### CARFDEXA Regimen

**Regimen Name**: Carfilzomib, Dexamethasone

<table>
<thead>
<tr>
<th>Disease Site</th>
<th>Hematologic - Multiple Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent</td>
<td>Palliative</td>
</tr>
<tr>
<td><strong>Regimen Category</strong></td>
<td>Evidence-Informed :</td>
</tr>
<tr>
<td></td>
<td>Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.</td>
</tr>
<tr>
<td><strong>Rationale and Uses</strong></td>
<td>For the treatment of patients with relapsed multiple myeloma and good performance status, who have received 1 to 3 prior treatments.</td>
</tr>
</tbody>
</table>

**Supplementary Public Funding**

- **carfilzomib**
  
  New Drug Funding Program (Carfilzomib (Doublet Therapy) - In Combination with Dexamethasone for Relapsed Multiple Myeloma)

- **dexamethasone**
  
  ODB - General Benefit (dexamethasone) ([ODB Formulary](#))

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B - Drug Regimen

Cycle 1:

- **carfilzomib** 20 mg /m² IV Days 1, 2
- **carfilzomib** 56 mg /m² IV Days 8, 9, 15, 16
- **dexamethasone** 20* mg /day IV / PO Days 1, 2, 8, 9, 15, 16, 22, 23

Cycle 2 and beyond:

- **carfilzomib** 56 mg /m² IV Days 1, 2, 8, 9, 15, 16
- **dexamethasone** 20* mg /day IV / PO Days 1, 2, 8, 9, 15, 16, 22, 23

^The dexamethasone dose should be reduced in elderly patients

*Outpatient prescription in 4 mg tablets for patients on PO route

C - Cycle Frequency

**REPEAT EVERY 28 DAYS**

Until disease progression or unacceptable toxicity.

D - Premedication and Supportive Measures

**Antiemetic Regimen:**  Low

**Other Supportive Care:**

Also refer to [CCO Antiemetic Summary](#)

**Carfilzomib:**

- Consider the use of antiviral prophylaxis during carfilzomib therapy to decrease the risk of herpes zoster reactivation.
• Thromboprophylaxis is recommended in patients being treated with carfilzomib in combination with dexamethasone. The choice of agent should be based on patient risk factors and clinical status.

• Hypertension should be well-controlled prior to initiation of treatment with carfilzomib.

• Adequate hydration is required prior to dosing in cycle 1, especially in patients at high risk for tumour lysis syndrome or renal toxicity. The total fluid volume may be adjusted as clinically indicated in patients with baseline or at high risk of cardiac failure.

• Cycle 1:
  ◦ oral fluids (30 mL/kg/day for 48 hours before start of cycle)
  ◦ 250-500 mL of IV fluid before and after each dose (if needed)

• Subsequent cycles:
  ◦ continue oral and/or IV hydration as needed

• Dexamethasone IV/PO should be given at least 30 minutes, but no more than 4 hours before carfilzomib.

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients with BSA > 2.2 m² should be dosed based on a maximum BSA of 2.2 m². Dose adjustments for carfilzomib do not need to be made for weight changes ≤ 20%.

Refer to carfilzomib drug monograph for additional details on dose modifications.

Dosage with toxicity

Dose levels

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Carfilzomib (mg/m²)</th>
<th>Dexamethasone* (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>-1</td>
<td>45</td>
<td>12</td>
</tr>
<tr>
<td>-2</td>
<td>36</td>
<td>8</td>
</tr>
<tr>
<td>-3</td>
<td>27</td>
<td>Discontinue</td>
</tr>
<tr>
<td>-4</td>
<td>Discontinue</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Dose Modifications for Hematological and Non-Hematological Toxicities:
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Carfilzomib Dose</th>
<th>Dexamethasone Dose**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>ANC &lt; 0.5 x 10⁹/L, febrile neutropenia or platelets &lt; 10 x 10⁹/L; thrombocytopenic bleeding</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; instance: hold until recovery* (and/or bleeding is controlled, fever resolves), and then restart at the same dose level. Subsequent instances: hold until recovery* (and/or bleeding is controlled); consider restarting at 1 dose level ↓.</td>
<td>N/A</td>
</tr>
<tr>
<td>Increased creatinine</td>
<td>Hold:</td>
<td>N/A</td>
</tr>
<tr>
<td>S&lt;sub&gt;Cr&lt;/sub&gt; ≥ 2 x baseline, or CrCl &lt; 15 mL/min (or CrCl decreases to ≤ 50% of baseline) or need for dialysis</td>
<td>• If attributable to carfilzomib, resume at 1 dose level ↓ when renal function has recovered to within 25% of baseline. • If not attributable to carfilzomib, may resume at physician’s discretion. If tolerated, the reduced dose may be increased to the previous dose.</td>
<td>N/A</td>
</tr>
<tr>
<td>Muscle weakness ≥ Grade 2</td>
<td>N/A</td>
<td>Hold until recovery to baseline. Resume at 1 dose level ↓. If persists, ↓ by one further dose level (8mg). If persists despite second reduction, discontinue.</td>
</tr>
<tr>
<td>Grade 3 or 4 cardiac events</td>
<td>Hold until resolved. Consider risk vs. benefit of restarting; resume at 1 dose level ↓.</td>
<td>N/A</td>
</tr>
<tr>
<td>Hypertensive crisis/emergency</td>
<td>Hold until resolves or under control. Consider the risk vs. benefit of restarting; consider restarting at 1 dose level ↓.</td>
<td>N/A</td>
</tr>
<tr>
<td>ARDS, ILD, pneumonitis, pulmonary hypertension, grade 3 or 4 dyspnea</td>
<td>Hold until resolves. Consider the risk vs. benefit of restarting.</td>
<td>N/A</td>
</tr>
<tr>
<td>Thrombotic microangiopathy</td>
<td>Hold and evaluate. Discontinue if confirmed.</td>
<td>N/A</td>
</tr>
<tr>
<td>(including TTP/HUS)</td>
<td>PRES</td>
<td>Hold and evaluate. Discontinue if confirmed.</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td><strong>All other drug related Grade 3 or 4 non-hematological toxicities</strong></td>
<td>Hold until resolved or at baseline. After resolution, if appropriate to reinitiate, consider restarting at 1 dose level ↓. If tolerated, the reduced dose may be increased to the previous dose.</td>
<td>For <strong>Edema (≥ grade 3)</strong>: Hold until recovery to baseline. Administer diuretics as needed. Resume at 1 dose level ↓. If persists, ↓ by one further dose level (8mg). If persists despite second reduction, discontinue. For <strong>Hyperglycemia</strong>: Hold until glucose ≤ Grade 2. Treat with insulin or other hypoglycemic agents as needed. If persists, ↓ by one dose level until recovery to ≤ Grade 2. For all other <strong>drug related Grade 3 or 4 non-hematological toxicities</strong>: Hold until recovery to baseline or ≤ Grade 2. Resume at 1 dose level ↓. 1st recurrence, hold until recovery to baseline or ≤ Grade 2. Resume at 2 dose level ↓ (8mg). 2nd recurrence, discontinue.</td>
</tr>
</tbody>
</table>

*Do not retreat until ANC ≥ 0.5 x 10⁹/L (or baseline values for febrile neutropenia) and platelets ≥ 10 x 10⁹/L with resolution of fever and bleeding

**Dexamethasone dose modifications referenced from ENDEAVOR trial.

**Hepatic Impairment**

In a pharmacokinetic study, carfilzomib AUC increased by 50% in patients with baseline mild or
The incidence of serious adverse events was higher in patients with hepatic impairment as well.

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Carfilzomib Starting Dose</th>
<th>Dexamethasone Starting Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (bilirubin &gt; 1-1.5 x ULN or AST &gt; ULN) or moderate (bilirubin &gt; 1.5-3 x ULN)</td>
<td>Reduce dose by 25%</td>
<td>No dosage adjustment necessary</td>
</tr>
<tr>
<td>Severe (bilirubin &gt; 3 x ULN)</td>
<td>No data</td>
<td></td>
</tr>
</tbody>
</table>

**Renal Impairment**

No dosage adjustment required for dexamethasone.

No dose adjustment is required for carfilzomib in patients with baseline renal impairment. For patients on dialysis receiving carfilzomib, administer dose after dialysis.

**Dosage in the Elderly**

There was a higher incidence of certain adverse effects (including cardiac failure) observed in patients ≥ 65 years of age, especially those more than 75 years, when carfilzomib was given in combination with lenalidomide and dexamethasone.

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Refer to carfilzomib drug monograph(s) for additional details of adverse effects

<table>
<thead>
<tr>
<th>Common (25-49%)</th>
<th>Less common (10-24%)</th>
<th>Uncommon (&lt; 10%), but may be severe or life-threatening</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Infusion related reaction (maybe severe)</td>
<td>• Nausea, vomiting • Musculoskeletal pain, weakness • Headache • Constipation • Peripheral neuropathy</td>
<td>• Cardiotoxicity • Venous thromboembolism • Arterial thromboembolism • Adult respiratory distress syndrome (ARDS) • Pneumonitis</td>
</tr>
<tr>
<td>• Diarrhea (maybe severe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypertension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Cough, dyspnea</td>
</tr>
<tr>
<td>Myelosuppression ± infection, bleeding</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Edema</td>
</tr>
<tr>
<td>Abnormal electrolyte(s)(K, Ca, PO4, Mg)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Creatinine increased</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Cataract</td>
</tr>
<tr>
<td>Tumor lysis syndrome (rare)</td>
</tr>
<tr>
<td>GI perforation (rare)</td>
</tr>
<tr>
<td>Thrombotic microangiopathy (rare) (includes TTP, HUS)</td>
</tr>
<tr>
<td>RPLS / PRES</td>
</tr>
</tbody>
</table>

**G - Interactions**

Refer to [carfilzomib](#) drug monograph(s) for additional details

- It is unknown whether carfilzomib is an inducer of CYP1A2, 2C8, 2C9, 2C19 and 2B6. Caution should be observed when combined with products which are substrates of these enzymes, including oral contraceptives. Carfilzomib does not induce, but may inhibit, CYP3A4/5.

- Caution with P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron) and monitor digoxin levels.

- Caution and consider non-hormonal method(s) of contraception as use of oral contraceptives or other hormonal methods of contraception may have reduced efficacy and may increase the risk of blood clots.

**H - Drug Administration and Special Precautions**

Refer to [carfilzomib](#) drug monograph(s) for additional details

**Administration:**

**Carfilzomib**

- Carfilzomib should be given as a 30 minute infusion.

- May further dilute dose in 50-100 mL D5W. Do not dilute in NS for IV administration.

- Carfilzomib should not be administered as an IV bolus. Maybe administered directly by IV infusion or in an IV bag.

- Flush line before and after carfilzomib administration with NS or D5W.
After reconstitution, gently swirl and/or invert the vial slowly for 1 minute. Do not shake.

If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear, colourless and free of visible particulates.

Stable in D5W. Do not mix with or administer as an infusion with other medications.

The time from reconstitution to administration should not exceed 24 hours.

Unreconstituted carfilzomib powder for injection should be stored in unopened vials at 2–8°C.

Dexamethasone

• Oral self-administration or may be given by IV route on carfilzomib clinic days.

• Give tablets with food, preferably in the morning.

Contraindications:

• Patients who have a hypersensitivity to these drugs or any of their components.

Other Warnings/Precautions:

• Use carfilzomib with caution in patients on a controlled sodium diet. Each mL contains 0.3 mmols (7 mg) of sodium.

• The risk of heart failure is increased in elderly patients (≥ 75 years). Patients with NYHA Class III/IV heart failure, recent MI, conduction abnormalities, angina or arrhythmias uncontrolled by medications were not eligible for carfilzomib-based clinical trials. These patients may be at greater risk of cardiac complications and should have their medical management optimized, including hypertension, prior to starting treatment with carfilzomib and monitored closely throughout.

• Use caution with driving or using machinery as fatigue, dizziness and a drop in blood pressure may occur with carfilzomib treatment.

Pregnancy and Lactation:

• Carfilzomib and dexamethasone is not recommended for use in pregnancy.

  ◦ Adequate contraception should be used by female patients and/or their male partners during carfilzomib treatment, and for 30 days after the last dose.

  ◦ Adequate contraception should be used by male patients and/or their female partners during carfilzomib treatment, and for 90 days after the last dose.
Breastfeeding is not recommended while taking carfilzomib.

Fertility effects: no information available for carfilzomib.

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Blood pressure; Baseline and before each treatment
- CBC with differential; Baseline and before each treatment week
- Electrolytes, including potassium; Baseline and before each cycle
- Liver function tests; Baseline and before each cycle
- Renal function tests; Baseline and before each cycle
- Clinical toxicity assessment for GI, skin, respiratory, cardiovascular, and neurological effects as well as infusion reactions, bleeding, infection, tumour lysis and venous or arterial thromboembolism; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Blood glucose levels; Baseline and regular
- ECG; Baseline; repeat if arrhythmia suspected
- LVEF assessment (especially in patients ≥ 75 years, or those at greater risk for cardiac complications); Baseline and as clinically indicated

J - Administrative Information

Dexamethasone PO - Outpatient prescription for home administration
Approximate Patient Visit

First cycle: 12 hours (includes pre- and post-IV hydration); Cycles 2 and onwards: 3 hours (if no IV hydration)

Pharmacy Workload (average time per visit) 19.850 minutes
Nursing Workload (average time per visit) 42.417 minutes

**K - References**

Carfilzomib drug monograph, Cancer Care Ontario.


**PEBC Advice Documents or Guidelines**

- Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

September 2019 Added note on dexamethasone dose in the elderly

**M - Disclaimer**

**Regimen Abstracts**

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Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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