

CARFILZOMIB with LENALIDOMIDE and DEXAMETHASONE (CarLenDex)

INDICATIONS

Multiple myeloma at first relapse (NICETA695), i.e. those who received one prior therapy which included bortezomib. **Requires Blueteq approval**

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:

- FBC & film
- Clotting screen
- U&Es
- LFTs
- Calcium
- Uric acid
- Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
- Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
- Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
- Serum free light chain assay (Freelite)
- Hevylite analysis (if paraprotein level difficult to quantify)
- Albumin & β_2 microglobulin for ISS staging
- Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below)
- Group and save
- Imaging as per NICE/network guidance and clinical presentation
- Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ

This is a controlled document and therefore must not be changed

1 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

ADDITIONAL INVESTIGATIONS

- Plasma viscosity if hyperviscosity suspected.
 - If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology.
 - Evaluate for presence of cardiac issues. This is usually done by clinical assessment although ECHO and ECG may be useful in occasional patients to document the extent of cardiac function prior to commencing therapy.
 - Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1.
2. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
 3. Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
 4. Counselling - all patients should receive verbal and written information on oral chemotherapy.
 5. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
 6. Fertility - all patients should be offered fertility advice, as appropriate.
 7. Hydration - fluid intake of at least 3 litres /day should be attempted.
 8. Document patient’s height and weight, dose on actual body weight.
 9. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE- ASSESSMENT

The conditions of the Lenalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients.

Clinical Assessment of thrombo-embolic risk.

DRUG REGIMEN

CYCLES 1 to 18

Pre- and Post Hydration	<p>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 (see section 4.4 of carfilzomib SPC).</p> <p>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.</p>
--------------------------------	--

This is a controlled document and therefore must not be changed

2 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

<p>Pre-medication</p>	<p>In this protocol, high dose dexamethasone is scheduled/due on all carfilzomib days. Dexamethasone has 2 roles: it is part of the triplet CarLenDex treatment combination, and is considered as a pre-med for carfilzomib</p> <p>See further details in the table, under dexamethasone</p> <p>Pre-med dexamethasone should ideally be given 30 minutes prior to all carfilzomib doses on carfilzomib days.</p>	
<p>Carfilzomib</p>	<p>For cycle 1 on Days 1 and 2, administer carfilzomib at 20mg/m² (maximum dose 44 mg) in 50mL or 100mL glucose 5% over 10 minutes.</p> <p>From cycle 1 Day 8 onwards, if tolerated, dose should be increased to 27 mg/m² (maximum dose 60 mg) intravenous infusion in 50mL glucose 5% over 10 minutes.</p> <p>Doses capped at BSA 2.2m².Dose adjustments do not need to be made for weight changes ≤ 20%</p>	<p>Cycles 1 to 12: Days 1,2, 8,9 and 15,16 Cycles 13 to 18: Days 1,2 and 15,16</p> <p>Patient must be monitored for 1 hour following carfilzomib infusions during cycle 1 and cycle 2 day 1.</p>
<p>WITH</p>		
<p>Dexamethasone</p>	<p>20 mg PO</p> <p>The dose may need to be reduced in the elderly or if steroid-related side effects develop.</p>	<p>On days 1, 2, 8, 9, 15, 16, 22 and 23</p> <p>On carfilzomib days, dexamethasone should be given 30 minutes to 4 hours before carfilzomib</p>
<p>WITH</p>		
<p>Lenalidomide</p>	<p>25mg PO once daily</p>	<p>Days 1 to 21</p>

CYCLE 19- onwards (continuous therapy):

Continuing carfilzomib, whilst 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. Patients in ASPIRE trial received only lenalidomide and dexamethasone beyond cycle 18.

This is a controlled document and therefore must not be changed

3 of 12

<p>MM.34 Car/Len/ Dex</p>	<p>Authorised by Myeloma lead Dr. Karthik Ramasamy</p>	<p>Review date: June 2021</p>	<p>V.2.1</p>
-------------------------------	--	-------------------------------	--------------

Following 18 cycles, continue on Lenalidomide and dexamethasone therapy. Consider reduction of dexamethasone dose in elderly patients or in case of steroid side effects. Continue therapy provided no significant toxicity or disease progression.

Lenalidomide (Continuous therapy)	25 mg orally once daily on days 1 to 21.
WITH	
Dexamethasone	40 mg PO on days 1, 8, 15 and 22. The dose may need to be reduced in the elderly or if steroid-related side effects develop.

CYCLE FREQUENCY

Repeat every 28 days, until signs of disease progression or unacceptable toxicity.

DOSE MODIFICATIONS

HAEMATOLOGICAL TOXICITY

Prior to initiating a new cycle of therapy:

- Platelets $\geq 75 \times 10^9/L$ and ANC $\geq 1.0 \times 10^9/L$. In the event of lower counts, discuss with Consultant
- Non-haem toxicities should resolve to G1 or baseline

Carfilzomib Dose Adjustments

Current dose	Reduce dose to
27 mg/m ²	20 mg/m ²
20mg/m ²	15 mg/m ² If toxicities do not resolve after this dose reduction, consider discontinuing carfilzomib

Haematological toxicity during a cycle	Carfilzomib dose modification or delay
<ul style="list-style-type: none"> • If Absolute neutrophil count $< 0.5 \times 10^9 /L$ 	Withhold Carfilzomib dose, If recovered to $\geq 0.5 \times 10^9/L$, continue at the same dose level. For subsequent drops to $< 0.5 \times 10^9/L$, follow the same recommendations as above and consider further dose level reduction when restarting Carfilzomib If toxicity does not resolve after a 15mg/m ² dose reduction, consider discontinuing carfilzomib

This is a controlled document and therefore must not be changed

4 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

<p>Febrile neutropenia:</p> <p>Absolute neutrophil count $< 0.5 \times 10^9/L$ and an oral temperature $> 38.5^\circ C$ or two consecutive readings of $> 38.0^\circ C$ for 2 hours</p>	<p>Withhold carfilzomib dose</p> <p>If absolute neutrophil count returns to baseline grade and fever resolves, resume at the same dose level</p>
<p>• If platelet $< 10 \times 10^9/L$ or evidence of bleeding with thrombocytopenia</p>	<p>Withhold Carfilzomib dose. if recovered to $\geq 10 \times 10^9/L$ and/or bleeding is controlled, continue at the same dose level</p> <p>For subsequent drops to $< 10 \times 10^9/L$, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilzomib.</p> <p>If toxicity does not resolve after a 15 mg/m^2 dose reduction, consider discontinuing carfilzomib</p>

Non-haematological toxicity	Recommended action
G3 or G4 toxicity	<p>Withhold carfilzomib until resolved or returned to baseline</p> <p>Consider restarting the next scheduled treatment at 1 dose level reduction</p> <p>If toxicity does not resolve after a 15 mg/m^2 dose reduction, consider discontinuing carfilzomib</p>

Lenalidomide Dose Adjustments

A new lenalidomide treatment cycle should not normally be started if the Absolute Neutrophil Counts (ANC) $< 1 \times 10^9/L$, and/or platelet count $< 75 \times 10^9/L$, or, dependent on bone marrow infiltration by plasma cells, platelet counts $< 30 \times 10^9/L$. If the low counts are thought to be due to myeloma per se, the use of G-CSF and platelet support should be considered

Table below summarises lenalidomide dose reduction levels:

Starting dose	25 mg
Dose level -1	15 mg
Dose level -2	10 mg
Dose level -3	5 mg

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

Note: Consider re-escalating lenalidomide dose provide toxicities have completely resolved.

Thrombocytopenia:

When platelets	Recommended Course
First fall to $< 30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at 15 mg/day

This is a controlled document and therefore must not be changed

5 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

For each subsequent drop below $30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.

Neutropenia:

When neutrophils	Recommended Course
First fall to $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.
Return to $\geq 0.5 \times 10^9/L$ when neutropenia is the only observed toxicity	Resume lenalidomide at the starting dose level
Return to $\geq 0.5 \times 10^9/L$ when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at one level dose reduction
For each subsequent drop below $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days.
Return to $\geq 0.5 \times 10^9/L$	Resume lenalidomide at the next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.

RENAL/HEPATIC IMPAIRMENT:

Carfilzomib

Renal	Hepatic
<p>Serum Creatinine $\geq 2 \times$ baseline, or CrCl < 15 mL/min, or CrCl $\leq 50\%$ of baseline, or if dialysis: withhold Carfilzomib</p> <p>Resume carfilzomib when renal function has recovered to within 25% of baseline: consider resuming at 1 dose level reduction.</p> <p>If toxicity does not resolve after a $15\text{mg}/\text{m}^2$ dose reduction, consider discontinuing carfilzomib</p> <p>For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure</p>	<p>No dedicated pharmacokinetic studies have been completed in patients with hepatic impairment</p>

Lenalidomide

Renal	Hepatic
<p>CrCl 30- < 50 mL/min 10 mg once daily*</p> <p>CrCl < 30 mL/min, no dialysis 15 mg every other day**</p> <p>CrCl < 30 mL/min, requiring dialysis 5 mg once daily***</p>	<p>No formal studies. No specific dose recommendations</p>

This is a controlled document and therefore must not be changed

6 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

*Can increase to 15mg OD if no response and patient tolerating
 ** Can increase to 10mg OD if no response and patient tolerating
 *** On dialysis day, administer dose after dialysis/

INVESTIGATIONS (at the beginning of each cycle unless otherwise noted)

- FBC
- U&E, LFTs, Ca⁺⁺
- Blood pressure
- Ig's, paraprotein, Freelite assay.
- Consider repeat BM aspirate and trephine after 3 cycles in non-secretory myeloma and check result prior to starting cycle #5.
- Random blood glucose/ blood sugar

EMETIC RISK

Low-Moderate emetic risk

CONCURRENT MEDICATIONS

- Consider prophylactic laxatives to be taken if needed.
- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Prophylactic fluconazole 50mg OD
- Consider levofloxacin prophylaxis at 500mg od for 12 weeks (i.e. cycles 1-3)
- Bone protection as per NSSG Bone Protection protocol MM.3
- Thromboprophylaxis/anticoagulation as below.
- Consider prophylactic co-trimoxazole if heavily pre-treated or previous autograft.
- Consider cholestyramine if suspicion of bile salt malabsorption
- Prophylactic acyclovir 200 mg bd to tid (depending on renal function).

Patients on oral hypoglycaemic may require close monitoring of blood sugar levels.

This is a controlled document and therefore must not be changed

7 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

Carfilzomib:

- Serious adverse reactions that may occur during carfilzomib treatment include: cardiac failure, myocardial infarction, cardiac arrest, myocardial ischaemia, interstitial lung disease, pneumonitis, acute respiratory distress syndrome, acute respiratory failure, pulmonary hypertension, dyspnoea, hypertension including hypertensive crises, acute kidney injury, tumour lysis syndrome, infusion related reaction, gastrointestinal haemorrhage, intracranial haemorrhage, pulmonary haemorrhage, thrombocytopenia, hepatic failure, hepatitis B virus reactivation, PRES, thrombotic microangiopathy and TTP/HUS. In clinical studies with carfilzomib, cardiac toxicity and dyspnoea typically occurred early in the course of therapy. The most common adverse reactions (occurring in > 20% of subjects) were: anaemia, fatigue, thrombocytopenia, nausea, diarrhoea, pyrexia, dyspnoea, respiratory tract infection, cough and neutropenia. Reference (carfilzomib SPC)
- **Infusion reactions:** 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 24 hours after administration. Dexamethasone should be administered prior to carfilzomib to reduce the incidence and severity of reactions.
- **Cardiac and pulmonary** toxicities have been reported.
- **Others:** Tumour lysis syndrome, acute renal failure, pulmonary hypertension, Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, Posterior reversible encephalopathy syndrome (PRES)

Lenalidomide:

- **Teratogenicity:** The manufacturer's pregnancy prevention programme must be observed. Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme.
- **Diarrhoea:** Diarrhea was reported in 42% of patients requiring use of antidiarrheal medication and supportive care. Bile salt malabsorption occurs in a small % of patients of lenalidomide, and consider addition of cholestyramine.
- **Venous thromboembolism (VTE):**

There is an increased risk of thrombosis with lenalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

1. Prophylactic low-molecular weight heparin OR
2. Prophylactic. apixaban 2.5mg bd (check product specific information)

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors

This is a controlled document and therefore must not be changed

8 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

If VTE occurs, lenalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

- **Myelosuppression**
- **Drowsiness, somnolence and sedation:** Dose best taken at night time.
- **Peripheral neuropathy:** Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant toxicity is uncommon. Patients should be advised to report prickling, numbness and paraesthesia.
- **Dizziness and orthostatic hypotension**
- Other warnings: Patients should be informed not to donate blood or semen during or within 8 weeks of stopping lenalidomide treatment.
- **There is an MHRA alert on an increased risk of secondary malignancies in three large trials of lenalidomide treatment.** The MHRA recommend vigilance in reporting such events promptly. Quoted incidence is 3 to 4% per annum.

TREATMENT RELATED MORTALITY

<5%

REFERENCES

1. Stewart K et al Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med. 2015 Jan 8;372(2):142-52. doi: 10.1056/NEJMoa1411321. Epub 2014 Dec 6
2. Kyprolis Summary of Product Characteristics. eMC. Last updated Dec 2016. <http://www.medicines.org.uk/emc/medicine/31222>
3. Kyprolis prescribing information. FDA. Last revised 7/2015 http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/202714s009lbl.pdf
4. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, May 2017

REVIEW

Name	Revision	Date	Version	Review date
Dr Ramasamy Consultant	New document	May 2016	1.0	May 2018

This is a controlled document and therefore must not be changed

9 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

Faouzi Djebbari (Haematology Pharmacist)	Updated concurrent medication and references	July 2017	1.1	June 2018
NSSG Myeloma Group	Update following NICE approval	May 2021	2.0	June 2021
Quality Manager	Nursing Care Plan added	May 2021	2.1	June 2021

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------------	-------

Nursing Care Plan Carfilzomib Lenalidomide Dexamethasone

Indication: Relapsed Myeloma.

Frequency: 28 day cycles until disease progression or unacceptable toxicity.

Alopecia: No

CARFILZOMIB: Proteasome inhibitor

Administered as IV infusion on **days 1, 2, 8, 9, 15, 16 for cycles 1-12, and days 1, 2, 15, 16 for cycles 13-18**. Carfilzomib is infused over 30 minutes. Carfilzomib comes in 5% glucose bags but is compatible to be flushed with 0.9% normal saline.

On cycle 1 and cycle 2 day 1 patients will have pre and post hydration either side of the Carfilzomib infusion (500mls 0.9% normal saline over 1 hour pre and post).

After cycle 2 day 1 pre and post hydration (at least 1 litre) can be taken orally as long as the patient's biochemistry profile is stable and there is no risk of TLS.

Classification of extravasation: Not vesicant (There is no data available regarding skin corrosion/irritation or extravasation).

Emetic risk: low.

Side effects: anaemia, thrombocytopenia, neutropenia, hypertension, peripheral oedema, upper respiratory tract infections, diarrhoea, fatigue, pyrexia, dyspnoea, cough, upper respiratory tract infection, pneumonia and hypokalaemia.

Dosing reaction: 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 24 hours after administration.**

LENALIDOMIDE: Immunomodulator and angiogenesis inhibitor.

Administered orally on **days 1-21**.

Emetic risk: minimal.

Side effects: neutropenia, peripheral neuropathy, diarrhoea, constipation, flu like syndrome, infections, fatigue, muscle cramps, rash/itching, venous thromboembolism, bone marrow depression, drowsiness/sedation (recommended taking at night time).

DEXAMETHASONE: Corticosteroid tablets

Administered orally on **days 1, 8, 15, 22**. Taken with or after food preferably at breakfast. Carfilzomib is given at least 30 minutes pre Carfilzomib infusion.

Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

Regime Specific Considerations:

This is a controlled document and therefore must not be changed

11 of 12

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------	-------

- Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1. Ensure BP well controlled prior to starting therapy and throughout. Baseline ECG required.
- Patients should attempt to drink 3 litres of water a day.
- Bloods are required at the start of each cycle. Patients with unstable blood counts may require more frequent monitoring. Random glucose monitoring required due to dexamethasone (unless patient is diabetic, then tighter blood glucose control is required).
- Pregnancy test for pre-menopausal women under the age of 55 before the start of each cycle (due to the teratogenic effect of lenalidomide).

MM.34 Car/Len/ Dex	Authorised by Myeloma lead Dr. Karthik Ramasamy	Review date: June 2021	V.2.1
-----------------------	---	------------------------------	-------