Indication	Carfilzomib in combination with lenalidomide and dexamethasone for the treatment of previously treated multiple myeloma in patients who have had 1 and only 1 prior line of systemic therapy. NB Patients must have been treated with a bortezomib-containing regimen as part of 1st line treatment and the patient responded to this bortezomib-containing therapy. With no previous carfilzomib therapy and have not been previously treated with lenalidomide unless lenalidomide was received as part of induction therapy prior to a stem cell transplant. In the event the patient's status changes to transplant eligible and they proceed to transplant, post-transplant treatment with carfilzomib, lenalidomide and dexamethasone cannot resume as funding is not available for this regimen as maintenance therapy post-transplant.
Treatment Intent	Disease modification
Frequency and number of cycles	Repeat every 28 days Carfilzomib, lenalidomide and dexamethasone should continue until disease progression or unacceptable toxicity or patient proceeds to stem cell transplant or patient choice to stop treatment, or a maximum of **18 cycles** whichever is the sooner. Following completion of 18 cycles of combination with carfilzomib, lenalidomide and dexamethasone alone can be continued until progressive disease or unacceptable toxicity or patient choice, whichever occurs first. A formal medical review to decide if treatment should continue should be scheduled to take place no later than the end of the cycle 2.
Monitoring Parameters pre-treatment	• **The conditions of the Pregnancy Prevention Programme must be fulfilled and the Lenalidomide Prescription Authorisation Form must be completed at time of prescribing.** • **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Monitor FBC at baseline and every 2 weeks for the first 2 cycles, then on day 1 of each cycle thereafter. • U&Es, LFTs, and LDH at each cycle. NB Serum potassium levels should be monitored each cycle, or more frequently as clinically indicated. • Blood glucose every cycle. • Neuts must be >/= 1.0 x 10^9/L, and/or platelet counts >/=75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts >/= 30 x 10^9/L before starting treatment. • BSA capped at 2.2m^2. • Dose adjustments of carfilzomib do not need to be made for weight changes of less than or equal to 20%. • 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. • 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. • 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. • Consider PCP prophylaxis/ antifungal therapy if lymphocyte count <1.0 x 10^9/L. • **Renal Impairment:** o **Carfilzomib:** 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. o **Lenalidomide:** No dose adjustments are required for patients with mild renal impairment. In moderate (CrCl >/=30 to <50mL/min) renal impairment dose reduce to 10mg OD, this can be increased to 15mg OD after 2 cycles if the patient is not responding to treatment but is tolerating 10mg OD. In severe renal impairment (CrCl <30 mL/min, without dialysis) dose reduce to 15mg on alternate days. In end stage renal disease (CrCl <30mL/min requiring dialysis) dose reduce to 5mg OD, if taking on a dialysis treatment day the dose should be taken after dialysis. • **Hepatic Impairment:** o **Carfilzomib:** No starting dose adjustment is recommended in patients with mild hepatic impairment. Limited efficacy and safety data in patients with moderate and severe hepatic impairment. o **Lenalidomide:** Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations. • **Infusion related reactions (IRRs):** • Infusion related reactions, including life threatening reactions, have occurred with carfilzomib. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24hours after administration. Pre-medication with dexamethasone can be considered. • **Management of adverse reactions and dose adjustments:** o **Carfilzomib:** 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, respiratory infections, pulmonary hypertension, rash, flu-like illness, blurred vision, dyspnoea, hypertension, acute renal failure, hepatic toxicity (potential effect on bilirubin and transaminases refer to table 1 for management), electrolyte disturbance, infusion reactions, venous thromboembolic events, cardiac toxicity, thrombocytopenia, haemorrhage and tinnitus have all been reported in patient receiving carfilzomib. ○ **Venous thromboembolic events:** Pulmonary embolism or deep vein thrombosis can occur with carfilzomib and lenalidomide, this risk in increased when given in combination with dexamethasone. 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. Thromboprophylaxis should be considered on an individual patient basis. ○ **Progressive multifocal leukoencephalopathy (PML):** PML has been reported in patients receiving carfilzomib and lenalidomide. 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. ○ **Lenalidomide:** **Haematological:** Dosing interruption or dose reduction may be required, see table 3 below. **Non-haematological:** Lenalidomide interruption or discontinuation should be considered for Grade 2 or 3 skin rash. Lenalidomide is to be permanently discontinued in the event of desquamating/blistering rash of any grade, erythema multiforme =/> grade 3, any rash of grade 4 severity or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected. Lenalidomide should be discontinued for grade 4 neuropathy or hypersensitivity, and grade 3 or higher bradycardia or cardiac arrhythmia. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, lenalidomide must be permanently discontinued. For other Grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to </=grade 2 depending on the physicians' discretion. • **Dose modification guidance for lenalidomide:** The first recommended dose reduction is to 15mg once daily, second dose reduction is to 10mg once daily and the third dose reduction is to 5mg once daily. If a patient is unable to tolerate 5mg day treatment should be discontinued. • **Common drug interactions (for comprehensive list refer to BNF/SPC):** **Carfilzomib:** ○ 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. o Use with caution when given concomitantly with other medications known to cause hypokalaemia. o Caution should be observed when carfilzomib is combined with substrates of P-gp (e.g. digoxin, colchicine) due to the potential to increase levels. **Lenalidomide:** o Lenalidomide may increase digoxin concentration, monitor digoxin levels during treatment. Increased risk of rhabdomyolysis when administered with statins. Combined hormonal contraceptives are predicted to increase the risk of venous thromboembolism when given with Lenalidomide. Manufacturer advises avoid. • **Missed Dose:** If a patient misses a dose of lenalidomide the patient can take the dose if it is less than 12hours delayed, if longer than 12 hours the dose should not be taken and the next dose should be taken as per the dosing schedule. • Ensure patient is informed of requirement for strict contraception precautions during treatment with Lenalidomide. Follow Lenalidomide risk management programme. • Pregnancy test – if patient is of child-bearing potential (every 4 weeks). • For oral self-administration: refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Cancerbackup information sheet. • Both lenalidomide and carfilzomib can have an effect on patients' ability to drive and operate machinery; patients should be advised to avoid driving or operating machinery if affected. • Carfilzomib contains 0.3 mmols (7 mg) of sodium per mL of reconstituted solution. This should be taken into consideration for patients on a controlled sodium diet.
References	HAEM-MYEL-045 V4

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[a] • 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**
Carfilzomib, lenalidomide and dexamethasone	27mg/m^2	20mg/m^2	15mg/m^2

Table 3 Dose modifications for haematological adverse reactions lenalidomide

Dose modifications for haematological adverse reactions	
Neutropenia	
First fall to <0.5 x 10^9/L	Interrupt lenalidomide treatment.
Return to ≥0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily
Return to ≥0.5 x 10^9/L when dose dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at next lower dose level
For each subsequent drop below <0.5 x 10^9/L	Interrupt lenalidomide treatment when return to ≥0.5 resume at next lower dose level. Do not dose below 5 mg once daily.
Thrombocytopenia	
First fall to <30 x 10^9/l	Interrupt lenalidomide treatment
Return to ≥30 x 10^9/L	Resume lenalidomide at next lower dose level.
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥30 x 10^9/L	Resume lenalidomide at next lower dose level once daily. Do not dose below 5mg once daily.

CYCLE 1: 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**40mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**20mg/m^2 maximum dose 44mg**	IV	10 mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
	Sodium Chloride 0.9%	500ml	IV	30 mins	
2	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**20mg/m^2 Maximum dose 44mg**	IV	10 mins	In 50ml -100ml 5% glucose Flush with 5% glucose before and after administration.
	Sodium Chloride 0.9%	500ml	IV	30 mins	
8	**DEXAMETHASONE**	**40mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10 mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
	Sodium Chloride 0.9%	500ml	IV	30 mins	
9	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10 mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
	Sodium Chloride 0.9%	500ml	IV	30 mins	
15	**DEXAMETHASONE**	**40mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10 mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
	Sodium Chloride 0.9%	500ml	IV	30 mins	
16	Sodium Chloride 0.9%	500ml	IV	30 mins	
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10 mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
	Sodium Chloride 0.9%	500ml	IV	30 mins	

TTOs cycle 1

TTO	Drug	Dose	Route	Directions
Day 1	**LENALIDOMIDE**	**25mg**	PO	OD on days 1-21 followed by a 7-day break. (available as 5mg, 10mg, 15mg and 25mg capsules)
	DEXAMETHASONE	**40mg**	PO	OM on day 22
	Omeprazole	20mg	PO	OM. Swallow this medicine whole. Do not chew or crush the capsule.
	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 consecutive days.
	NB Consider prophylactic anticoagulation			

Cycle 2-12: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**40mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
2	**CARFILZOMIB**	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
8	**DEXAMETHASONE**	**40mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
9	**CARFILZOMIB**	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
15	**DEXAMETHASONE**	**40mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
16	**CARFILZOMIB**	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.

TTOs cycle 2-12

TTO	Drug	Dose	Route	Directions
Day 1	**LENALIDOMIDE**	**25mg**	PO	OD on days 1-21 followed by a 7-day break. (available as 5mg, 10mg, 15mg and 25mg capsules)
	DEXAMETHASONE	**40mg**	PO	OD on day 22 only.
	Omeprazole	20mg	PO	OM. Swallow this medicine whole. Do not chew or crush the capsule.
	Aciclovir	400mg	PO	BD
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 consecutive days.
	NB Consider prophylactic anticoagulation			

Cycle 13 -18 repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	**DEXAMETHASONE**	**40mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
2	**CARFILZOMIB**	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
15	**DEXAMETHASONE**	**40mg**	PO		Administer 30 minutes to 4 hours before carfilzomib
	CARFILZOMIB	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.
16	**CARFILZOMIB**	**27mg/m^2 Maximum dose 60mg**	IV	10mins	In 50ml - 100ml 5% glucose Flush with 5% glucose before and after administration.

TTO cycle 13-18

TTO	Drug	Dose	Route	Directions
Day 1	**LENALIDOMIDE**	**25mg**	PO	OD on days 1-21 followed by a 7-day break. (available as 5mg, 10mg, 15mg and 25mg capsules)
	DEXAMETHASONE	**40mg**	PO	OD on day 8 and day 22.
	Omeprazole	20mg	PO	OM. Swallow this medicine whole. Do not chew or crush the capsule.
	Aciclovir	400mg	PO	BD
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 consecutive days.
	NB Consider prophylactic anticoagulation			

Cycle 19 onwards repeat every 28 days

TTO	Drug	Dose	Route	Directions
Day 1	**LENALIDOMIDE**	**25mg**	PO	OD on days 1-21 followed by a 7-day break. (available as 5mg, 10mg, 15mg and 25mg capsules)
	DEXAMETHASONE	**40mg**	PO	OD on day 1,8,15 and 22 only.
	Omeprazole	20mg	PO	OM. Swallow this medicine whole. Do not chew or crush the capsule.
	Aciclovir	400mg	PO	BD
	Metoclopramide	10mg	PO	10mg up to 3 times a day as required. Do not take for more than 5 consecutive days.
	NB Consider prophylactic anticoagulation			