Indication	In combination with dexamethasone alone for the treatment of multiple myeloma where the patient has had one and only one previous therapy.
Treatment Intent	Disease Modification
Frequency and number of cycles	Every 28 days Continue until disease progression or until unacceptable toxicity occurs or patient choice to stop treatment. A formal medical review as to whether to continue treatment will be scheduled to occur by the end of cycle 2.
Monitoring parameters pre-treatment	• Check virology status prior to start of treatment. • Monitor FBC, U&Es, LFTs, and LDH at each cycle. NB Serum potassium levels should be monitored each cycle, or more frequently as clinically indicated. • A thorough assessment for cardiovascular risk factors prior to starting treatment is recommended. • Blood pressure should be stable prior to treatment and monitored at each cycle. Patients should be assessed for signs of cardiac toxicity and arrhythmias as directed by the consultant based on risk factors. • Dose adjustments do not need to be made for weight changes of less than or equal to 20%. • BSA capped at 2.2m^2 • Ensure patient has taken oral fluids (30 mL/kg/day for 48 hours) before day 1 of cycle 1 • 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 • If lactate dehydrogenase (LDH) or uric acid is elevated and / or patients considered at risk for TLS at cycle 2, day 1, then the recommended IV hydration should be repeated for Cycle 2. Maintain urine output ≥ 2 L/day. Monitor for evidence of fluid overload. • 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 be assessed with an ECG and ECHO/MUGA, prior to starting treatment. These patients should be treated with caution and remain under close follow-up. The risk of cardiac failure is increased in elderly patients (>/= 75 years), these patients should be assessed with an ECG (and if clinically appropriate ECHO/MUGA) prior to treatment and closely monitored. • **Renal Impairment:** No starting dose adjustment for carfilzomib is recommended in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis, however there are limited efficacy and safety data on patients with baseline creatinine clearance < 30 mL/min. • **Hepatic Impairment:** No starting dose adjustment is recommended in patients with mild or moderate hepatic impairment. Limited efficacy and safety data in patients with moderate and severe hepatic impairment. • **Management of adverse reactions and dose adjustments:** Dosing should be modified based on toxicity. Recommended actions and dose modifications are presented in table 1 and 2 below. ○ **Common side effects:** Pulmonary toxicity, dyspnoea, hypertension, acute renal failure, hepatic toxicity, tumour lysis syndrome, infusion reactions, venous thromboembolic events, posterior reversible encephalopathy syndrome, cardiac toxicity, thrombocytopenia, haemorrhage and tinnitus have all been reported in patient receiving cafilzomib. ○ **Venous thromboembolic events:** Pulmonary embolism or deep vein thrombosis can occur with carfilzomib. If patients develop symptoms of PE or DVT they should immediately seek medical care. Patients at high risk should be closely monitored. Caution should be used in the concomitant administration of other agents that may increase the risk of thrombosis. ○ **Progressive multifocal leukoencephalopathy (PML):** PML has been reported in patients receiving carfilzomib. Patients should be monitored for new or worsening neurological, cognitive or behavioural changes. All treatment should be held if PML is suspected and permanently discontinued if PML is confirmed. ○ **Posterior Reversible Encephalopathy Syndrome (PRES)**: has been reported in patients receiving carfilzomib. In patients developing suspected or confirmed PRES, treatment should be discontinued. ○ **Tumour Lysis Syndrome: (TLS)** Monitor for signs and symptoms of TLS. Patients with a high tumour burden should be considered to be at greater risk for TLS. Appropriate measures (hydration, allopurinol,

	rasburicase) must be taken to prevent hyperuricemia as clinically indicated. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** ○ It is unknown whether carfilzomib is an inducer of CYP1A2, 2C8, 2C9, 2C19 and 2B6 at therapeutic concentrations. Caution should be observed when carfilzomib is combined with medicinal products that are substrates of these enzymes, such as oral contraceptives. ○ Caution should be observed when carfilzomib is combined with substrates of P-gp (e.g. digoxin, colchicine). • Carfilzomib may cause fatigue and dizziness; patients should be advised to avoid driving or operating machinery if affected. • Contains 0.3mmols (7 mg) of sodium per mL of reconstituted solution. This should be taken into consideration for patients on a controlled sodium diet.
Reference(s)	SpC accessed online 22.12.20 blueteq form accessed online 22.12.20 https://www.nice.org.uk/guidance/ta657 Changes made in line with 'SOP for removal of ranitidine on KMCC protocols and on aria regimens'
Funding	NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1 Dose modifications during Carfilzomib treatment

Haematologic toxicity	**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
• 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
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	• 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* • For patients on dialysis receiving Carfilzomib, the dose is to be administered after the dialysis procedure
Other non-haematologic toxicity	**Recommended action**
• All other grade 3 or 4 non-haematologic toxicities	• Stop until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction

Table 2 Dose level reductions for Carfilzomib

Regimen	**Carfilzomib Dose**	**First Carfilzomib dose reduction**	**Second Carfilzomib dose reduction**	**Third Carfilzomib dose reduction**
Carfilzomib and dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2 *

* If symptoms do not resolve, discontinue Carfilzomib treatment

Cycle 1: 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration Details
D1	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**20mg/m² (max. 44mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
	Sodium Chloride 0.9%	500ml	IV	30 mins	
D2	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**20mg/m² (max. 44mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
	Sodium Chloride 0.9%	500ml	IV	30 mins	
D8	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**56mg/m² (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
	Sodium Chloride 0.9%	500ml	IV	30 mins	
D9	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**56mg/m² (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
	Sodium Chloride 0.9%	500ml	IV	30 mins	

Day	Drug	Dose	Route	Infusion Duration	Administration Details
D15	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**56mg/m² (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
	Sodium Chloride 0.9%	500ml	IV	30 mins	
D16	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**56mg/m² (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
	Sodium Chloride 0.9%	500ml	IV	30 mins	

TTO	Drug	Dose	Route	Directions
1	**Dexamethasone**	**20mg**	PO	OM to be taken on day 22 and 23. Take with or after food.
	Omeprazole	20mg	PO	OD
	Allopurinol	300mg	PO	OD for 4 weeks (first cycle only)
	Aciclovir	400mg	PO	BD
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	NB Consider prophylactic anticoagulation			

Cycle 2 onwards: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration Details
D1	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**56mg/m^2 (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
D2	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**56MG/M^2 (MAX. 123MG)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
D8	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**56mg/m^2 (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
D9	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	C**ARFILZOMIB**	**56mg/m^2 (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
D15	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**56mg/m^2 (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration
D16	**DEXAMETHASONE**	**20mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**56mg/m^2 (max. 123mg)**	IV	30 mins	In 100ml 5% glucose Flush with 5% glucose before and after administration

TTO	Drug	Dose	Route	Directions
D1	**Dexamethasone**	**20mg**	PO	OM to be taken on day 22 and 23. Take with or after food.
	Omeprazole	20mg	PO	OD
	Aciclovir	400mg	PO	BD
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 days continuously.
	NB Consider prophylactic anticoagulation			