Regimen Monograph

A - Regimen Name

CARFDEXALENA Regimen

Carfilzomib-Dexamethasone-Lenalidomide

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 or refractory multiple myeloma, with good performance status and adequate renal function, who have received at least 1 prior treatment.

Refer to NDFP form for details on other funding criteria, especially for patients who were previously on lenalidomide-based or bortezomib-based treatments.

Supplementary Public Funding

carfilzomib
New Drug Funding Program (Carfilzomib (Triplet Therapy) - In Combination with Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma) (Funded by NDFP for up to 18 cycles)

dexamethasone
ODB - General Benefit (dexamethasone) (tablets)

lenalidomide
ODB Limited Use (lenalidomide - For the treatment of patients with multiple myeloma, who are deemed to be lenalidomide sensitive, and/or have not experienced progression while on a lenalidomide-based regimen in the treatment or maintenance setting, according to clinical criteria) (ODB Formulary) (Funded for second or third line)

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B - Drug Regimen

Cycle 1:

carfilzomib†	20 mg /m²	IV	Days 1, 2
carfilzomib†	27 mg /m²	IV	Days 8, 9, 15, 16
dexamethasone^	40 mg /day	IV / PO	Days 1, 8, 15, 22
lenalidomide*	25 mg /day	PO	Days 1 to 21

Cycles 2 to 12:

carfilzomib†	27 mg /m²	IV	Days 1, 2, 8, 9, 15, 16
dexamethasone^	40 mg /day	IV / PO	Days 1, 8, 15, 22
lenalidomide*	25 mg /day	PO	Days 1 to 21

(Continued on next page)

Cycles 13 to 18[#]:

carfilzomib[†]	27 mg /m²	IV	Days 1, 2, 15, 16
dexamethasone^	40 mg /day	IV / PO	Days 1, 8, 15, 22
lenalidomide*	25 mg /day	PO	Days 1 to 21

Cycle 19 onwards[#] (Report as regimen code DEXALENA):

dexamethasone^	40 mg /day	IV / PO	Days 1, 8, 15, 22
lenalidomide*	25 mg /day	PO	Days 1 to 21

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

^In elderly patients, the dexamethasone dose should be reduced (i.e. to 20 mg once weekly).

*Lenalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

[#]per Stewart 2015

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Unless disease progression or unacceptable toxicity occurs.

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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:

- Patients must be registered and meet all conditions of a controlled distribution program, including contraception, for lenalidomide.
- Patients at risk of tumour lysis syndrome (i.e. high tumour burden) should have appropriate prophylaxis and be monitored closely.
- Prophylaxis for venous thromboembolism is recommended. The choice of agent should be based on patient risk factors and clinical status.
- Careful consideration and monitoring must be taken with erythropoietin stimulating agents (ESAs), since the concomitant use of ESAs with lenalidomide may potentiate the risk of thrombosis. RBC or platelet transfusions with lenalidomide dose reductions/interruptions may be appropriate in severe / symptomatic anemia or thrombocytopenia.
- Consider the use of antiviral prophylaxis during carfilzomib therapy to decrease the risk of herpes zoster and HBV reactivation.
- Adequate hydration is required prior to carfilzomib 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.

Women of child bearing potential must have two negative pregnancy tests before initiating treatment.

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%.

Optimal control of thyroid function is recommended prior to starting treatment with lenalidomide.

Dosage with toxicity

Dose Level	Carfilzomib (mg/m^2)	Lenalidomide (mg)	Dexamethasone (mg)
0	27	25	40
-1	20	15	20
-2	15	10	12
-3	Discontinue	5	Discontinue

Dexamethasone doses may be held or reduced for dexamethasone-related adverse events (e.g. hyperglycemia, fluid retention) to improve tolerability.

Hematologic toxicities

Toxicity (counts x 10^9/L)	Carfilzomib	Lenalidomide
1st occurrence: platelets < 30*	If platelets 10-30 without evidence of bleeding, maintain full dose.	Hold until platelets ≥ 30, then resume at one dose level reduction.
	If evidence of bleeding or platelets < 10, hold until platelets ≥ 10 and/or bleeding is controlled, then resume at full dose.	

Subsequent occurrences: platelets < 30*	If platelets 10-30 without evidence of bleeding, maintain full dose.	Hold until platelets ≥ 30, then resume at one further dose level reduction.
	If evidence of bleeding or platelets < 10, hold until platelets ≥ 10 and/or bleeding is controlled, then resume at one dose level reduction.	
1st occurrence: ANC < 1	If ANC 0.5-1, continue at full dose.	Hold, add G-CSF, and resume at full dose when ANC ≥ 1.
	If ANC < 0.5, hold until ANC ≥ 0.5, then resume at full dose.	
Subsequent occurrences: ANC < 1	If ANC 0.5-1, continue at full dose.	Hold, add G-CSF, and resume at one dose level reduction when ANC ≥ 1.
	If ANC < 0.5, hold until ANC ≥ 0.5, then resume at one dose level reduction.	

*A lower threshold of 20 x 10^9/L may be considered for lenalidomide dose reductions for patients with myeloma involvement in the bone marrow > 50%.

Non-hematologic toxicities

Toxicity	Carfilzomib	Lenalidomide
Grade 2 to 3 rash	Grade 3: If related to carfilzomib, follow actions for ≥ Grade 3 non-hematologic toxicity.	Hold or consider discontinuing.
Angioedema OR Grade 4 skin rash OR Exfoliative or bullous rash OR Suspected Stevens Johnson Syndrome, Toxic epidermal necrolysis or DRESS	Discontinue.	
Grade 3 or 4 cardiac events	Hold until resolved. Consider risk vs. benefit of restarting; resume at one dose level reduction.*	Hold until resolved. Consider risk vs. benefit of restarting; resume at one dose level reduction.
Hypertensive crisis/emergency	Hold until resolved or under control. Consider the risk vs. benefit of restarting; consider dose reduction.*	n/a
Tumour lysis syndrome	Hold until resolved. Managed promptly.	Hold until resolved.
ARDS, ILD, pneumonitis, pulmonary hypertension, Grade 3 or 4 dyspnea	Hold until resolved. Consider the risk vs. benefit of restarting.	For suspected pneumonitis, hold and investigate; discontinue if confirmed.
Thrombotic microangiopathy (including TTP/HUS)	Hold and evaluate; discontinue if confirmed.	n/a

PRES	Hold and evaluate; discontinue if confirmed.	n/a
PML	Hold and evaluate; discontinue if confirmed.	n/a
Increased LFTs	n/a	Hold until returns to baseline. Consider dose reduction when resuming.
CrCl < 30 mL/min	Refer to row below.	Hold until CrCl recovers to baseline, then resume at one dose level reduction. If recurs, reduce dose to 15 mg q 48 hours. If dialysis required, reduce dose to 5 mg once daily and administer after dialysis.
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	Refer to row above.
Solid organ transplant rejection	Discontinue.	

Other drug related Grade 3 or 4 non-hematologic toxicity[1,2]	Hold until resolved to ≤ Grade 2 or baseline; then consider resuming at one dose level reduction. If tolerated, the reduced dose may be increased to the previous dose.	Hold until resolved to ≤ Grade 2 or baseline; then resume at one dose level reduction.

[1]In the event of possible drug-related non-hematologic toxicity, the physician should determine causality to the affected agent(s) and the recommended action(s) for each should be instituted.

[2]Carfilzomib, lenalidomide and dexamethasone do not need to be held in the following cases: grade 3 nausea, vomiting or diarrhea (unless persisting more than 3 days with adequate treatment of antiemetics or antidiarrheals); grade 3 dexamethasone-related hyperglycemia; grade 3 fatigue (unless persisting for > 14 days).

[*]Discontinue in patients receiving 15 mg/m^2.

Hepatic Impairment

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

Renal Impairment

Refer to Dosage with Toxicity section for renal toxicity during treatment.

Pre-existing renal impairment

Patients with a CrCl < 50 mL/min were excluded from the pivotal Phase 3 trial.

Creatinine Clearance (mL/min)	Carfilzomib Starting Dose	Lenalidomide Starting Dose†	Dexamethasone Starting Dose
≥ 60	No dose adjustment is required for carfilzomib in patients with baseline renal impairment. For patients on dialysis receiving carfilzomib, administer dose after dialysis.	No change.	No change.
30 to 59		Reduce dose to 10 mg daily.^	
< 30		Reduce dose to 15 mg q 48 hours. If dialysis required, reduce to 5 mg daily and give post-dialysis.	

†Maintain a 3 weeks on, 1 week off schedule (q28 days).

^May be escalated to 15 mg q24h after 2 cycles if patient is not responding to treatment and is tolerating the drug.

Dosage in the Elderly

There were no differences in effectiveness of carfilzomib, in combination with lenalidomide and 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 incidences of serious and non-serious adverse events are significantly higher in patients > 65 years with lenalidomide and this may be related to renal impairment. Monitor elderly patients closely, especially cardiac and renal function. Dose modification based on degree of renal impairment is required.

In elderly patients, the dexamethasone dose should be reduced (i.e. to 20 mg once weekly).

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F - Adverse Effects

Refer to carfilzomib, lenalidomide and dexamethasone 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 • Myelosuppression ± infection (includes atypical, viral reactivation), bleeding (may be severe) • Infusion-related reactions • Cough, dyspnea • Fatigue • Abnormal electrolyte(s) (↓ K, ↓ Ca, ↓ PO4, ↓ Mg) • Musculoskeletal pain (including spasms)	• Constipation • Nausea, vomiting • Insomnia • Edema - limbs • Hypertension (may be severe) • Venous thromboembolism (may be severe) • Abdominal pain • Peripheral neuropathy • Dizziness • Headache • Hyperglycemia • Rash (may be severe; SJS, TEN, DRESS) • Anorexia • Blurred vision, cataract	• Atrial fibrillation • Arterial thromboembolism • Cardiotoxicity • Increased QTc • Pericarditis • Tumour lysis syndrome • Thrombotic microangiopathy (includes TTP, HUS) • Hemolysis • Hypersensitivity • GI perforation • GI obstruction • Hepatoxicity • Pancreatitis • Cholecystitis • Renal failure • Adult respiratory distress syndrome (ARDS) • Pneumonitis • Pulmonary hypertension • RPLS / PRES • PML • Rhabdomyolysis • Hyper/hypothyroidism • Adrenal insufficiency • GVHD or transplant rejection • Solid organ transplant rejection • Secondary malignancy

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G - Interactions

Refer to carfilzomib, lenalidomide and dexamethasone 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.
- Lenalidomide can increase the concentration of digoxin. Use caution and monitor digoxin levels.
- Lenalidomide increases risk of thromboembolic events and would have an additive effect if co-administered with other thromboembolic agents.

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H - Drug Administration and Special Precautions

Refer to carfilzomib, lenalidomide and dexamethasone 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. Maybe administered directly by IV infusion or in an IV bag.
- Do not mix with or administer as an infusion with other medications.
- Infuse over at least 10 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: lenalidomide

- Drug available by outpatient prescription in pharmacy registered with a controlled distribution program
- Oral self-administration; swallow capsules whole; they should not be broken, chewed, or opened. Do not extensively handle the capsules.
- Give capsules preferably with water, either with or without food. Do not remove from blister packs until ready to take the dose.
- People who could become pregnant, or who plan to become pregnant can handle lenalidomide capsules if they are using latex gloves.
- If a dose is missed, it may be taken up to 12 hours after the time it is normally taken. Otherwise, skip this and take the next dose on the following day at its usual scheduled time.
- Store capsules at room temperature (15 to 30°C).

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 (including severe rash) to these drugs, pomalidomide, thalidomide or any ingredient in the formulation
- Pregnant or breastfeeding people
- Patients at risk of being pregnant and patients who can get someone pregnant who do not comply with contraception requirements (see Pregnancy section in lenalidomide drug monograph for additional details)

Warnings/Precautions

Carfilzomib

- Use with caution in patients on a controlled sodium diet. Each mL of the reconstituted carfilzomib solution contains 0.3 mmol (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 in patients with a CrCl < 50 mL/min as they were excluded from the pivotal Phase 3 trial.
- Patients should use caution when driving or using machinery as fatigue, dizziness and a drop in blood pressure may occur with treatment.

Lenalidomide

- Contains lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.
- Patients should not donate blood while taking lenalidomide and for **4 weeks** after stopping therapy to prevent fetal exposure via transfusion of pregnant women.
- Use with caution and consider venous thromboembolism prophylaxis when used in combination with corticosteroids or thrombogenic agents, such as hormones and erythropoietin (see Adverse Effects section in lenalidomide drug monograph for additional details).
- Exercise caution in patients with risk factors for arterial thromboembolism (e.g. hypertension and hyperlipidemia), or risk factors for atrial fibrillation (e.g. electrolyte abnormalities, pre-existing heart disease, hypertension, infection).
- Use with caution in patients with high tumour burden; monitor closely and use appropriate precautions for tumour lysis syndrome.
- Use with caution and monitor closely in patients with previous viral infections such as HBV and herpes zoster.

Pregnancy/Lactation

- This regimen is **contraindicated in pregnancy and in patients who do not comply with the contraception conditions of the controlled distribution program for lenalidomide.** Refer to the lenalidomide product monograph for details on contraception.
- Adequate contraception must 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.
- Breastfeeding is **contraindicated** 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
  - Lenalidomide: Unlikely

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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, 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
- Thyroid function tests; Baseline and as clinically indicated
- Blood glucose levels; Baseline and as clinically indicated

- Specific to lenalidomide: Pregnancy testing requirements for women of child-bearing potential; Before starting treatment and as indicated by the controlled distribution program
- Cancer screening for occurrence of second primary malignancy; assess risk prior to starting treatment, then at each visit or as clinically indicated
- Clinical toxicity assessment of fatigue, infusion reactions, hypersensitivity, bleeding, infection (including viral reactivation), arterial or venous thromboembolism, TLS, GVHD and organ transplant rejection (if applicable), GI, skin, respiratory, ophthalmic, cardiovascular, neurological, and steroid-related 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
- INR in patients receiving warfarin; 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

lenalidomide, 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, lenalidomide drug monographs, Ontario Health (Cancer Care Ontario).

Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, Lenalidomide, and Dexamethasone for Relapsed Multiple Myeloma. N Engl J Med. 2015;372:142-52.

PEBC Advice Documents or Guidelines

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

January 2024 Modified Dose modifications, pregnancy/lactation, 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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