Drug Monograph

A - Drug Name

carfilzomib

COMMON TRADE NAME(S): Kyprolis®

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B - Mechanism of Action and Pharmacokinetics

Carfilzomib is a proteasome inhibitor that irreversibly binds to the N terminal threonine containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Inhibition of the ubiquitin-proteasome pathway affects multiple signaling cascades within the cell, resulting in apoptosis.

Distribution	Rapid distribution to tissues	
	PPB	97%
	Cross blood brain barrier?	No
Metabolism	Carfilzomib is rapidly and extensively metabolized via peptidase and epoxide hydrolase activity.	
	Inactive metabolites	Yes
Elimination	Carfilzomib is eliminated primarily via metabolism with subsequent excretion of predominantly inactive metabolites in urine.	
	Half-life	Doses ≥ 15 mg/m^2: ≤ 1 hour on day 1 of cycle 1

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C - Indications and Status

Health Canada Approvals:

- Multiple myeloma

Refer to the product monograph for a full list of approved indications.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: None

The following table lists adverse effects that occurred in ≥ 5% of patients in a phase III trial comparing carfilzomib and dexamethasone therapy (twice weekly dosing) versus bortezomib and dexamethasone therapy. Severe adverse events from other studies or post-marketing may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (1%)	I E
	Cardiotoxicity (6%)	E
	Hypertension (32%) (15% severe, including < 1% hypertensive crisis/emergency)	I E
	Pericarditis (rare)	E
	Pulmonary hypertension (2%)	E
	QT interval prolonged (rare)	E
	Venous thromboembolism (13%)	E D
Dermatological	Rash (9%)	I E
Gastrointestinal	Abdominal pain (11%)	I E
	Constipation (16%)	E
	Diarrhea (36%) (4% severe)	I E

	Dyspepsia (8%)	E
	GI obstruction (rare)	E
	GI perforation (rare)	E
	Nausea, vomiting (24%)	I
General	Edema - limbs (25%)	E
	Fatigue (32%) (7% severe)	E
Hematological	Myelosuppression ± infection, bleeding (32%) (12% severe) (including viral reactivation)	E
	Thrombotic microangiopathy (rare) (including TTP, HUS)	E
Hepatobiliary	Hepatic failure (<1%)	E
	↑ LFTs (5%)	E
	Pancreatitis (rare)	E
Hypersensitivity	Infusion related reaction (34%) (may be severe)	I
Metabolic / Endocrine	Abnormal electrolyte(s) (13%) (including ↓ K, ↓ Ca, ↓ PO4)	E
	Hyperglycemia (12%)	E
	Hyperuricemia (7%)	E
	Tumor lysis syndrome (1%)	E
Musculoskeletal	Muscle weakness (10%)	E
	Musculoskeletal pain (23%) (including spasms)	E
Nervous System	Anxiety (4%)	E
	Dizziness (9%)	I E
	Headache (21%)	E
	Insomnia (27%)	I E
	Leukoencephalopathy (PML - rare)	E
	Peripheral neuropathy (16%) (including hypoesthesia)	E
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
Ophthalmic	Cataract (7%)	E
Renal	Creatinine increased (11%) (1% severe)	E
	Renal failure (10%) (6% severe)	E
Respiratory	Acute respiratory distress syndrome (ARDS) (2%)	E
	Cough, dyspnea (32%) (6% severe)	E
	Pneumonitis (rare)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for carfilzomib include diarrhea, infusion related reaction, cough, dyspnea, fatigue, hypertension, myelosuppression ± infection, bleeding, insomnia, edema - limbs, nausea, vomiting and musculoskeletal pain.

Infusion-related reactions are common when carfilzomib is given as a bolus, but are less common and less severe as long as appropriate infusion time, adequate hydration and pre-medication are given. These reactions can occur immediately following or up to 24 hours after carfilzomib administration and may be life-threatening. Ensure patients are adequately hydrated and given dexamethasone prior to carfilzomib to reduce the incidence and severity of reactions.

Patients at risk for **tumour lysis syndrome** should be well hydrated prior to administration of carfilzomib with appropriate prophylaxis and clinical monitoring.

A new onset or exacerbation of **heart failure** has occurred following carfilzomib use. Fatal outcomes have been reported with heart failure and myocardial infarction (MI). All patients should be closely monitored for evidence of volume overload, especially those at risk for heart failure.

Infections, including serious and fatal events, have been reported. **Cytomegalovirus (CMV) chorioretinitis** and **hepatitis B virus (HBV) reactivation** have been reported. Consult an infection specialist for patients who test positive for HBV infection prior to or during treatment. Consider risks and benefits when resuming treatment after HBV reactivation.

Progressive multifocal leukoencephalopathy (PML) has been reported in patients with prior or concomitant immunosuppressive therapy. Monitor for any new or worsening neurologic, cognitive or behavioral signs or symptoms.

Myelosuppression is common. **Thrombocytopenia** may be expected with platelet nadirs observed on Day 8 or Day 15 of each 28-day cycle, with usual recovery to baseline counts by the start of the next cycle. Cases of **hemorrhage** (including GI, intracranial and pulmonary), thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome have been reported, some of which have been fatal.

Acute Respiratory Distress Syndrome (ARDS) and pulmonary disease such as pneumonitis and interstitial lung disease have been reported in patients receiving carfilzomib, some of which have been fatal. Patients should be closely monitored and promptly investigated for any new onset pulmonary findings.

Renal failure (including fatal cases) has been reported and the risk is higher in patients with renal dysfunction at baseline.

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E - Dosing

Refer to protocol by which patient is being treated.

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

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.

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

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.

*Oral and/or IV hydration is not required on the days when IV daratumumab is administered with carfilzomib.

On carfilzomib treatment days, dexamethasone IV/PO should be given at least 30 minutes, but no more than 4 hours before carfilzomib.

Adults:

Patients with a BSA > 2.2 m^2 should be dosed based upon a maximum BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes ≤ 20%.

Combination (with dexamethasone - once weekly dosing)

Cycle 1: *(28-day cycle)*

Intravenous: 20 mg/m^2 Day 1, and if tolerated,

70 mg/m^2 days 8 and 15

Cycles 2 and beyond:

Intravenous: 70 mg/m^2 Days 1, 8, and 15

Q28 days

Combination (with dexamethasone - twice weekly dosing)

Cycle 1: *(28-day cycle)*

Intravenous: 20 mg/m^2 Days 1 & 2, and if tolerated,

56 mg/m^2 days 8, 9, 15 and 16

Cycles 2 and beyond:

Intravenous: 56 mg/m^2 Days 1, 2, 8, 9, 15 and 16

Q28 days

Other Combination Therapies

Various dosing and schedules are used depending on the regimen. Refer to the product monograph or related regimen monographs for details.

Dosage with Toxicity:

Dose levels may vary from those listed in the table below, depending on the regimen. Refer to the product monograph or related regimen monographs for details.

Dose Level	Carfilzomib Dose (mg/m^2) Once Weekly in CARFDEXA	Carfilzomib Dose (mg/m^2) Twice Weekly in CARFDEXA
0	70	56
-1	56	45
-2	45	36
-3	36	27
-4	Discontinue	Discontinue

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), then restart at the same dose level. Subsequent occurrences: Hold* until recovery (and fever resolves, bleeding is controlled); consider restart 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 resuming 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 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.

Dosage with 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
Mild (bilirubin >1 - 1.5 x ULN or AST > ULN) or Moderate (bilirubin >1.5 - 3 x ULN)	Reduce dose by 25%
Severe (bilirubin > 3 x ULN)	No data

Dosage with Renal Impairment:

No starting dose adjustment is required 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, in combination with either dexamethasone or 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.

Dosage based on gender:

There is no evidence to suggest that gender affects the pharmacokinetics of carfilzomib.

Dosage based on ethnicity:

Heart failure was observed more frequently in Asian patients treated with carfilzomib.

Children:

The safety and effectiveness of carfilzomib in children have not been established.

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F - Administration Guidelines

- 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 for regimens with a usual dose of 56 mg/m^2 and 70 mg/m^2. Regimens with a usual dose of 27 mg/m^2 must be infused 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.
- If a dose is missed, a minimum of 5 days between doses is required for once weekly dosing.
- 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.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Use 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 with a CrCl < 50 mL/min were excluded from the pivotal Phase 3 trial of carfilzomib combined with lenalidomide and dexamethasone.
- Patients should use caution when driving or using machinery as fatigue, dizziness and a drop in blood pressure may occur with treatment.

Other Drug Properties:

- Carcinogenicity: Unknown
  Carcinogenicity studies have not been conducted.

Pregnancy and Lactation:

- Clastogenicity: Yes
- Mutagenicity: No
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Teratogenicity: Unknown
  Carfilzomib is not recommended for use in pregnancy.
  - Adequate contraception should be used by patients who can become pregnant and their partners during treatment, and for at least **30 days** after the last dose.
  - Adequate contraception should be used by patients who produce sperm and their partners during treatment, and for at least **90 days** after the last dose.

  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.
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Unknown

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H - Interactions

The pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 or P-gp inhibitors and inducers.

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.

AGENT	EFFECT	MECHANISM	MANAGEMENT
P-glycoprotein substrates (i.e. verapamil, digoxin, morphine, ondansetron)	↑ substrate concentration and/or toxicity	Carfilzomib is a P-glycoprotein inhibitor (in vitro)	Caution
Oral contraceptives	↓ concentration and/or efficacy of contraceptives	Unknown	Caution; consider alternative method of contraception
Oral contraceptives or other hormonal methods of contraception	↑ risk of blood clots	Additive	Caution; consider non-hormonal method of contraception

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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

Monitor Type	Monitor Frequency
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
Clinical toxicity assessment for infusion reactions, bleeding, infection, TLS, thromboembolism, GI, skin, respiratory, cardiovascular and neurological effects	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
LVEF assessment (especially in patients ≥ 75 years, or those at greater risk for cardiac complications)	Baseline and as clinically indicated
ECG	Baseline and as clinically indicated
Blood glucose levels	Baseline and as clinically indicated

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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Carfilzomib (Doublet Therapy) - In Combination with Dexamethasone for Relapsed Multiple Myeloma
- Carfilzomib (Triplet Therapy) - In Combination with Lenalidomide and Dexamethasone for Relapsed Multiple Myeloma
- Isatuximab and Carfilzomib - In Combination with Dexamethasone for Relapsed or Refractory Multiple Myeloma

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K - References

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

Prescribing Information: Kyprolis ® (carfilzomib). Amgen Inc. 03/2021.

Product Monograph: Kyprolis ® (carfilzomib). Amgen Canada Inc. July 25, 2023.

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

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L - Disclaimer

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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