DRUG NAME: Carfilzomib

SYNONYM(S): L01XX45[1]

COMMON TRADE NAME(S): KYPROLIS®

CLASSIFICATION: molecular targeted therapy

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Carfilzomib is an irreversible inhibitor of the 20S core of the 26S proteasome, an enzyme responsible for degrading cellular proteins. Proteasome inhibition causes accumulation of polyubiquinated proteins, which induces cell cycle arrest and apoptosis. Because carfilzomib is an irreversible inhibitor of this enzyme, it exhibits a more sustained enzyme inhibition compared to bortezomib. Carfilzomib appears to have less off-target activity which may result in a lower incidence of adverse effects such as peripheral neuropathy than bortezomib. Carfilzomib is cell cycle phase-specific and leads to cell cycle arrest at the G_2-M phase.[2-7]

PHARMACOKINETICS:

Distribution	dose-dependent increase in C_{max} and AUC	
	cross blood brain barrier?[8]	no
	volume of distribution	28 L
	plasma protein binding	97%
Metabolism	rapid and extensive metabolism via peptidase cleavage and epoxide hydrolysis[9]	
	active metabolite(s)	none
	inactive metabolite(s)[2,8]	~21 metabolites; predominately M14, M15, M16
Excretion	rapidly cleared from systemic circulation	
	urine[9]	25%, primarily as metabolites
	feces[9]	negligible
	terminal half life	≤ 1 hour
	clearance	151-263 L/hour

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Multiple myeloma

Other uses:

Waldenström's macroglobulinemia[1]

*Health Canada approved indication

SPECIAL PRECAUTIONS

Caution:

- reconstituted product contains 7 mg of ***sodium*** per mL (0.3 mmol); consider sodium content in patients on a controlled sodium diet[2]
- risk of ***cardiotoxicity***; caution in patients with angina, arrhythmia, recent MI, conduction abnormalities, or pre-existing heart failure[2]

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- control ***hypertension*** prior to starting carfilzomib and monitor throughout treatment; hypertensive crisis and emergency have occurred[2]
- ***herpes zoster reactivation*** may occur; consider antiviral prophylaxis in patients with a history of herpes zoster infection[10]
- ensure ***adequate hydration*** prior to carfilzomib therapy, especially in patients at risk of tumour lysis syndrome or renal toxicity[11]
- ***dexamethasone premedication*** is recommended prior to every carfilzomib dose to reduce infusion reaction incidence and severity[11]

Special populations: Patients 75 years or older and patients of Asian descent may be at a ***greater risk of heart failure***.[12]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test. Carfilzomib is clastogenic in mammalian *in vitro* chromosome tests but not in other mammalian *in vivo* chromosome tests.[2]

Fertility: Formal fertility studies have not been conducted. No effects on reproductive tissues were noted in animal testing.[2]

Pregnancy: In animal studies, carfilzomib was not teratogenic during organogenesis, but did cause embryo-fetal toxicity (pre- and post-implantation loss and decreased fetal weights) when administered to animals at doses lower than the equivalent human doses. Female patients of childbearing potential should use effective contraception during therapy and for 30 days following treatment completion. Male patients should use effective contraception during treatment and for 90 days after discontinuation.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[13,14]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (27-56%, severe 12-25%)[4,9,15]
	febrile neutropenia (1%)
	leukopenia (6-11%, severe 3-5%)[4,15]
	lymphopenia (8-18%, severe 6-18%)[15,16]
	neutropenia (15-16%, severe 8-10%)[4,15]
	thrombocytopenia (27-38%, severe 9-25%)[15,17]; platelet nadir on day 8 and 15 of each cycle and recovery to baseline by the start of the next cycle
	thrombotic microangiopathy (<1%)[17]
cardiac (see paragraph following	cardiac arrhythmia (13%, severe 2%)
	cardiac failure (5-21%, severe 2-11%)[4,12,15]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
Side Effects table)	cardiomyopathy (2%, severe <1%)
	chest pain (3-8%)[4,16]
	myocardial infarction, ischemia (3%, severe 1%)[15,18]
eye	blurred vision (4%)[16]
	cataract (4%)[16]
gastrointestinal	*emetogenic potential:* low[19]
	abdominal pain (7%)[16]
	constipation (11-13%)[9,15]
	diarrhea (22-27%, severe 1%)[9,15]
	dyspepsia (7%, severe 1%)[16]
	hemorrhage (<1%)[2]; see paragraph following **Side Effects** table
	nausea (15-35%, severe 1%)[4,9,15]
	vomiting (10-17%, severe 1%)[9,15]
general disorders and administration site conditions	*extravasation hazard:* none[20]
	asthenia (15%, severe 2%)[9]
	fatigue (24-41%, severe 3-8%)[9,15]
	infusion site reaction (<10%)[9]
	peripheral edema (11-20%, severe <1%)[9,15]
	pyrexia (15-30%, severe 2-3%)[4,9,15]
hepatobiliary	hepatic failure (<1%); see paragraph following **Side Effects** table
immune system	***infusion reaction*** (43%, severe 4%)[2]; see paragraph following **Side Effects** table
infections and infestations	bronchitis (12%, severe 1%)[9]
	herpes virus infection (5%)
	nasopharyngitis (10%)[17]
	pneumonia (6-13%, severe 6-11%)[4,15]; sometimes fatal
	respiratory tract infection (7-19%, severe 1-3%)[9,15]
	urinary tract infection (7%, severe 2%)[16]
investigations	AST increase (13%, severe 3%)
	ALT increase (8%, severe 3%)
	creatinine increase (8-18%, severe 2-3%)[4,15]
metabolism and nutrition	appetite decrease (8-15, severe <1%)[17,18]
	hypercalcemia (11%, severe 4%)[4,15]
	hyperglycemia (severe 2-4%)[16]
	hyperuricemia (6%, severe 1%)[16]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypocalcemia (severe 2-4%)
	hypokalemia (14%, severe 2-4%)
	hypomagnesemia (14%)
	hyponatremia (severe 7%)
	hypophosphatemia (severe 5%)
	tumour lysis syndrome (<1%)
musculoskeletal and connective tissue	arthralgia (10%)[16]
	back pain (19%, severe 3%)[15,17]
	muscle spasms (10%, severe <1%)[9,16]
	musculoskeletal chest pain (8%)[16]
	myalgia (5%)[16]
nervous system	dizziness (8-11, severe 1%)[17,18]
	headache (15-24%, severe 1%)[9,15]
	intracranial hemorrhage (<1%)[9]; see paragraph following **Side Effects** table
	peripheral neuropathy (5-14%, severe 1%)[4,15]; including sensory and motor neuropathy
	posterior reversible encephalopathy syndrome (<1%)[9]; if suspected evaluate by neuro-radiological imaging
psychiatric	anxiety, depression (4%)[16]
	insomnia (13%)[17]
renal and urinary (see paragraph following **Side Effects** table)	***acute renal failure*** (5-10%, severe 4-8%)[4,15]
	renal failure (4-6%, severe 1-5%)[4,15]
respiratory, thoracic and mediastinal	cough (7-22%, severe 1%)[4,15]
	dyspnea (15-42%, severe 1-5%)[4,15]
	epistaxis (5%, severe 1%)[16]; see paragraph following **Side Effects** table
	hemorrhage (<1%)[2]; see paragraph following **Side Effects** table
	acute respiratory distress, acute respiratory failure, interstitial lung disease, pneumonitis (<1%)[9]; has been fatal
	pleural effusion (4%)
	pulmonary embolism (1%)
	pulmonary hypertension (2%); has been fatal
skin and subcutaneous tissue	rash (6%, severe 1%)[16]
vascular	deep vein thrombosis (4%, severe 1%)[16]
	flushing (5%)[16]
	hemorrhage (<1%)[2]
	hypotension (5%)[16]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hypertension (14-15%, severe 3-4%)[4,9,15]; including hypertensive emergency and crisis

Adapted from standard reference[15] unless specified otherwise.

Infusion reactions are common, but are generally low grade with dexamethasone premedication. Reactions can occur immediately following or within 24 hours of carfilzomib infusion. Symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, and/or angina. Adequate pre-hydration and premedication are recommended to decrease the incidence and intensity of reactions. Incremental starting doses and longer infusions for higher doses appear to mitigate the risk of reactions.[1,2]

Cardiotoxicity has been observed***,*** including new onset or worsening of pre-existing cardiac failure (e.g., pulmonary edema, decreased ejection fraction, congestive heart failure), myocardial ischemia, and infarction. Individuals at increased risk of cardiotoxicity include patients 75 years or older, patients of Asian descent, and patients with a prior history of heart failure, recent myocardial infarction, conduction abnormalities, or angina.[1,2,9,12,21] Infusion durations of 10 minutes have been associated with an increased risk of cardiotoxicity when used for doses greater than 27 mg/m^2 and should be avoided for these regimens.[22] Monitor patients for volume overload and tailor fluid requirements as necessary in patients at high risk of or having pre-existing cardiac failure. During treatment, monitor patients for clinical signs and symptoms of cardiac failure/ischemia. Withhold carfilzomib until recovery for grade 3 or 4 cardiac adverse events and restart at a reduced dose if appropriate.[1,2,9,21]

Hepatic toxicity and ***hepatic failure***, including fatal cases, have been reported. Carfilzomib may cause elevation of liver enzymes and may require dose reduction or temporary interruption of therapy.[2]

Fatal and serious ***hemorrhage*** may occur, including gastrointestinal, pulmonary, and intracranial hemorrhage. Serious cases of epistaxis have also been reported. Spontaneous bleeding may be experienced by patients with low or normal platelets, as well as by patients not on antiplatelet therapy or anticoagulation. Carfilzomib dose reduction or temporary discontinuation may be required following signs of blood loss.[2,9]

Renal toxicity occurs in up to 10% of patients and may require dose reduction, interruption, or therapy discontinuation. The risk of renal failure may be greater in patients with a reduced creatinine clearance at baseline. To mitigate the risk of renal toxicity, adequate oral and intravenous hydration should be ensured prior to each carfilzomib treatment. Hold carfilzomib and investigate the cause of renal toxicity if:

- creatinine increases to two or more times baseline,
- creatinine clearance decreases to 50% of baseline or is less than 15 mL/min, or
- dialysis is required.

Carfilzomib may be resumed if it is determined not to be the cause of the renal toxicity. If the decline in renal function is attributable to treatment, carfilzomib may be restarted at a reduced dose once renal function has recovered to within 25% of baseline. If tolerated at the reduced dose, carfilzomib dose may subsequently be increased to the previous higher dose to maximize drug efficacy.[2,9]

INTERACTIONS: none known[2]

SUPPLY AND STORAGE:

Injection**:** Amgen Canada Inc. supplies carfilzomib as 60 mg single use vials of lyophilized powder. Refrigerate. Protect from light.[2]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

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SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

- reconstituted product contains 7 mg/mL sodium (0.3 mmol)[2]
- following reconstitution, carfilzomib may be diluted in D5W; normal saline should NOT be used for dilution[2]
- lines may be flushed with either NS or D5W before and after administration[2]
- if a closed system transfer device is not used for the preparation of carfilzomib, a 21 (or larger) gauge needle is recommended to prevent coring of vial stopper[11,23,24]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[10,11]	do NOT use
Intermittent infusion[25-27]	• ***over 30 minutes*** for regimens with a ***target dose of 56 mg/m^2 or 70 mg/m^2*** • over 10 minutes for regimens with a target dose of 27 mg/m^2 Note: infusion time is not reduced for dose modifications
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

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***Adults*:**

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	***4 weeks***[25,27-29]:	Cycle 1: ***20 mg/m^2 IV for one dose on day 1, followed by 70 mg/m^2*** (range 36-70 mg/m^2) ***IV for one dose on days 8 and 15*** (total dose for cycle 1 = 160 mg/m^2 [range 92-160 mg/m^2]) Cycle 2 onward: ***70 mg/m^2*** (range 36-70 mg/m^2) ***IV for one dose on days 1, 8, and 15*** (total dose per cycle 210 mg/m^2 [range 108-210 mg/m^2]) • maximum BSA for dose calculation: 2.2 m^2 • no dose adjustment required for weight change ≤ 20%
	4 weeks[26,30,31]:	Cycle 1: ***20 mg/m^2 IV for one dose on day 1, followed by 56 mg/m^2*** (range 36-70 mg/m^2) ***IV for one dose on days 8 and 15*** (total dose for cycle 1 = 160 mg/m^2 [range 92-160 mg/m^2]) Cycle 2 onward: ***56 mg/m^2*** (range 36-70 mg/m^2) ***IV for one dose on days 1, 8, and 15*** (total dose per cycle 210 mg/m^2 [range 108-210 mg/m^2]) • maximum BSA for dose calculation: 2.2 m^2 • no dose adjustment required for weight change ≤ 20%
	4 weeks[25,32]:	Cycle 1: 20 mg/m^2 (range 15-20 mg/m^2) IV for one dose on days 1 and 2, followed by 27 mg/m^2 (range 15-27 mg/m^2) IV for one dose on days 8, 9, 15, and 16 (total dose for cycle 1 = 148 mg/m^2 [range 90-148 mg/m^2]) Cycle 2-12: 27 mg/m^2 (range 15-27 mg/m^2) IV for one dose on days 1, 2, 8, 9, 15, and 16 (total dose per cycle 162 mg/m^2 [range 90-162 mg/m^2]) Cycle 13 onward: 27 mg/m^2 (range 15-27 mg/m^2) IV for one dose on days 1, 2, 15, and 16 (total dose per cycle 108 mg/m^2 [range 60-108 mg/m^2]) • maximum BSA for dose calculation: 2.2 m^2 • no dose adjustment required for weight change ≤ 20%

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BC Cancer usual dose noted in ***bold, italics***

Cycle Length:
4 weeks[16,18,25]:

Cycle 1:
20 mg/m^2 IV for one dose on days 1 and 2, followed by 56 mg/m^2 (range 27-56 mg/m^2) IV for one dose on days 8, 9, 15, and 16
(total dose for cycle 1 = 264 mg/m^2 [range 148-264 mg/m^2])

Cycle 2 onward:
56 mg/m^2 (range 27-56 mg/m^2) IV for one dose on days 1, 2, 8, 9, 15, and 16
(total dose per cycle 336 mg/m^2 [range 162-336 mg/m^2])

- maximum BSA for dose calculation: 2.2 m^2
- no dose adjustment required for weight change ≤ 20%

Dosage in myelosuppression: modify according to protocol by which patient is being treated

Dosage in renal failure: no starting dose adjustment required[2,9,33]

Dosage in hepatic failure: mild/moderate impairment[11]: reduce dose by 25%
severe hepatic impairment: no information found

Dosage in dialysis: administer carfilzomib after dialysis procedure[1]

Children: no information found

REFERENCES:

1. Lexicomp Online® (database on the Internet). Carfilzomib. Lexi-Comp Inc., 1 September 2016. Available at: http://online.lexi.com. Accessed 6 September 2016.
2. Amgen Canada Inc. KYPROLIS® product monograph. Mississauga, Ontario; 15 January 2016.
3. Gu JJ, Hernandez-Ilizaliturri FJ, Kaufman GP, et al. The novel proteasome inhibitor carfilzomib induces cell cycle arrest, apoptosis and potentiates the anti-tumour activity of chemotherapy in rituximab-resistant lymphoma. Br J Haematol 2013;162(5):657-669.
4. Hájek R, Masszi T, Petrucci MT, et al. A randomized phase III study of carfilzomib vs low-dose corticosteroids with optional cyclophosphamide in relapsed and refractory multiple myeloma (FOCUS). Leukemia 2016:1-8.
5. McBride A, Klaus JO, Stockerl-Goldstein K. Carfilzomib: A second-generation proteasome inhibitor for the treatment of multiple myeloma. American Journal of Health-System Pharmacy March 2015;72(5):353-360.
6. Redic K. Carfilzomib: a novel agent for multiple myeloma. J Pharm Pharmacol Aug 2013;65(8):1095-1106.
7. Arastu-Kapur S, Anderl JL, Kraus M, et al. Nonproteasomal targets of the proteasome inhibitors bortezomib and carfilzomib: a link to clinical adverse events. Clin Cancer Res 2011;17(9):2734-2743.
8. Pautasso C, Bringhen S, Cerrato C, et al. The mechanism of action, pharmacokinetics, and clinical efficacy of carfilzomib for the treatment of multiple myeloma. Expert Opin Drug Metab Toxicol Oct 2013;9(10):1371-1379.
9. Amgen Inc. Carfilzomib (KYPROLIS®) - Full Prescribing Information. Thousand Oaks, California USA; January 2016.
10. AHFS Drug Information® (database on the Internet). Carfilzomib. Lexi-Comp Inc., 6 April 2016. Available at: http://online.lexi.com. Accessed 6 September 2016.
11. Amgen Canada Inc. KYPROLIS® product monograph. Mississauga, Ontario; 6 July 2017.
12. Amgen Canada Inc. KYPROLIS® product monograph. Mississauga, Ontario; 19 October 2018.
13. Kevin Song MD. BC Cancer Agency Lymphoma and Myeloma Tumour Group. Personal communication. 27 November 2016.
14. Linda Hamata. BC Cancer Agency Lymphoma and Myeloma Tumour Group. Personal communication. 31 October 2016.
15. Siegel D, Martin T, Nooka A, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologia 2013;98(11):1753-1761.

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16. 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. Supplementary appendix. The Lancet Oncology January 2016;17(1):S1-S34.
17. Amgen Inc. Carfilzomib (KYPROLIS®) - Full Prescribing Information. Thousand Oaks, California USA; Aug 2016.
18. 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. The Lancet Oncology January 2016;17(1):27-38.
19. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
20. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; January 2016.
21. Wang M, Cheng J. Overview and management of cardiac and pulmonary adverse events in patients with relapsed and/or refractory multiple myeloma treated with single-agent carfilzomib. Oncology (Williston) Dec 2013;27(Suppl 3):24-30.
22. Kim GY, Ahuja T, Papadopoulos J, et al. Cardiotoxicity with carfilzomib at doses greater than 27 mg/m2: A case series. J Oncol Pharm Pract 2019;25(1):229-233.
23. Diane Lord. Medical Information, Amgen Canada Inc. Personal communication. 8 May 2018.
24. Luis Simao. Area Manager, ICU Medical Canada. Personal communication. 11 May 2018.
25. Amgen Canada Inc. KYPROLIS® product monograph. Mississauga, Ontario; 6 September 2019.
26. BC Cancer Lymphoma, Leukemia/BMT Tumour Group. (UMYCARLD) BC Cancer Protocol Summary for Therapy of Multiple Myeloma Using Carfilzomib, Lenalidomide with Dexamethasone. Vancouver, British Columbia: BC Cancer; 1 March 2020.
27. BC Cancer Lymphoma, Leukemia/BMT Tumour Group. (UMYCARDEX) BC Cancer Protocol Summary for Therapy of Multiple Myeloma Using Carfilzomib and Dexamethasone. Vancouver, British Columbia: BC Cancer; 1 March 2020.
28. Moreau P, Mateos MV, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomized, phase 3 study. Lancet Oncol 2018;19(7):953-964.
29. Berenson JR, Cartmell A, Bessudo A, et al. CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma. Blood 2016;127(26):3360-3368.
30. Richez V, Gruchet C, Guidez S, et al. Carfilzomib weekly 20/56 mg/m2, lenalidomide and dexamethasone for early relapsed refractory multiple myeloma. Am J Hematol. 2019;94(1):E17-E20.
31. Biran N, Siegel D, Berdeja JG, et al. Weekly carfilzomib, lenalidomide, and dexamethasone in relapsed or refractory multiple myeloma: a phase 1b study. Am J Hematol 2019;94(7):794-802.
32. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372(2):142-152.
33. Badros AZ, Vij R, Martin T, et al. Carfilzomib in multiple myeloma patients with renal impairment: pharmacokinetics and safety. Leukemia Aug 2013;27(8):1707-1714.

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