Regimen Monograph

A - Regimen Name

CARFDEXA Regimen

Carfilzomib-Dexamethasone

Disease Site
Hematologic
Multiple Myeloma

Intent
Palliative

Regimen Category
Evidence-Informed :

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.

Rationale and Uses
For the treatment of patients with relapsed multiple myeloma and good performance status, who have received 1 to 3 prior treatments

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

†Patients with BSA > 2.2 m^2 should be dosed based on a maximum BSA of 2.2 m^2.

^The dexamethasone dose should be reduced in elderly patients.

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

- Also refer to CCO Antiemetic Summary

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Other Supportive Care:

Carfilzomib:

- Consider the use of antiviral prophylaxis during carfilzomib therapy to decrease the risk of herpes zoster and HBV reactivation.
- Consider thromboprophylaxis in patients being treated with carfilzomib. The choice of agent should be based on patient risk factors and clinical status.
- Patients at risk of tumour lysis syndrome (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.
- 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), and
        - IV fluids: 250-500 mL before each dose, and if needed after each dose
    - Subsequent cycles:
        - Continue oral and/or IV hydration as needed
- On carfilzomib treatment days, dexamethasone IV/PO should be given at least 30 minutes, but no more than 4 hours before carfilzomib.

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E - Dose Modifications

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

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

Carfilzomib doses do not need to be re-calculated for weight changes ≤ 20%.

Dosage with toxicity

Dose Level	Carfilzomib Dose (mg/m^2)	Dexamethasone Dose (mg)
0	56	20
-1	45	12
-2	36	8
-3	27	Discontinue
-4	Discontinue	N/A

Dexamethasone doses may be held or reduced for dexamethasone-related adverse events (e.g. hyperglycemia, fluid retention) to improve tolerability. Also refer to the ENDEAVOR trial for dexamethasone dose modifications.

Toxicity	Carfilzomib Dose
ANC < 0.5 x 10^9/L, febrile neutropenia or platelets < 10 x 10^9/L ; thrombocytopenic bleeding	1st occurrence: Hold* until recovery (and fever resolves, bleeding is controlled), and then restart at the same dose level. Subsequent occurrences: Hold* until recovery (and fever resolves, bleeding is controlled); consider restarting at 1 dose level ↓.
Serum creatinine ≥ 2 x baseline, or CrCl < 15 mL/min (or CrCl decreases to ≤ 50% of baseline) or need for dialysis	Hold: • 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.

Grade 3 or 4 cardiac events	Hold until resolved. Consider risk vs. benefit of restarting; resume at 1 dose level ↓.
Hypertensive crisis/emergency	Hold until resolved or under control. Consider the risk vs. benefit of restarting; consider restarting at 1 dose level ↓.
Tumour lysis syndrome	Hold until resolved. Manage promptly.
ARDS, ILD, pneumonitis, pulmonary hypertension, Grade 3 or 4 dyspnea	Hold until resolved. Consider the risk vs. benefit of restarting.
Thrombotic microangiopathy (including TTP/HUS)	Hold and evaluate. Discontinue if confirmed.
PRES	Hold and evaluate. Discontinue if confirmed.
PML	Hold and evaluate. Discontinue if confirmed.
Other drug related Grade 3 or 4 non-hematological toxicities	Hold until resolved or at baseline. Then, if appropriate to reinitiate, consider restarting at 1 dose level ↓ If tolerated, the reduced dose may be increased to the previous dose.

*Do not restart until ANC ≥ 0.5 x 10^9/L (or baseline values for febrile neutropenia) and platelets ≥ 10 x 10^9/L with resolution of fever and bleeding.

Hepatic Impairment

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

Hepatic Impairment	Carfilzomib Starting Dose	Dexamethasone Starting Dose
Mild (bilirubin >1 - 1.5 x ULN or AST > ULN) or Moderate (bilirubin >1.5 - 3 x ULN)	Reduce dose by 25%.	No dosage adjustment necessary.
Severe (bilirubin > 3 x ULN)	No data.	

Renal Impairment

No dosage adjustment required for dexamethasone.

No starting 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 were no differences in effectiveness of carfilzomib, when given in combination with dexamethasone, in any of the studied age groups. There was a higher incidence of certain adverse effects (including cardiac failure) observed in patients ≥ 65 years of age, especially in those ≥ 75 years of age.

The dexamethasone dose should be reduced in elderly patients.

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F - Adverse Effects

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

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea (may be severe) • Infusion related reaction (may be severe) • Hypertension (may be severe) • Fatigue (may be severe) • Cough, dyspnea • Myelosuppression ± infection, bleeding (including viral reactivation) (may be severe) • Insomnia • Edema	• Nausea, vomiting • Musculoskeletal pain, weakness • Headache • Constipation • Peripheral neuropathy • Abnormal electrolyte(s) (↓ K, ↓ Ca, ↓ PO4) • Venous thromboembolism • Hyperglycemia • Abdominal pain • Creatinine increased (may be severe)	• Cardiotoxicity • Arterial thromboembolism • QT interval prolonged • Pericarditis • Adult respiratory distress syndrome (ARDS) • Pneumonitis • Pulmonary hypertension • Cataract • Tumour lysis syndrome • GI perforation • GI obstruction • Pancreatitis • Hepatic failure • Thrombotic microangiopathy (including TTP, HUS) • RPLS / PRES • PML

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G - Interactions

Refer to carfilzomib drug monograph(s) for additional details.

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

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H - Drug Administration and Special Precautions

Refer to carfilzomib drug monograph(s) for additional details.

Administration: carfilzomib

- Reconstitute vials with Sterile Water for Injection. Volume for reconstitution depends on vial size; refer to product monograph for instructions.
- 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.
- May further dilute dose in 50-100 mL D5W. Do not dilute in NS for IV administration.
- DO NOT administer as an IV bolus. May be administered directly by IV infusion or in an IV bag.
- Do not mix with or administer as an infusion with other medications.
- Infuse over 30 minutes. Keep infusion time consistent during treatment regardless of any dose modifications.
- Flush line with NS or D5W before and after carfilzomib administration.
- Store unopened vials refrigerated at 2–8°C in original package and protected from light. Reconstituted or diluted drug do not require protection from light during administration.

Administration: dexamethasone

- Oral self-administration or may be given by IV route on carfilzomib clinic days.
- Dexamethasone IV/PO should be given at least 30 minutes, but no more than 4 hours before carfilzomib.
- Give tablets with food, preferably in the morning.

Contraindications

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

Warnings/Precautions

- Use carfilzomib with caution in patients on a controlled sodium diet. Each mL of the reconstituted carfilzomib solution 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.
- Patients should use caution when driving or using machinery as fatigue, dizziness and a drop in blood pressure may occur with carfilzomib treatment.

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- 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.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects:
    - Carfilzomib: Unknown

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC with differential; Baseline and before each cycle; more frequently as clinically indicated
- Liver function tests; Baseline and before each cycle
- Renal function tests; Baseline and before each cycle
- Electrolytes, including potassium; Baseline and before each cycle
- Blood pressure; Baseline and before each treatment
- Blood glucose levels; Baseline and as clinically indicated
- Clinical toxicity assessment for infusion reactions, bleeding, infection, TLS, thromboembolism, GI, skin, respiratory, ophthalmic, cardiovascular and neurological effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- ECG; Baseline and as clinically indicated
- LVEF assessment (especially in patients ≥ 75 years, or those at greater risk for cardiac complications); Baseline and as clinically indicated

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J - Administrative Information

Dexamethasone PO - Outpatient prescription for home administration

Approximate Patient Visit	1 to 2 hours
Pharmacy Workload (average time per visit)	19.850 minutes
Nursing Workload (average time per visit)	42.417 minutes

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K - References

Carfilzomib drug monograph, Ontario Health (Cancer Care Ontario).

Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2016;17:27-38.

PEBC Advice Documents or Guidelines

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

January 2024 Updated drug regimen, premedication/supportive measures, dose modifications, and monitoring sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not

undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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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