.

[b]Patients with a BSA greater than 2.2m^2 should receive a dose based upon a BSA of 2.2m^2. Dose adjustments do not need to be made for weight changes of ≤20%.

[c]Dexamethasone should be administered 30 minutes to 4 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, 2	Carfilzomib	[a]20mg/m^2	IV infusion	100ml Glucose 5%[c] over 30mins
1	8, 9, 15,16	Carfilzomib	[b]56mg/m^2	IV infusion	100ml Glucose 5%[c] over 30mins
[a]Maximum dose of carfilzomib is 44mg					
[b]Maximum dose of carfilzomib is 123mg					
[c]Carfilzomib may be administered in 50-100ml Glucose 5% over 30mins.					
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).					

ELIGIBILTY:

- 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	**56mg/m^2**
Dose level -1	45mg/m^2
Dose level -2	36mg/m^2
Dose level- 3	[a]27mg/m^2

[a] If symptoms do not resolve, discontinue carfilzomib treatment

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
Absolute neutrophil count < 0.5 x 10^9/L	• Stop 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[a]
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	• Stop 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 evidence of bleeding with thrombocytopenia	• Stop dose ○ If recovered to ≥ 10 x 10^9/L and/or 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]

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 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	• No starting dose adjustment is recommended in patients with mild or moderate hepatic 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.

ATC CODE:

Carfilzomib - L01XX45

REFERENCES:

1. Dimopoulos MA et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol.2016 Jan;17(1):27-38. (Including supplementary material)
2. Carfilzomib (Kyprolis®) Summary of Product Characteristics EMA. Accessed 27/07/2020. Available at https://www.ema.europa.eu/en/documents/product-information/kyprolis-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	24/09/2020		NCCP Plasma Cell Disorder CAG

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.