Infusion Smart Guide

Target the approved KYPROLIS® dose for the best chance of achieving outcomes observed in clinical trials[1]

	2nd-generation PI + IMiD + Dex **KRd 27 mg/m² TWICE WEEKLY**	2nd-generation PI + Dex **Kd 70 mg/m² ONCE WEEKLY**	2nd-generation PI + Dex **Kd 56 mg/m² TWICE WEEKLY**
Infusion time	**10 minutes**	**30 minutes**	**30 minutes**
Treatment schedule	• Administer 27 mg/m² on 2 consecutive days each week for 3 weeks • Follow with 12-day rest period, as part of 28-day treatment cycle • For Cycles 13 and beyond, omit Day 8 and 9 doses • Continue until disease progression or unacceptable toxicity occurs • Discontinue KYPROLIS® after Cycle 18	• Administer 70 mg/m² on 1 day each week for 3 weeks • Follow with 13-day rest period, as part of 28-day treatment cycle • For Cycles 10 and beyond, dexamethasone is not given on Day 22 • Continue until disease progression or unacceptable toxicity occurs	• Administer 56 mg/m² on 2 consecutive days each week for 3 weeks • Follow with 12-day rest period, as part of 28-day treatment cycle • Continue until disease progression or unacceptable toxicity occurs
KYPROLIS® priming dose	20 mg/m² on Days 1 and 2 of Cycle 1 to evaluate tolerability	20 mg/m² on Day 1 of Cycle 1 to evaluate tolerability	20 mg/m² on Days 1 and 2 of Cycle 1 to evaluate tolerability
Target KYPROLIS® therapeutic dose	27 mg/m² starting Day 8 of Cycle 1	70 mg/m² starting Day 8 of Cycle 1	56 mg/m² starting Day 8 of Cycle 1
Calculating the priming and therapeutic dose for all regimens: Patient's body surface area (BSA; m²) x dose (mg/m²)	**EXAMPLES:** **Calculate the correct KRd 27 mg/m² twice weekly dose for a patient with a BSA of 1.8 m²** **PRIMING DOSE:** 1.8 m² x 20 mg/m² = 36 mg **THERAPEUTIC DOSE:** 1.8 m² x 27 mg/m² = 49 mg In patients with a BSA > 2.2 m², calculate the dose based upon a BSA of 2.2 m²	**EXAMPLES:** **Calculate the correct Kd 70 mg/m² once weekly dose for a patient with a BSA of 1.8 m²** **PRIMING DOSE:** 1.8 m² x 20 mg/m² = 36 mg **THERAPEUTIC DOSE:** 1.8 m² x 70 mg/m² = 126 mg In patients with a BSA > 2.2 m², calculate the dose based upon a BSA of 2.2 m²	**EXAMPLES:** **Calculate the correct Kd 56 mg/m² twice weekly dose for a patient with a BSA of 1.8 m²** **PRIMING DOSE:** 1.8 m² x 20 mg/m² = 36 mg **THERAPEUTIC DOSE:** 1.8 m² x 56 mg/m² = 101 mg In patients with a BSA > 2.2 m², calculate the dose based upon a BSA of 2.2 m²

PI = proteasome inhibitor; IMiD = immunomodulatory drug; Dex = dexamethasone; KRd = KYPROLIS®+lenalidomide and dexamethasone; Kd = KYPROLIS®+dexamethasone.

Please refer to important hydration information on the next page

Refer to the full Prescribing Information and Administration and Dose Modifications instructions for more information.

INDICATION

- KYPROLIS® (carfilzomib) is indicated in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities

- New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of KYPROLIS. Some events occurred in patients with normal baseline ventricular function. Death due to cardiac arrest has occurred within one day of administration.
- Monitor patients for signs or symptoms of cardiac failure or ischemia. Evaluate promptly if cardiac toxicity is suspected. Withhold KYPROLIS for Grade 3 or 4 cardiac adverse reactions until recovery, and consider whether to restart at 1 dose level reduction based on a benefit/risk assessment.

Please see additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

Points for patient preparation[1]

Hydration

- ☐ Ensure adequate hydration **prior to dosing in Cycle 1**, especially in patients at high risk of **tumor lysis syndrome** or **renal toxicity**
  - The recommended hydration includes **both oral fluids** (30 mL per kg at least 48 hours before Cycle 1, Day 1) **and IV fluids** (250 mL to 500 mL of appropriate IV fluid prior to each dose in Cycle 1)
  - If needed, give an **additional 250 mL to 500 mL** of IV fluids following KYPROLIS® administration
  - Continue oral and/or IV hydration, as needed, in subsequent cycles
- ☐ Monitor patients for evidence of **volume overload** and adjust hydration to individual patient needs, especially in patients with or at risk for **cardiac failure**
  - Adjust **total fluid intake** as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure

Premedication

- ☐ Administer **dexamethasone** orally or intravenously **at least 30 minutes before, but no more than 4 hours prior to, all doses of KYPROLIS®** during Cycle 1 to reduce the incidence and severity of infusion-related reactions. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles
- ☐ Consider **antiviral prophylaxis** to decrease risk of herpes zoster reactivation
- ☐ Recommend **thromboprophylaxis** for patients being treated with the combination of KYPROLIS® with dexamethasone **(Kd)** or KYPROLIS® with lenalidomide plus dexamethasone **(KRd)**. The thromboprophylaxis regimen should be based on the patient's underlying risks

Hypertension management

- ☐ Control hypertension **before starting KYPROLIS®**, and **monitor blood pressure regularly** in all patients
  - If hypertension cannot be adequately controlled, withhold KYPROLIS® and evaluate. Consider whether to restart based on a benefit/risk assessment

IV = intravenous.

Refer to the full **Prescribing Information** and **Administration and Dose Modifications instructions** for more information.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Cardiac Toxicities (cont'd)

- While adequate hydration is required prior to each dose in Cycle 1, monitor all patients for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate.
- For patients ≥ 75 years, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina, or arrhythmias may be at greater risk for cardiac complications and should have a comprehensive medical assessment prior to starting treatment with KYPROLIS and remain under close follow-up with fluid management.

Please see additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

Dose modifications for hematologic toxicity, nonhematologic toxicity, renal toxicity, or hepatic impairment during KYPROLIS® treatment[1]

Hematologic toxicity	Recommended action
• Absolute neutrophil count (ANC) less than 0.5 x 10^9/L	• Withhold dose – If recovered to greater than or equal to 0.5 x 10^9/L, continue at the same dose level • For subsequent drops to less than 0.5 x 10^9/L, follow the same recommendations as above and consider **1 dose-level reduction** when restarting KYPROLIS®*
• Febrile neutropenia (ANC less than 0.5 x 10^9/L) and an oral temperature more than 38.5°C or 2 consecutive readings of more than 38.0°C for 2 hours	• Withhold dose – If ANC returns to baseline grade and fever resolves, resume at the same dose level
• Platelets less than 10 x 10^9/L or evidence of bleeding with thrombocytopenia	• Withhold dose – If recovered to greater than or equal to 10 x 10^9/L and/or bleeding is controlled, continue at the same dose level • For subsequent drops to less than 10 x 10^9/L, follow the same recommendations as above and consider **1 dose-level reduction** when restarting KYPROLIS®*
Renal toxicity	**Recommended action**
• Serum creatinine greater than or equal to 2x baseline, or • Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for hemodialysis	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance) – If attributable to KYPROLIS®, resume when renal function has recovered to within 25% of baseline; start at **1 dose-level reduction*** – If not attributable to KYPROLIS®, dosing may be resumed at the discretion of the healthcare provider • For patients on hemodialysis receiving KYPROLIS®, the dose is to be administered after the hemodialysis procedure
Other nonhematologic toxicity	**Recommended action**
• All other CTCAE Grade 3 or 4 nonhematological toxicities	• Withhold until resolved or returned to baseline • Consider restarting the next scheduled treatment at **1 dose-level reduction***
Hepatic impairment	**Recommended action**
• Mild or moderate impairment†	• Reduce the dose of KYPROLIS® by 25%
• Severe impairment	• Dosing recommendation cannot be made

*See Dose-level Reductions table on page 4.

†Mild hepatic impairment was defined as having a total bilirubin of 1 to 1.5 x ULN and any AST or total bilirubin ≤ ULN and AST > ULN. Moderate hepatic impairment was defined as having a total bilirubin of > 1.5 to 3 x ULN and any AST.

CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal; AST = aspartate aminotransferase.

Refer to the full **Prescribing Information** and **Administration and Dose Modifications instructions** for more information.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Acute Renal Failure

- Cases of acute renal failure, including some fatal renal failure events, and renal insufficiency (including renal failure) have occurred. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS monotherapy. Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate.

Tumor Lysis Syndrome

- Cases of Tumor Lysis Syndrome (TLS), including fatal outcomes, have occurred. Patients with a high tumor burden should be considered at greater risk for TLS. Adequate hydration is required prior to each dose in Cycle 1, and in subsequent cycles as needed. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly, and withhold until resolved.

Please see additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

Dose-level reductions for adverse reactions during KYPROLIS® treatment[1]

Regimen	Dose	First dose reduction	Second dose reduction	Third dose reduction
KRd KYPROLIS®+lenalidomide and dexamethasone	27 mg/m²	20 mg/m²	15 mg/m²*	--
Kd ONCE-WEEKLY KYPROLIS®+dexamethasone	70 mg/m²	56 mg/m²	45 mg/m²	36 mg/m²*
Kd TWICE-WEEKLY KYPROLIS®+dexamethasone	56 mg/m²	45 mg/m²	36 mg/m²	27 mg/m²*

Kd 27 mg/m² is not an FDA-approved dose for KYPROLIS®.

Note: Infusion times remain unchanged during dose reduction(s).
*If toxicity persists, discontinue KYPROLIS® treatment.
FDA = Food and Drug Administration.

Select from 3 vial sizes

KYPROLIS® is offered in 3 single-dose vial sizes: 10 mg, 30 mg, and 60 mg

Refer to the full Prescribing Information and Administration and Dose Modifications instructions for more information.

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Pulmonary Toxicity

- Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue KYPROLIS.

Pulmonary Hypertension

- Pulmonary arterial hypertension (PAH) was reported. Evaluate with cardiac imaging and/or other tests as indicated. Withhold KYPROLIS for PAH until resolved or returned to baseline and consider whether to restart based on a benefit/risk assessment.

Please see additional Important Safety Information throughout.

Kyprolis® (carfilzomib) for Injection

IMPORTANT SAFETY INFORMATION FOR KYPROLIS

Dyspnea

- Dyspnea was reported in patients treated with KYPROLIS. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop KYPROLIS for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart based on a benefit/risk assessment.

Hypertension

- Hypertension, including hypertensive crisis and hypertensive emergency, has been observed, some fatal. Control hypertension prior to starting KYPROLIS. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold KYPROLIS and evaluate. Consider whether to restart based on a benefit/risk assessment.

Venous Thrombosis

- Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed. Thromboprophylaxis is recommended for patients being treated with the combination of KYPROLIS with dexamethasone or with lenalidomide plus dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks.
- Patients using hormonal contraception associated with a risk of thrombosis should consider an alternative method of effective contraception during treatment.

Infusion-Related Reactions

- Infusion-related reactions, including life-threatening reactions, have occurred. Signs and symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, laryngeal edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration. Premedicate with dexamethasone to reduce the incidence and severity of infusion-related reactions. Inform patients of the risk and of symptoms and seek immediate medical attention if they occur.

Hemorrhage

- Fatal or serious cases of hemorrhage have been reported. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. Promptly evaluate signs and symptoms of blood loss. Reduce or withhold dose as appropriate.

Thrombocytopenia

- KYPROLIS causes thrombocytopenia with recovery to baseline platelet count usually by the start of the next cycle. Monitor platelet counts frequently during treatment. Reduce or withhold dose as appropriate.

Hepatic Toxicity and Hepatic Failure

- Cases of hepatic failure, including fatal cases, have occurred. KYPROLIS can cause increased serum transaminases. Monitor liver enzymes regularly regardless of baseline values. Reduce or withhold dose as appropriate.

Thrombotic Microangiopathy

- Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal outcome have occurred. Monitor for signs and symptoms of TTP/HUS. Discontinue if diagnosis is suspected. If the diagnosis of TTP/HUS is excluded, KYPROLIS may be restarted. The safety of reinitiating KYPROLIS is not known.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Cases of PRES have occurred in patients receiving KYPROLIS. If PRES is suspected, discontinue and evaluate with appropriate imaging. The safety of reinitiating KYPROLIS is not known.

Progressive Multifocal Leukoencephalopathy (PML)

- Cases of PML, including fatal cases, have occurred. In addition to KYPROLIS, other contributary factors may include prior or concurrent use of immunosuppressive therapy. Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, discontinue and initiate evaluation for PML including neurology consultation.

Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-ineligible Patients

- In a clinical trial of transplant-ineligible patients with newly diagnosed multiple myeloma comparing KYPROLIS, melphalan, and prednisone (KMP) vs bortezomib, melphalan, and prednisone (VMP), a higher incidence of serious and fatal adverse reactions was observed in patients in the KMP arm. KMP is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

Embryo-fetal Toxicity

- KYPROLIS can cause fetal harm when administered to a pregnant woman.
- Advise pregnant women of the potential risk to a fetus. Females of reproductive potential should use effective contraception during treatment with KYPROLIS and for 6 months following the final dose. Males of reproductive potential should use effective contraception during treatment with KYPROLIS and for 3 months following the final dose.

Adverse Reactions

- The most common adverse reactions in the combination therapy trials: anemia, neutropenia, diarrhea, dyspnea, fatigue, thrombocytopenia, pyrexia, insomnia, muscle spasm, cough, upper respiratory tract infection, hypokalemia.

Please click here for the full Prescribing Information.

Reference: 1. KYPROLIS® (carfilzomib) prescribing information, Onyx Pharmaceuticals Inc., an Amgen Inc. subsidiary.

Kyprolis® (carfilzomib) for Injection

AMGEN®

Oncology