Carfilzomib (56mg/m^2 once weekly), Lenalidomide and dexAMETHasone (KRd) Therapy - 28 day[i]

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Carfilzomib, lenalidomide and dexAMETHasone therapy is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy	C90	00598a	ODMS

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 patient's individual clinical circumstances.

Table 1: Carfilzomib in combination with lenalidomide 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		56		56			
dexAMETHasone (mg)[c]	40		40		40		40	
Lenalidomide[d]	25mg daily						Rest	Rest
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]	56		56		56			
dexAMETHasone (mg)[c]	40		40		40		40	
Lenalidomide[d]	25mg daily						Rest	Rest
DRUG	**CYCLE 10 -12**							
	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]	56		56		56			
dexAMETHasone (mg)[c]	40		40		40			
Lenalidomide[d]	25mg daily						Rest	
DRUG	**CYCLE 13 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]	56				56			
dexAMETHasone (mg)[c]	40		40		40			
Lenalidomide[d]	25mg daily						Rest	

[a]Infusion time for first infusion of 20mg/m^2 is 30 minutes and then subsequent infusions of 56mg/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 ≤ 20%.

[c]dexAMETHasone should be administered 30 minutes to 4 hours before carfilzomib.

[d]Consider appropriate dose reduction for the starting dose of lenalidomide according to current lenalidomide summary of product characteristics. This is especially important for patients with baseline renal impairment in whom excessive myelosuppression due to lenalidomide may occur.

- When combined with lenalidomide and dexAMETHasone, carfilzomib is administered on day 1, 8 and 15 of a 28 day treatment cycle as shown in table 1.
- Carfilzomib is administered at a starting dose of 20 mg/m^2 (maximum dose 44 mg), in cycle 1 on day 1.
- If tolerated, the dose should be increased on day 8 of cycle 1 to 56 mg/m^2 (maximum dose 123 mg).
- From cycle 10 onwards, dexAMETHasone is administered on days 1, 8 and 15 only (day 22 dose of dexAMETHasone is omitted)
- From cycle 13, carfilzomib is administered on days 1 and 15 only (day 8 dose is omitted).
- Treatment may be continued until disease progression or until unacceptable toxicity occurs.
- Treatment with carfilzomib combined with lenalidomide and dexAMETHasone for longer than 18 cycles should be based on an individual benefit-risk assessment, as the data on the tolerability and toxicity of carfilzomib beyond 18 cycles are limited.

Administration guidelines:
dexAMETHasone and lenalidomide are both administered orally.
Carfilzomib is administered as detailed in Table 2 below.

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 30 mins
1	8, 15	Carfilzomib	[b]56mg/m^2	IV infusion	100ml Glucose 5%[c] over 30 mins
[a]Maximum dose of carfilzomib is 44mg.					
[b]Maximum dose of carfilzomib is 123mg.					
[c]Carfilzomib may be administered in 50-100ml Glucose 5%.					
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. Available on the NCCP website .					

ELIGIBILITY:

- Indication as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to carfilzomib, lenalidomide, dexAMETHasone or any of the excipients
- Pregnancy
- Breastfeeding
- Patients who are unable to comply with the Lenalidomide Pregnancy Prevention Programme

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
- VTE risk assessment (Carfilzomib treatment is associated with an increased risk of thrombosis)
- Urine pregnancy testing or serum hCG test for women of child bearing potential as per Pregnancy Prevention Programme
- Assessment and registration as per Pregnancy Prevention Program for both male and female patients
- Virology screen -Hepatitis B (HBsAg, HBcoreAb), Hepatitis C, HIV
  *__See Adverse Effects/Regimen Specific Complications re Hepatitis B Reactivation__

Regular tests:

- FBC, renal and liver profile monthly.
- Blood pressure, *blood glucose if being treated with oral hypoglycaemics (* See Drug Interactions)
- Urine pregnancy testing or serum hCG test every 28 days for females of childbearing potential as per Pregnancy Prevention Programme
- Consider monitoring thyroid function tests.

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
- Lenalidomide treatment must not be started if the ANC is < 1x 10^9/L and/or platelets < 75 x 10^9/L or dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L
- Dose level reductions for carfilzomib and lenalidomide are described in Table 3 below

Treatment guidelines for specific haematologic toxicities (thrombocytopenia and neutropenia) are outlined in Tables 4 and 5.

Table 3: Dose Level Reductions for Carfilzomib and Lenalidomide

	Carfilzomib	Lenalidomide
Starting Dose	**56 mg/m^2**	**25mg**
Dose level -1	45 mg/m^2	20mg
Dose level -2	36 mg/m^2	15mg
Dose level- 3	27 mg/m^2	10mg
Dose level-4	Discontinue carfilzomib	5mg
Dose level-5		2.5mg

Haematological:

Table 4: Dose Modifications for Thrombocytopenia

Platelets	Lenalidomide	Platelets	Carfilzomib
Fall to < 30 x 10^9/L	Hold lenalidomide therapy, follow FBC weekly. Hold prophylactic anticoagulation until platelets return to ≥30x10^9/L then resume at 1 dose decrement.	If 10-30 x 10^9/L without evidence of bleeding	Maintain full dose
		If < 10 x 10^9/L or evidence of bleeding	Hold dose until platelets return to ≥ 10 x 10^9/L and/or bleeding is controlled then resume at same dose level.
For each subsequent drop to < 30 x 10^9/L	Hold lenalidomide therapy, follow FBC weekly. Hold prophylactic anticoagulation until platelets return to ≥30x10^9/L then resume at additional dose decrement. Do not dose below 5mg once daily.	If 10-30 x 10^9/L without evidence of bleeding	Maintain full dose
		If < 10 x 10^9/L or evidence of bleeding	Hold dose until platelets return to ≥ 10 x 10^9/L and/or bleeding is controlled, then consider 1 dose level reduction when restarting carfilzomib.

Table 5: Dose Modifications for Neutropenia

ANC	Lenalidomide	ANC	Carfilzomib
Falls to < 1.0 x 10^9/L	Hold lenalidomide therapy, administer G-CSF, follow FBC weekly; then resume at full dose when ANC ≥ 1.0x10^9/L	0.5-1.0 x 10^9/L	Maintain full dose
		< 0.5 x 10^9/L	Hold dose Resume at full dose when ANC ≥ 0.5 x 10^9/L
For each subsequent drop to <1.0 x 10^9/L	Hold lenalidomide therapy, administer G-CSF, follow FBC weekly; then resume at 1 dose decrement when ANC ≥ 1.0x10^9/L	0.5-1.0 x 10^9/L	Maintain full dose
		For subsequent drops to < 0.5 x 10^9/L	Hold dose Resume when ANC ≥ 0.5 x 10^9/L and consider 1 dose level reduction
		Febrile neutropenia ANC < 0.5 x 10^9/L and an oral temperature > 38.5^{0}C or two consecutive readings of > 38.0^{0}C for 2 hours	Hold dose If ANC returns to baseline grade and fever resolves, resume at same dose level
In the case of neutropenia, the use of growth factors in patient management should be considered.			

Renal Impairment:

Table 6: Dose modification of carfilzomib and lenalidomide based on renal function

Carfilzomib	• No starting dose adjustment for carfilzomib is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. • Renal function should be monitored, 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. • There are limited efficacy and safety data on patients with baseline creatinine clearance < 30 mL/min.	
Lenalidomide	**Creatinine Clearance ml/min**	**Dose modification**
	30 to 50	Reduce dose to 10mg once daily*
	<30 not requiring dialysis	15mg every other day
	<30 requiring dialysis	Reduce dose to 5mg once daily. On dialysis days dose should be administered after dialysis.
	*The dose may be escalated to 15mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment	

Hepatic impairment:

Table 7: Dose modification of carfilzomib and lenalidomide based on hepatic function

Carfilzomib	• Mild and moderate: 75% of the original dose. • Severe: not recommended
Lenalidomide	• Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations

Management of adverse events

Table 8: Dose modifications for non-haematological toxicity for carfilzomib

Adverse Event	**Carfilzomib**
Non-haematologic toxicity (renal) Serum creatinine ≥ 2 × baseline; **OR** Creatinine clearance < 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis	Hold 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[a] For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure
All other grade 3 or 4 non-haematologic toxicities	Stop carfilzomib until resolved or returned to baseline. Consider restarting the next scheduled treatment at 1 dose level reduction[a]
[a] see table 3 for dose level reductions	

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting - Available on the NCCP website

Carfilzomib: Low (**Refer to local policy).**
Lenalidomide: Minimal to low (**Refer to local policy).**

For information:
Within NCIS regimens, antiemetics have been standardised by Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) - Available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - Available on the NCCP website

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 (30 mL/kg/day for 48 hours before day 1 of cycle 1) and
  - intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid before each dose in cycle 1)
  - Give an additional 250 mL to 500 mL 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).**
- Thromboprophylaxis **(Refer to local policy**).
- In case of neutropenia the consultant may consider the use of filgrastim (G-CSF).
- Prophylactic laxatives to prevent lenalidomide-induced constipation **(Refer to local policy).**
- 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).**

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Tumour lysis syndrome:** Cases of tumour lysis syndrome (TLS), including with fatal outcome, have been reported in patients receiving both carfilzomib and lenalidomide. Patients with a high tumour burden should be considered to be at greater risk for TLS and should be monitored closely and appropriate precautions taken.
    - Stop carfilzomib until TLS is resolved.
- **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
- **Pulmonary hypertension:** Cases of pulmonary hypertension, some fatal, have been reported in patients treated with carfilzomib and lenalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during therapy.
    - Stop carfilzomib for pulmonary hypertension until resolved or returned to baseline and consider whether to restart carfilzomib based on a benefit/risk assessment

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. Some of these events have been fatal. 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. Some of these events have been fatal. 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.

Lenalidomide

- **Teratogenic effects:** Lenalidomide is structurally related to thalidomide a powerful human teratogen. Lenalidomide must never be used by women who are pregnant or by women who could become pregnant unless all the conditions of the Lenalidomide Pregnancy Prevention Programme are met. These conditions must be fulfilled for all male and female patients.
- **Skin reactions:** Lenalidomide must be discontinued permanently for exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected.
- **Cardiovascular:** Patients with known risk factors for MI, including prior thrombosis should be closely monitored and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension and hyperlipidaemia). There is an increased risk of venous and arterial thromboembolism in patients treated with lenalidomide and dexAMETHasone. Previous history of thromboembolic events or concomitant administration of erythropoietic agents or other agents such as hormone replacement therapy, may also increase thromboembolic risk in these patients. Particularly, a haemoglobin concentration above 12g/dl should lead to discontinuation of erythropoietic agents. Thromboprophylaxis should be considered especially in patients with additional thrombotic risk factors.
- **Peripheral Neuropathy:** Lenalidomide is structurally related to thalidomide which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with lenalidomide in combination with dexAMETHasone or melphalan and prednisone or lenalidomide monotherapy or with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma. The combination of lenalidomide with intravenous bortezomib and dexAMETHasone in multiple myeloma patients is associated with a higher frequency of peripheral neuropathy. The frequency was lower when bortezomib was administered subcutaneously.
- **Thyroid function:** Cases of hypothyroidism have been reported and baseline and ongoing monitoring of thyroid function is recommended.

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.
- Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving lenalidomide with dexAMETHasone
- There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.
- Current drug interaction databases should be consulted for more information.

COMPANY SUPPORT RESOURCES/Useful Links:

Lenalidomide

- Please refer to the HPRA website (www.hpra.ie) for the individual product for list of relevant support resources
- Prescribers are required to read and understand the relevant HCP Information Guide and to adhere to the PPP

REFERENCES:

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Version	Date	Amendment	Approved By
1	06/04/2020		Prof Paul Browne
2	14/04/2020	Clarification of carfilzomib dosing schedule from cycle 13 onwards	Prof Paul Browne
3	30/07/2020	Update of carfilzomib infusion time	Plasma Cell Disorder CAG
4	08/12/2023	Reviewed. Updated exclusions, baseline and regular tests, emetogenic potential and adverse events. Aligned dose modifications in hepatic impairment to recommendations by Krens et al 2019.	Plasma Cell Disorder CAG
4a	13/02/2024	Updated company support resources/ useful links section in line with NCCP standardisation.	NCCP
4b	27/11/2024	Updated emetogenic potential section with standard wording.	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] The administration of carfilzomib 56mg/m^2 once weekly in combination with lenalidomide is an unlicensed dosing posology for this indication 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" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy