PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr Kyprolis®

carfilzomib for injection

Powder for solution for intravenous infusion, 10, 30, 60 mg per vial

Professed Standard

Antineoplastic Agent

Amgen Canada Inc.
6775 Financial Drive, Suite 300
Mississauga, ON L5N 0A4

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RECENT MAJOR LABEL CHANGES

1 INDICATIONS	07/2023
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

KYPROLIS (carfilzomib) is indicated for the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy in combination with:

- Dexamethasone; or
- Lenalidomide and dexamethasone; or
- Daratumumab and dexamethasone; or
- Isatuximab and dexamethasone

The clinical effectiveness of KYPROLIS when combined with lenalidomide and dexamethasone (KRd) has not been established in patients with renal impairment (creatinine clearance [CrCL] < 50 mL/min). The clinical effectiveness of KRd or KYPROLIS and dexamethasone (Kd) has not been established in patients who progressed during prior bortezomib therapy (see 7 WARNINGS AND PRECAUTIONS and 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (< 18 years of age):

The safety and effectiveness of KYPROLIS in pediatric patients have not been established.

1.2 Geriatrics

Geriatrics (≥ 65 years of age):

No overall differences in effectiveness of KYPROLIS in combination with dexamethasone or lenalidomide and dexamethasone were observed between younger (< 65 years of age) and older (≥ 65 years of age) patients. Overall, the patient incidence of certain adverse events (including cardiac failure) in clinical trials was higher for patients who were ≥ 65 years of age compared to patients who were < 65 years of age (see 7 WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

KYPROLIS is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

KYPROLIS should be administered under the supervision of a physician experienced in the use of anticancer agents.

KYPROLIS dosed at 56 mg/m^2 and 70 mg/m^2 must be infused over 30 minutes and KYPROLIS dosed at 27 mg/m^2 must be infused over at least 10 minutes (see 7 WARNINGS AND PRECAUTIONS, General and 4 DOSAGE AND ADMINISTRATION).

The following are clinically significant adverse events:

- Cardiac toxicities (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- Pulmonary toxicities (see 7 WARNINGS AND PRECAUTIONS, Respiratory)
- Hepatic failure (see 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic)
- Thrombotic Microangiopathy (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Posterior reversible encephalopathy syndrome (PRES, see 7 WARNINGS AND PRECAUTIONS, Neurologic)
- Hemorrhage (see 7 WARNINGS AND PRECAUTIONS, Hematologic)
- Venous Thrombosis (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Refer to the lenalidomide, daratumumab, isatuximab, and/or dexamethasone Product Monographs for additional dosing considerations when using these agents in combination with KYPROLIS.

Administration Precautions

KYPROLIS dosed at 56 mg/m^2 and 70 mg/m^2 must be infused over 30 minutes and KYPROLIS dosed at 27 mg/m^2 must be infused over at least 10 minutes. The highest carfilzomib dose studied with a 10-minute infusion is 27 mg/m^2. The dose of 56 mg/m^2 carfilzomib infused over 30 minutes, given twice weekly as monotherapy, was determined to be the maximum tolerated dose of carfilzomib when given as the twice weekly dosing regimen, and was also evaluated in the clinical trial ENDEAVOR. The dose of 70 mg/m^2 carfilzomib infused over 30 minutes, given once weekly in combination with dexamethasone, was determined to be the maximum tolerated dose of carfilzomib when given as the once weekly dosing regimen, and was also evaluated in the clinical trial ARROW.

KYPROLIS vials contain no antimicrobial preservatives and are intended for single use only. Proper aseptic technique must be observed.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

On the days where both isatuximab and KYPROLIS are administered, administer dexamethasone first, followed by isatuximab infusion, then followed by KYPROLIS infusion.

Concomitant Medications

Consider antiviral prophylaxis in patients being treated with KYPROLIS to decrease the risk of herpes zoster reactivation.

Thromboprophylaxis is recommended in patients being treated with KYPROLIS, and the choice of antithrombotic agent should be based on an assessment of the patient's underlying risks and clinical status (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Sodium Content

Following reconstitution, each mL of this medicinal product contains 0.3 mmols (7 mg) of sodium. This should be taken into consideration for patients on a controlled sodium diet.

Hydration and Fluid Monitoring

Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumour lysis syndrome or renal toxicity. All patients should be monitored for evidence of volume overload and fluid requirements should be tailored to individual patient needs. The total volume of fluids may be adjusted as clinically indicated in patients with baseline cardiac failure or who are at high risk for cardiac failure (see 7 WARNINGS AND PRECAUTIONS).

Recommended hydration includes both oral fluids (30 mL/kg/day for 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). Give an additional 250 mL to 500 mL of intravenous fluids as needed following KYPROLIS administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles.

When given in combination with IV daratumumab, oral and/or intravenous hydration is not required on days when IV daratumumab is dosed.

Premedication

Premedicate with the recommended dose of dexamethasone either orally or intravenously at least 30 minutes but no more than 4 hours prior to all doses of KYPROLIS to reduce the incidence and severity of infusion reactions.

When given in combination with daratumumab or isatuximab, more premedication options should be considered. Please see the respective Product Monographs for details.

Patients with Hepatic Impairment

Patients with mild or moderate hepatic impairment require a reduced carfilzomib starting dose (see 4.2 Recommended Dose and Dosage Adjustment). Liver enzymes and bilirubin should be assessed at treatment initiation and monitored during treatment with carfilzomib.

4.2 Recommended Dose and Dosage Adjustment

Health Canada has not authorized an indication for pediatric use (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics)

Recommended Dose

Table 1. KYPROLIS Dosing Information

Regimen	KYPROLIS Starting Dose	If Tolerated, Increase KYPROLIS Dose on Day 8 of Cycle 1 to:	KYPROLIS Infusion Time[a]
KYPROLIS, lenalidomide, and dexamethasone (KRd) twice weekly	20 mg/m^2	27 mg/m^2	10 minutes
KYPROLIS with dexamethasone (Kd), with dexamethasone and daratumumab (KdD), or with isatuximab and dexamethasone (IsaKd) twice weekly	20 mg/m^2	56 mg/m^2	30 minutes
KYPROLIS with dexamethasone (Kd)[b] once weekly	20 mg/m^2	70 mg/m^2	30 minutes

[a] Infusion time remains consistent throughout each regimen regardless of any dose modifications.
[b] The once weekly Kd regimen can be a treatment option, if the patient cannot adhere to the twice weekly Kd regimen due to the burden of dosing frequency. The once weekly Kd 20/70 mg/m^2 regimen has not been compared with the twice weekly Kd 20/56 mg/m^2 regimen within a clinical trial.

Calculate the dose using the patient's baseline body surface area (BSA). Patients with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.

KYPROLIS dosed at 20/27 mg/m^2 must be infused over at least 10 minutes. KYPROLIS dosed at 20/56 mg/m^2 and 20/70 mg/m^2 must be infused over 30 minutes (see Table 1). Treatment should be continued until disease progression or unacceptable toxicity.

KYPROLIS in combination with lenalidomide and dexamethasone (KRd)

KYPROLIS is administered by intravenous (IV) infusion twice weekly, on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28) for the first 12 treatment cycles. KYPROLIS is omitted on Days 8 and 9 of Cycles 13 and higher. Each 28-day period is considered one treatment cycle.

KYPROLIS is administered at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, the dose should be increased to a target dose of 27 mg/m^2 on Day 8 of Cycle 1.

Lenalidomide is administered as 25 mg orally on Days 1-21 and dexamethasone is administered as 40 mg orally or IV on Days 1, 8, 15, and 22 of the 28-day cycles. Appropriate dose reduction for the starting dose of lenalidomide should be considered according to the recommendations in the lenalidomide Product Monograph, for example, for patients with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before KYPROLIS.

The treatment schedule is outlined in Table 2.

KYPROLIS in combination with dexamethasone (Kd)

20/56 mg/m^2 twice weekly dosing regimen

KYPROLIS is administered by IV infusion twice weekly, on two consecutive days, each week for three weeks (Days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (Days 17 to 28). Each 28-day period is considered one treatment cycle.

KYPROLIS is administered at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, the dose should be increased to a target dose of 56 mg/m^2 on Day 8 of Cycle 1. Dexamethasone is administered as 20 mg orally or IV on Days 1, 2, 8, 9, 15, 16, 22 and 23 of the 28-day cycles. Dexamethasone should be administered 30 minutes to 4 hours before KYPROLIS.

The treatment schedule is outlined in Table 3.

20/70 mg/m^2 once weekly dosing regimen

KYPROLIS administered by IV infusion once weekly can be a treatment option, if the patient cannot adhere to the twice weekly Kd regimen due to the burden of dosing frequency. The once weekly Kd 20/70 mg/m^2 regimen has not been compared with the twice weekly Kd 20/56 mg/m^2 regimen within a clinical trial.

With this once weekly dosing regimen, KYPROLIS is administered by IV infusion once weekly for three weeks (Days 1, 8, and 15), followed by a 13-day rest period (Days 16 to 28). Each 28-day period is considered one treatment cycle.

KYPROLIS is administered at a starting dose of 20 mg/m^2 in Cycle 1 on Day 1. If tolerated, the dose should be increased to a target dose of 70 mg/m^2 on Day 8 of Cycle 1.

Dexamethasone is administered as 40 mg orally or IV on Days 1, 8, 15 and 22. Dexamethasone is omitted on Day 22 of Cycles 10 and higher. Dexamethasone should be administered 30 minutes to 4 hours before KYPROLIS.

The treatment schedule is outlined in Table 4.

KYPROLIS in combination with dexamethasone and daratumumab (KdD)

For the combination regimen KdD, administer KYPROLIS intravenously twice weekly as a 30-minute infusion as described in Table 5 below.

Twice weekly 20/56 mg/m^2 regimen by 30-minute infusion

KYPROLIS is administered intravenously as a 30-minute infusion on two consecutive days, each week for three weeks followed by a 12-day rest period as shown in Table 5. Each 28-day period is considered one treatment cycle. Administer KYPROLIS at a starting dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Day 8 of Cycle 1 and thereafter. Dexamethasone 20 mg is taken by mouth or intravenously on Days 1, 2, 8, 9, 15 and 16 and 40 mg by mouth or intravenously on Day 22 of each 28-day cycle. Administer dexamethasone 30 minutes to 4 hours before KYPROLIS.

Daratumumab is administered intravenously at a dose of 16 mg/kg actual body weight; with a split dose of 8 mg/kg in Cycle 1 on Days 1 and 2. Administer 16 mg/kg once weekly on Days 8, 15 and 22 of Cycle 1 and Days 1, 8 and 15 and 22 of Cycle 2, then every 2 weeks for 4 cycles (cycles 3 to 6) and then every 4 weeks for the remaining cycles or until disease progression.

Treatment may be continued until disease progression or unacceptable toxicity occurs. Refer to the dexamethasone and daratumumab Product Monographs for additional information on those products.

KYPROLIS in combination with isatuximab and dexamethasone (IsaKd)

Twice weekly 20/56 mg/m^2 regimen by 30-minute infusion

Administer KYPROLIS intravenously as a 30-minute infusion on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle as shown in Table 6 in combination with isatuximab plus dexamethasone until disease progression or unacceptable toxicity. The recommended starting dose of KYPROLIS is 20 mg/m^2 on Cycle 1, Days 1 and 2. If tolerated, escalate the dose to 56 mg/m^2 on Cycle 1, Day 8.

Refer to the Product Monographs for isatuximab and dexamethasone for additional information on those products.

Table 2. KYPROLIS Twice Weekly (10-minute Infusion) in Combination with Lenalidomide and Dexamethasone (KRd)

	Cycle 1										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23–28**
KYPROLIS (mg/m^2)	20	20	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 2 to 12										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23–28**
KYPROLIS (mg/m^2)	27	27	-	27	27	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-
	Cycles 13 and Later[a]										
	Week 1			**Week 2**			**Week 3**			**Week 4**	
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Days 23–28**
KYPROLIS (mg/m^2)	27	27	-	-	-	-	27	27	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-
Lenalidomide	25 mg daily on Days 1-21									-	-

[a] KYPROLIS is administered through Cycle 18; lenalidomide and dexamethasone continue thereafter.

Table 3. KYPROLIS Twice Weekly (30-minute Infusion) in Combination with Dexamethasone (Kd)

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
KYPROLIS (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
	Cycles 2 and Later											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
KYPROLIS (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

Table 4. KYPROLIS Once Weekly (30-minute Infusion) in Combination with Dexamethasone (Kd)

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
KYPROLIS (mg/m^2)	20	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-	-
	Cycles 2 to 9											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
KYPROLIS (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	40	-	-
	Cycles 10 and Later											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Days 17–21	Day 22	Day 23	Days 24-28
KYPROLIS (mg/m^2)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)	40	-	-	40	-	-	40	-	-	-	-	-

Table 5. KYPROLIS Twice Weekly (30-Minute Infusion) in Combination with Dexamethasone and Daratumumab (KdD)

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3–7	Day 8	Day 9	Days 10–14	Day 15	Day 16	Day 17–21	Day 22	Day 23	Days 24-28
KYPROLIS (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	8	8	-	16	-	-	16	-	-	16	-	-
	Cycle 2											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
KYPROLIS (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
	Cycles 3 to 6											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
KYPROLIS (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-	-	-	-
	Cycles 7 and Later											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3–7**	**Day 8**	**Day 9**	**Days 10–14**	**Day 15**	**Day 16**	**Days 17–21**	**Day 22**	**Day 23**	**Days 24-28**
KYPROLIS (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	-	-	-	-	-	-

* For patients > 75 years of age, administer 20 mg of dexamethasone by mouth or intravenously weekly after the first week.

Table 6. KYPROLIS Twice Weekly (30-Minute Infusion) in Combination with Isatuximab and Dexamethasone (IsaKd)

	Cycle 1											
	Week 1			Week 2			Week 3			Week 4		
	Day 1	Day 2	Days 3-7	Day 8	Day 9	Days 10-14	Day 15	Day 16	Days 17-21	Day 22	Day 23	Days 24-28
KYPROLIS (mg/m^2)	20	20	-	56	56	-	56	56	-	-	-	-
Isatuximab (mg/kg)	10	-	-	10	-	-	10	-	-	10	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-
	Cycles 2 and later											
	Week 1			**Week 2**			**Week 3**			**Week 4**		
	Day 1	**Day 2**	**Days 3-7**	**Day 8**	**Day 9**	**Days 10-14**	**Day 15**	**Day 16**	**Days 17-21**	**Day 22**	**Day 23**	**Days 24-28**
KYPROLIS (mg/m^2)	56	56	-	56	56	-	56	56	-	-	-	-
Isatuximab (mg/kg)	10	-	-	-	-	-	10	-	-	-	-	-
Dexamethasone (mg)	20	20	-	20	20	-	20	20	-	20	20	-

Recommended Dosage Adjustments

Patients with hepatic impairment

For patients with baseline mild or moderate hepatic impairment, reduce the dose of KYPROLIS by 25%. Dosing recommendation cannot be made in patients with baseline severe hepatic impairment (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

Patients with renal impairment

No dosage adjustment is required for patients with baseline renal impairment (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

Dose Adjustments for Adverse Reactions

Modify dosing based on toxicity. Recommended actions and dose modifications are presented in Table 7. KYPROLIS dose level reductions are presented in Table 8.

Table 7. Dose Modifications During KYPROLIS Treatment

Hematologic Toxicity	Recommended Action
○ Absolute neutrophil count (ANC) < 0.5 ×10^9 /L	• Withhold dose • If recovered to ≥ 0.5 ×10^9/L, continue at the same dose level • For subsequent drops to < 0.5 ×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting KYPROLIS
○ Febrile neutropenia ANC < 0.5 × 10^9/L and an oral temperature > 38.5°C or two consecutive readings of > 38.0°C for 2 hours	• Withhold dose ○ If ANC returns to baseline grade and fever resolves, resume at the same dose level
○ Platelets < 10 ×10^9/L or evidence of bleeding with thrombocytopenia	○ Withhold dose ○ If recovered to ≥ 10 ×10^9/L and/or bleeding is controlled, continue at the same dose level ○ For subsequent drops to < 10 ×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting KYPROLIS.
Renal Toxicity	**Recommended Action**
• Serum creatinine equal to or greater than 2 × baseline, or • Creatinine clearance < 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis	• 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 physician • If tolerated, the reduced dose may be increased to the previous dose at the discretion of the physician • For patients on dialysis receiving KYPROLIS, the dose is to be administered after the dialysis procedure
Other Non-hematologic Toxicity	**Recommended Action**
• All other Grade 3 or 4 non-hematological toxicities	• Withhold until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction • If tolerated, the reduced dose may be increased to the previous dose at the discretion of the physician
• PML	• Withhold if PML is suspected • If PML has been ruled out, resuming KYPROLIS should be based on above criteria • If PML is confirmed, discontinue KYPROLIS treatment permanently

Table 8. Recommended Dose Level Reductions for KYPROLIS

Regimen	Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction
KYPROLIS, lenalidomide, and dexamethasone (KRd) twice weekly	27 mg/m^2	20 mg/m^2	15 mg/m^2[a]	—
KYPROLIS and dexamethasone (Kd), or KYPROLIS with dexamethasone and daratumumab (KdD), or KYPROLIS with isatuximab and dexamethasone (IsaKd) twice weekly	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2[a]
KYPROLIS and dexamethasone (Kd) once weekly	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2[a]

Note: Infusion times remain unchanged during dose reduction(s).

[a] If symptoms do not resolve, discontinue KYPROLIS treatment.

4.3 Reconstitution

The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. Read the complete preparation instructions prior to reconstitution.

1. Calculate the dose (mg/m^2) and number of vials of KYPROLIS required using the patient's BSA at baseline. Patients with a BSA greater than 2.2 m^2 should receive a dose based upon a BSA of 2.2 m^2. Dose adjustments do not need to be made for weight changes of ≤ 20%.
2. Remove vial from refrigerator just prior to use.
3. Use only a 21-gauge or larger gauge hypodermic needle (0.8 mm or smaller external diameter needle) to aseptically reconstitute each vial by slowly injecting **5 mL** (for 10 mg vial), **15 mL** (for 30 mg vial), or **29 mL** (for 60 mg vial) Sterile Water for Injection through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming. Do not reconstitute KYPROLIS with normal saline.
4. Gently swirl and/or invert the vial slowly for approximately 1 minute, or until complete dissolution. 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.
5. Visually inspect for particulate matter and discolouration prior to administration. The reconstituted product should be a clear, colourless to slightly yellow solution and should not be administered if any discolouration or particulate matter is observed.
6. Withdraw the calculated dose from the vial and discard any unused portion left in the vial.
7. KYPROLIS can be administered directly by IV infusion or optionally administered in an IV bag. Do not administer as an IV push or bolus.
8. When administering in an IV bag, use only a 21-gauge or larger gauge hypodermic needle (0.8 mm or smaller external diameter needle) to withdraw the calculated dose from the vial and dilute into a 50 or 100 mL IV bag containing 5% Dextrose Injection (D5W). Reconstituted KYPROLIS for injection should not be diluted into a 0.9% sodium chloride (normal saline) IV bag for IV administration.

4.4 Administration

Administer KYPROLIS intravenously (IV) as a 10-minute or 30-minute infusion depending on the KYPROLIS dose regimen (see Table 1). KYPROLIS should not be administered as a bolus. The intravenous administration line should be flushed with normal saline or 5% dextrose injection immediately before and after KYPROLIS administration.

Do not mix KYPROLIS with or administer as an infusion with other medicinal products.

4.5 Missed Dose

For once weekly dosing, when making up for the missed dose, a minimum of 5 days is required between doses of KYPROLIS.

For twice weekly dosing, if a dose is missed, priority should be given to maintaining consecutive dosing days.

5 OVERDOSAGE

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia has been reported following a dose of 200 mg of KYPROLIS administered in error.

There is no known specific antidote for KYPROLIS overdose. In the event of an overdose, the patient should be monitored, specifically for the side effects and/or adverse drug reactions listed in section 8 ADVERSE REACTIONS.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 9. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Powder for Solution / 10, 30, 60 mg carfilzomib per vial	anhydrous citric acid, sodium hydroxide (for pH adjustment), sulfobutylether beta-cyclodextrin

KYPROLIS single-use vial contains 10, 30, or 60 mg of carfilzomib. After reconstitution, each mL contains 2 mg of carfilzomib.

- Single-use 10 mL (10 mg vial), 30 mL (30 mg vial), or 50 mL (60 mg vial) vial Type 1 clear glass vial fluoropolymer laminated elastomeric stopper and aluminum seal with plastic flip off cap
- Pack size of one vial (10, 30 or 60 mg carfilzomib per vial)

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

KYPROLIS as a monotherapy did not show a benefit over an active comparator (corticosteroids and cyclophosphamide) in a Phase 3 trial in patients with relapsed and refractory multiple myeloma. There were no differences in overall survival (HR = 1.09 [0.84, 1.41]) or progression-

free survival (HR = 0.98 [95% CI: 0.76-1.25]) between the two arms. KYPROLIS is not indicated as a monotherapy for the treatment of relapsed and refractory multiple myeloma.

The safety and efficacy of KYPROLIS when combined with lenalidomide and dexamethasone (KRd) have not been established in patients with renal impairment (creatinine clearance [CrCL] < 50 mL/min). These patients were excluded from the ASPIRE study, which is the pivotal Phase 3 combination study comparing KRd to lenalidomide and dexamethasone (Rd) alone. Limited data are available in KRd-treated patients with renal impairment at baseline (< 5% of patients were enrolled into ASPIRE with a CrCL = 30-50 mL/min and no patients had CrCL < 30 mL/min).

KYPROLIS administered with a short infusion time, without pre-medication with dexamethasone and adequate hydration, or without stepped up dosing, may not be well tolerated. In early studies, where a 1 to 2 minute intravenous (IV) bolus was used without pre-medication, adverse reactions were observed that appeared to be most severe within the first few doses. These reactions were characterized by chills, dyspnea, arthralgia or myalgia, and rigors. A longer infusion time, pre-medication and adequate hydration, and stepped up dosing in subsequent studies appeared to mitigate this risk. Nonclinical studies in rats have demonstrated that the tolerability of KYPROLIS is significantly lower when administered as an IV bolus compared to a 30-minute infusion. KYPROLIS dosed at 56 mg/m^2 and 70 mg/m^2 must be infused over 30 minutes, and KYPROLIS dosed at 27 mg/m^2 must be infused over at least 10 minutes (see 4 DOSAGE AND ADMINISTRATION and 16 NON-CLINICAL TOXICOLOGY).

Infusion Reactions

Infusion reactions, including life-threatening reactions, have been reported in patients who received KYPROLIS. In a pooled KYPROLIS safety population (n = 3878), 34.3% of patients reported an adverse event potentially associated with an infusion reaction within a day of any dose of KYPROLIS and 3.4% of patients reported an event within a day of the first dose of KYPROLIS. Following the introduction of management strategies (see below and 4 DOSAGE AND ADMINISTRATION), most adverse events that were potentially associated with an infusion reaction in Phase 3 trials were low grade and non-serious.

In IKEMA, infusion-related reactions (IRRs), were reported in patients treated with isatuximab in combination with KYPROLIS and dexamethasone (IsaKd). Please refer to the isatuximab Product Monograph for further details.

Signs and symptoms have included 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 of KYPROLIS.

Ensure patients are appropriately hydrated and are administered dexamethasone prior to KYPROLIS to reduce the incidence and severity of reactions (see 4 DOSAGE AND ADMINISTRATION).

Tumour Lysis Syndrome

Cases of tumour lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received KYPROLIS. In the ENDEAVOR study, which is the Phase 3 study comparing KYPROLIS and dexamethasone (Kd) versus bortezomib and dexamethasone (Vd), the incidence of TLS events was 0.6% in patients receiving Kd. In the ARROW study, a Phase 3 study evaluating the once weekly dosing of Kd, the incidence of TLS events was 2.9% in patients receiving Kd once weekly. In the ASPIRE study, the incidence of TLS events was 0.8% in patients receiving KRd. In the CANDOR study, the Phase 3 study comparing KYPROLIS in

combination with dexamethasone and daratumumab (KdD) versus Kd twice weekly, the incidence of TLS events was 1.0% in patients receiving KdD.

Patients with a high tumour burden should be considered to be at greater risk for TLS. Ensure that patients are well hydrated before administration of KYPROLIS in Cycle 1, and in subsequent cycles as needed. Uric acid lowering drugs should be considered in patients at high risk for TLS (see 4 DOSAGE AND ADMINISTRATION). Monitor for evidence of TLS during treatment including regular measurement of serum electrolytes, and manage promptly. Interrupt KYPROLIS until TLS is resolved (see 4 DOSAGE AND ADMINISTRATION).

Infections

Infections, including serious and fatal events have been reported in patients receiving KYPROLIS (see 8 ADVERSE REACTIONS). Patients should be monitored for signs and symptoms of infection, and treated promptly.

Carcinogenesis and Mutagenesis

Second Primary Malignancies (SPMs)

The incidence of second primary malignancies is increased in patients treated with isatuximab-containing regimens. In IKEMA, SPMs were reported in 13 (7.3%) patients treated with IsaKd and in 6 (4.9%) patients treated with Kd. Please refer to the isatuximab Product Monograph for further details.

Cardiovascular

Cardiac Disorders

New or worsening cardiac failure (eg, congestive cardiac failure, pulmonary edema, decreased ejection fraction), cardiomyopathy, and myocardial ischemia and infarction have occurred following administration of KYPROLIS. Death due to cardiac arrest has occurred within a day of KYPROLIS administration and fatal outcomes have been reported with cardiac failure and myocardial infarction. In the ASPIRE study, the incidences of cardiac failure events in the KRd and Rd arms were 7.1% and 4.1%, respectively, and the incidences of myocardial infarction events were 6.9% versus 4.6%, respectively. In the ENDEAVOR study, the incidences of cardiac failure events in the Kd and Vd arms were 10.8% and 3.3%, respectively. In the ARROW study, the incidence of cardiac failure events in the Kd 20/70 mg/m^2 once weekly arm was 3.8%. In the CANDOR study, the incidences of cardiac failure events in the KdD and Kd twice weekly arms were 7.5% and 10.5%, respectively.

In IKEMA, cardiac failure (including cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure and pulmonary edema) was reported in 7.3% of patients in the IsaKd group (4.0% of Grade ≥ 3) and in 6.6% of patients in the Kd group (4.1% of Grade ≥ 3). Serious cardiac failure was observed in 4.0% of patients in the IsaKd group and in 3.3% of patients in the Kd group. Fatal events of cardiac disorders occurred in 1.1% of patients in the IsaKd group (cardiac failure) and in 0.8% of patients in the Kd group (acute myocardial infarction).

The risk of cardiac failure is increased in Asian patients. In the ENDEAVOR study, the incidence of cardiac failure events for the Kd arm was 21% (11/53) for patients from Asian countries and 10% (40/410) for patients from non-Asian countries. Grade ≥ 3 cardiac failure events were reported in 11% of patients from Asian countries and 5% of patients from non-Asian countries. In the ARROW study, the incidence of cardiac failure events for the Kd 20/70 mg/m^2 arm was 19% (5/26) for patients from Asian countries and 2% (4/212) for patients from non-Asian

countries. Grade ≥ 3 cardiac failure events were reported in 15% of patients from Asian countries and 1% of patients from non-Asian countries. In the CANDOR study, the incidence of cardiac failure events for the KdD twice weekly arm was 6.8% (3/44) for patients from Asian countries and 7.6% (20/264) for patients from non-Asian countries.

While adequate hydration is required prior to dosing in Cycle 1, all patients should be monitored for evidence of volume overload, especially patients at risk for cardiac failure. The total volume of fluids may be adjusted as clinically indicated in patients with baseline cardiac failure or who are at high risk for cardiac failure (see 4 DOSAGE AND ADMINISTRATION).

Withhold KYPROLIS until Grade 3 or 4 cardiac events resolve. Carefully consider the benefit and risks when deciding if treatment with KYPROLIS should be re-initiated and, if so, resume at a 1 dose level reduction (see 4 DOSAGE AND ADMINISTRATION).

The risk of cardiac failure is increased in elderly patients (≥ 75 years).

Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, conduction abnormalities, angina or arrhythmias uncontrolled by medications were not eligible for enrollment in KYPROLIS clinical trials and patients with left ventricular ejection fraction < 40% were also not eligible for enrollment in the ENDEAVOR study. These patients may be at greater risk for cardiac complications and should have a comprehensive medical assessment (particularly, blood pressure control and fluid management) prior to starting treatment with KYPROLIS and remain under close follow up.

Electrophysiology

There have been cases of QT interval prolongation reported in patients receiving KYPROLIS in clinical studies. An effect of KYPROLIS on QT interval cannot be excluded (see 10 CLINICAL PHARMACOLOGY).

Venous Thrombosis

Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal outcomes, have been reported in patients who received KYPROLIS. In the ASPIRE study, the incidence of venous thromboembolic events was 15.6% in the KRd arm vs. 9.0% in the control arm (Rd). In the ENDEAVOR study, the incidence of venous thromboembolic events was 12.5% in the Kd arm vs. 3.3% in the control arm (Vd). In the ARROW study, the incidence of venous embolic and thrombotic events in the Kd 20/70 mg/m^2 once weekly arm was 4.2%. In the CANDOR study, the incidence of venous thromboembolic events was 6.2% in the KdD twice weekly arm vs. 11.1% in the control arm (Kd twice weekly). In the IKEMA study, thromboembolic events, venous and/or arterial, were reported at a similar incidence in the IsaKd and Kd arms (15.3% and 16.4%, respectively) and most events were not severe (Grade ≥ 3 4.0% and 5.7%, respectively).

The ASPIRE and IKEMA study protocols required thromboprophylaxis (including aspirin), while the ENDEAVOR, ARROW, and CANDOR study protocols did not.

Thromboprophylaxis is recommended in patients being treated with KYPROLIS, and the choice of antithrombotic agent should be based on an assessment of the patient's underlying risks and clinical status. Monitor for signs and symptoms of venous thromboembolic events and pulmonary embolism.

Hypertension

Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of hypertension events in KRd-treated patients was 15.8% and the incidence of hypertensive crisis/emergency events was 0.5%. In the ENDEAVOR and ARROW studies, the incidences of hypertension events in Kd 20/56 mg/m^2 twice weekly and 20/70 mg/m^2 once weekly treated patients were 33.7% and 21.8%, respectively, and the incidences of hypertensive crisis/emergency events were 0.9% and none, respectively. In the CANDOR study, the incidence of hypertension events in patients receiving KdD twice weekly was 31.8%, and there were no events of hypertensive crisis/emergency. In the IKEMA study, there was a > 5% difference between the IsaKd and Kd arms for the incidence of hypertension, all grade (36.7% for IsaKd, 31.1% for Kd) however, a similar incidence of Grade ≥ 3 hypertension was reported in both arms (20.3% for IsaKd and 19.7% for Kd).

Hypertension should be well-controlled prior to initiation of treatment with KYPROLIS and all patients should be routinely evaluated for hypertension and treated as needed. Withhold KYPROLIS until events of hypertensive crisis and hypertensive emergency resolve or hypertension is under control. Consider a dose reduction when resuming KYPROLIS and carefully consider the benefits and risks when deciding if treatment with KYPROLIS should be re-initiated following hypertensive crisis and hypertensive emergency (see 4 DOSAGE AND ADMINISTRATION).

Cardiac Impairment

Patients with New York Heart Association Class III and IV heart failure were not eligible for the clinical trials. Safety and efficacy in this population have not been established.

Hematologic

Hemorrhage

Cases of hemorrhage (eg, gastrointestinal, intracranial and pulmonary hemorrhage) have been reported in patients treated with KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of hemorrhage events in KRd-treated patients was 17.3% (the incidence of Grade ≥ 3 events was 1.3%; the incidence of fatal events was 0.5%). In the ENDEAVOR and ARROW studies, the incidences of hemorrhage events in Kd 20/56 mg/m^2 twice weekly and 20/70 mg/m^2 once weekly treated patients were 22.7% and 8.8%, respectively (the incidences of Grade ≥ 3 events were 2.8% and 2.5%, respectively; the incidences of fatal events were none and 0.4%, respectively). In the CANDOR study, the incidence of hemorrhage events in patients receiving KdD twice weekly was 14.3% (the incidence of Grade ≥ 3 events was 1.9%; there were no fatal events in the study). In the IKEMA study, hemorrhages were reported more frequently in the IsaKd arm (19.8%) than in the Kd arm (12.3%). Grade 3 or 4 hemorrhages were reported in the IsaKd arm in 4 (2.3%) patients and 1 (0.6%) patient, respectively, and in the Kd arm Grade 3 in 1 (0.8%) patient and no Grade 4.

Thrombocytopenia

KYPROLIS causes thrombocytopenia with platelet nadirs observed on Day 8 or Day 15 of each 28-day cycle, which usually recovers to baseline platelet counts by the start of the next cycle (see 8 ADVERSE REACTIONS). In the ASPIRE study, the incidence of thrombocytopenia events in KRd-treated patients was 32.7% (the incidence of Grade ≥ 3 events was 20.2%). In the ENDEAVOR and ARROW studies, the incidences of thrombocytopenia events in Kd 20/56 mg/m^2 twice weekly and 20/70 mg/m^2 once weekly treated patients were 31.7% and 22.3%, respectively (the incidences of Grade ≥ 3 events were 12.3% and 10.9%, respectively). In the CANDOR study, the incidence of thrombocytopenia events in patients receiving KdD twice weekly was 37.3% (the incidences of Grade ≥ 3 events was 24.7%). In the IKEMA study, thrombocytopenia was reported more frequently in the Kd arm (9.8%) than in the IsaKd arm (2.8%).

Monitor platelet counts frequently during treatment with KYPROLIS. Reduce or withhold therapy as appropriate (see 4 DOSAGE AND ADMINISTRATION).

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), have been reported in patients who received KYPROLIS. Some of these events have been fatal.

Monitor for signs and symptoms of TTP/HUS. Withhold KYPROLIS if TTP/HUS is suspected and evaluate. If TTP/HUS is confirmed, discontinue KYPROLIS.

Hepatic/Biliary/Pancreatic

Hepatic Toxicity

Cases of hepatic failure, including fatal cases, have been reported in patients who received KYPROLIS. In a pooled KYPROLIS safety population (n = 3878), hepatic failure events were reported in 0.2% of patients.

KYPROLIS can cause elevations of serum transaminases (ALT and AST) and bilirubin (see 8 ADVERSE REACTIONS). Monitor liver enzymes regularly, regardless of baseline values. Reduce or withhold therapy as appropriate (see 4 DOSAGE AND ADMINISTRATION).

Hepatitis B Virus (HBV) Reactivation

Cases of Hepatitis B Virus (HBV) reactivation have been reported in patients receiving KYPROLIS.

Patients should be tested for HBV infection before initiating treatment. For patients who are carriers of HBV, prophylaxis with antivirals should be considered before, throughout, and for at least 6 months after the end of the treatment. Carriers of HBV who require treatment with KYPROLIS should be closely monitored for signs and symptoms of active HBV infection (jaundice, abdominal pain, joint pain, weakness and fatigue, nausea and vomiting) throughout and following the end of treatment. Consider consulting a specialist for patients who test positive for HBV infection prior to or during treatment.

The safety of resuming KYPROLIS after HBV reactivation is adequately controlled is not known. Therefore, prescribers should weigh the risks and benefits when considering resumption of therapy in this situation.

Hepatic Impairment

Reduce the dose of KYPROLIS by 25% in patients with baseline mild or moderate hepatic impairment (see 4 DOSAGE AND ADMINISTRATION, Patients with Hepatic Impairment). Dosing recommendation cannot be made in patients with baseline severe hepatic impairment.

In a pharmacokinetic study, the AUC of carfilzomib increased by approximately 50% in patients with baseline mild or moderate hepatic impairment compared to patients with normal hepatic function. The incidence of serious adverse events was higher in patients with baseline hepatic impairment (22/35 or 63%) than in patients with normal hepatic function (3/11 or 27%). Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency).

The pharmacokinetics of KYPROLIS has not been evaluated in patients with severe hepatic impairment (see 10 CLINICAL PHARMACOLOGY).

Monitoring and Laboratory Tests

Blood pressure, complete blood cell count (CBC) including white blood cell count with differential, hemoglobin, platelets, blood chemistries including AST, ALT, total bilirubin, creatinine [or creatinine clearance (CrCL)], and electrolytes (including potassium) should be monitored at baseline and throughout treatment with KYPROLIS.

Patients treated with KYPROLIS should be monitored for hepatitis B virus infection at baseline and carriers of HBV should be monitored throughout treatment with KYPROLIS.

Neurologic

Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES), also termed reversible posterior leukoencephalopathy syndrome (RPLS), have been reported in patients receiving KYPROLIS. These patients presented with seizure, headache, lethargy, confusion, blindness, altered consciousness, and/or other visual and neurological disturbances, along with hypertension. Withhold KYPROLIS if PRES is suspected and evaluate by neuro-radiological imaging (eg, MRI). If PRES is confirmed, discontinue KYPROLIS.

Progressive Multifocal Leukoencephalopathy

Cases of Progressive Multifocal Leukoencephalopathy (PML) [blurred or double vision, blindness, aphasia, muscle weakness, coordination and gait difficulties, persistent numbness, sensory deficit, cognitive dysfunction], which can be fatal, have been reported in patients treated with KYPROLIS who have had prior or concurrent immunosuppressive therapy.

Patients should be monitored for any new or worsening neurologic, cognitive or behavioral signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders.

If PML is suspected, withhold administration of KYPROLIS; patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue KYPROLIS if PML diagnosis is confirmed.

Renal

Acute Renal Failure

Cases of acute renal failure have been reported in patients who received KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of acute renal failure events in KRd-treated patients was 9.2% (the incidence of ≥ Grade 3 events was 3.8%; the incidence of serious adverse events was 2.6%). In the ENDEAVOR and ARROW studies, the incidences of acute renal failure events in Kd 20/56 mg/m^2 twice weekly and 20/70 mg/m^2 once weekly treated patients were 10.4% and 7.1%, respectively (the incidences of ≥ Grade 3 events were 5.6% and 3.8%, respectively; the incidences of serious adverse events were 3.9% and 4.6%, respectively). In the CANDOR study, the incidence of acute renal failure events in patients receiving KdD twice weekly was 5.8% (the incidence of Grade ≥ 3 events was 2.9%; the incidence of serious adverse events was 2.3%).

Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce, withhold or discontinue KYPROLIS as appropriate (see 4 DOSAGE AND ADMINISTRATION).

Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

There are limited safety data for patients with renal impairment (CrCL < 50 mL/min) treated with KYPROLIS in combination with lenalidomide and dexamethasone (KRd). Patients with moderate (CrCL = 30 - 50 mL/min) and severe (CrCL = 15 - < 30 mL/min) renal impairment were included in the following studies: Phase 3 ENDEAVOR study comparing the safety and efficacy of Kd vs. Vd, and Phase 3 CANDOR study comparing the safety and efficacy of KdD vs. Kd. Patients with severe renal impairment at baseline were not enrolled in the ARROW study. The incidence of acute renal failure adverse events increased with the extent of renal impairment at baseline in patients treated with Kd 56 mg/m^2 twice weekly and Kd 70 mg/m^2 once weekly. The incidence of serious adverse events increased in patients with baseline renal impairment (CrCL < 50 mL/min) treated with KdD in the CANDOR study (see 8 ADVERSE REACTIONS). The systemic concentrations of a major carfilzomib metabolite increase with the extent of renal impairment (see 10 CLINICAL PHARMACOLOGY).

Carefully monitor renal function in patients and make appropriate KYPROLIS dosing modifications (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY).

Since dialysis clearance of carfilzomib concentrations has not been studied, the drug should be administered after the dialysis procedure. Refer also to the lenalidomide Product Monograph for appropriate dosing modifications of lenalidomide in patients with impaired renal function.

Respiratory

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease, such as pneumonitis and interstitial lung disease, have been reported in patients receiving KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of ARDS events in KRd-treated patients was 2.0% and incidence of interstitial lung disease events was 1.8%. In the ENDEAVOR and ARROW studies, the incidences of ARDS events in Kd 20/56 mg/m^2 twice weekly and 20/70 mg/m^2 once weekly treated patients were 0.4% and 0.4%, respectively, and the incidences of interstitial lung disease events were 1.5% and 0.8%, respectively. In the CANDOR study, the incidence of

ARDS events in patients receiving KdD twice weekly was 1%, and the incidence of interstitial lung disease events was 1.9%.

KYPROLIS should be withheld until these events resolve. Carefully consider the benefits and risks when deciding if treatment with KYPROLIS should be re-initiated (see 4 DOSAGE AND ADMINISTRATION).

Pulmonary Hypertension

Pulmonary hypertension has been reported in patients treated with KYPROLIS. Some of these events have been fatal. In the ASPIRE study, the incidence of pulmonary hypertension events in KRd-treated patients was 0.8%. In the ENDEAVOR and ARROW studies, the incidences of pulmonary hypertension events in Kd 20/56 mg/m^2 twice weekly and 20/70 mg/m^2 once weekly treated patients were 1.7% and 1.7%, respectively. In the CANDOR study, the incidence of pulmonary hypertension events in patients receiving KdD twice weekly was 1.9%. Evaluate as appropriate.

Withhold KYPROLIS until pulmonary hypertension resolves or returns to baseline. Carefully consider the benefits and risks when deciding if treatment with KYPROLIS should be re-initiated (see 4 DOSAGE AND ADMINISTRATION).

Dyspnea

Dyspnea was commonly reported in patients treated with KYPROLIS. In the ASPIRE study, the incidence of dyspnea events in KRd-treated patients was 23.0% (the incidence of ≥ Grade 3 events was 2.8%). In the ENDEAVOR and ARROW studies, the incidences of dyspnea events in Kd 20/56 mg/m^2 twice weekly and 20/70 mg/m^2 once weekly treated patients were 35.2% and 11.8%, respectively (the incidences of ≥ Grade 3 events were 6.5% and 0.4%, respectively). In the CANDOR study, the incidence of dyspnea events in patients receiving KdD twice weekly was 22.4% (the incidence of ≥ Grade 3 events was 3.9%). In the IKEMA study, the incidence of dyspnea was 27.7% (Grade ≥ 3: 5.1%] in the IsaKd arm and 21.3% [Grade ≥ 3: 0.8%) in the Kd arm.

Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Withhold KYPROLIS until Grade 3 and 4 dyspnea resolves or returns to baseline. Carefully consider the benefits and risks when deciding if treatment with KYPROLIS should be re-initiated (see 8 ADVERSE REACTIONS and 4 DOSAGE AND ADMINISTRATION).

7.1 Special Populations

7.1.1 Pregnant Women

There are no data on the use of KYPROLIS in pregnant woman. Carfilzomib was clastogenic in *in vitro* tests. In animals, carfilzomib caused embryo-fetal toxicity and although it was not teratogenic during the period of organogenesis, exposure levels were lower in the animals than in patients receiving recommended clinical doses of KYPROLIS (see 16 NON-CLINICAL TOXICOLOGY). Based on these findings and its mechanism of action, KYPROLIS can cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. If pregnancy occurs during this time, patients should be apprised of the potential hazard to the fetus. KYPROLIS should not be used during pregnancy unless the potential benefits to the mother outweigh the potential risks to the fetus.

Female patients of child bearing potential treated with KYPROLIS and/or their male partners should use effective contraception methods or abstain from sexual activity during therapy and for 30 days after treatment with KYPROLIS.

Male patients and/or their female partners (if of childbearing potential) should use effective contraceptive methods or abstain from sexual activity while treated with KYPROLIS and for 90 days after treatment.

KYPROLIS is associated with an increased risk of venous thrombosis (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular, Venous Thrombosis) and it is not known if carfilzomib will reduce the efficacy of oral contraceptives as a result of drug-drug interactions (see 9 DRUG INTERACTIONS). Therefore, the concomitant use of oral contraceptives or hormonal methods of contraception associated with a risk of thrombosis should be carefully considered and be based on an individual benefit-risk assessment in patients receiving KYPROLIS.

7.1.2 Breast-feeding

It is not known whether carfilzomib is present in human breast milk. KYPROLIS should not be administered to women who are breast-feeding. Due to the potential for adverse effects in nursing infants from KYPROLIS, a decision should be made whether to discontinue nursing or to discontinue KYPROLIS, taking into account the potential benefit of KYPROLIS to the mother.

7.1.3 Pediatrics

Pediatrics (< 18 years of age)

The safety and effectiveness of KYPROLIS in pediatric patients have not been established.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age)

A total of 392 patients were treated with KYPROLIS in combination with lenalidomide and dexamethasone (KRd); the median age was 64 years. Of these, 185 patients (47%) were ≥ 65 years of age and 43 patients (11%) were ≥ 75 years of age. The incidence of serious adverse events was 57% in patients < 65 years of age, 73% in patients 65 to 74 years of age, and 81% in patients ≥ 75 years of age.

A total of 463 patients were treated with KYPROLIS in combination with dexamethasone (Kd); the median age was 65 years. Of these, 240 patients (52%) were ≥ 65 years of age and 77 patients (17%) were ≥ 75 years of age. The incidence of serious adverse events was 54% in patients < 65 years of age, 60% in patients 65 to 74 years of age, and 69% in patients ≥ 75 years of age.

A total of 308 patients were treated with KYPROLIS twice weekly in combination with dexamethasone and daratumumab (KdD); the median age was 64 years. Of these, 146 patients (47%) were ≥ 65 years of age and 28 patients (9%) were ≥ 75 years of age. The incidence of serious adverse events was 52% in patients < 65 years of age, 61% in patients 65 to 74 years of age, and 57% in patients ≥ 75 years of age. In the KdD arm, fatal treatment-emergent adverse events (TEAEs) occurred in 6% of patients < 65 years of age and 14% of patients ≥ 65 years of age. In the Kd arm, fatal TEAEs occurred in 8% of patients < 65 years of age and 3% of patients ≥ 65 years of age (see 8 ADVERSE REACTIONS).

There are increased risks for cardiovascular events in patients ≥ 75 years of age compared to patients < 75 years of age when treated with either KRd, Kd, or KdD.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Safety data for KYPROLIS are available from clinical trials of a pooled patient population (n = 3878). The most common adverse reactions (> 20%) from this pooled safety set were: anemia, thrombocytopenia, neutropenia, nausea, diarrhea, fatigue, pyrexia, respiratory tract infection, dyspnea, cough, and hypertension. The most common serious adverse reactions (≥ 2%) from this pooled safety set that occurred during KYPROLIS treatment included: pneumonia (10.2%), acute kidney injury (4.1%), pyrexia (3.1%), cardiac failure (3.0%), respiratory tract infection (2.6%), sepsis (2.1%), dyspnea (2.1%), and anaemia (2.0%). The most common adverse events leading to discontinuation of any study drug (≥ 1%) included disease progression, pneumonia, and acute kidney injury, however the patient incidences were < 2% for each of these events.

In the ASPIRE study, which included 392 patients treated with at least one dose of KRd, the most common adverse reactions (> 20% in the KRd arm) included: diarrhea, anemia, neutropenia, fatigue, upper respiratory tract infection, pyrexia, cough, hypokalemia, thrombocytopenia, muscle spasms, pneumonia, nausea, constipation, insomnia, viral upper respiratory tract infection, and bronchitis. The most common serious adverse reactions reported in the KRd arm as compared with the Rd arm were pneumonia (17.1% vs. 13.4%), respiratory tract infection (4.1% vs. 2.1%), pyrexia (3.6% vs. 2.8%), pulmonary embolism (3.1% vs. 2.1%), atrial fibrillation (2.3% vs. 2.1%), deep vein thrombosis (2.3% vs. 1.5%), acute kidney injury (2.0% vs. 1.0%), and febrile neutropenia (2.0% vs. 1.0%). The most common adverse events leading to discontinuation of KYPROLIS included pneumonia (1.0%), myocardial infarction (0.8%) and upper respiratory tract infection (0.8%).

In the ENDEAVOR study, which included 463 patients in the KYPROLIS and dexamethasone (Kd) arm, the most common adverse reactions (> 20% in the Kd arm) included: anemia, thrombocytopenia, diarrhea, nausea, fatigue, pyrexia, peripheral edema, asthenia, respiratory tract infection, bronchitis, back pain, headache, insomnia, dyspnea, cough, and hypertension (Table **11**). The most common serious adverse reactions reported in the Kd arm as compared with the bortezomib and dexamethasone (Vd) arm were pneumonia (2.6% vs. 2.9%), dyspnea (2.4% vs. none), pyrexia (2.2% vs. 0.2%), cardiac failure (1.3% vs. 0.2%), pulmonary embolism (1.1% vs. 0.4%), bronchitis (0.9% vs. 0.4%), and diarrhea (0.9% vs. 2.0%). The most frequent adverse events leading to discontinuation of KYPROLIS included cardiac failure (1.7%), asthenia (1.1%), ejection fraction decreased (1.1%), acute renal failure (1.1%), dyspnea (0.9%), multiple myeloma (0.9%), pyrexia (0.9%), disease progression (0.6%), and pneumonia (0.6%).

In the ARROW study, which included 238 patients in the Kd once weekly dosing arm, the most common adverse reactions (> 20%) included: respiratory tract infection, anemia, pyrexia, thrombocytopenia, hypertension, and fatigue (Table 12). The most common serious adverse reactions occurring with ≥ 2% incidences in the Kd once weekly treatment arm were pneumonia (8.4%), acute kidney injury (4.2%), sepsis (2.5%), and septic shock (2.1%). The most common adverse events leading to discontinuation of KYPROLIS in the Kd once weekly treatment arm included acute kidney injury (1.7%), plasma cell myeloma (1.3%), cardiac failure (0.8%), cardiac failure acute (0.8%), ejection fraction decreased (0.8%), acute lung injury (0.8%), pulmonary embolism (0.8%), and sepsis (0.8%).

In the CANDOR study, which either included 153 patients in the Kd twice weekly dosing arm or 308 patients in the KdD twice weekly dosing arm, the most common adverse reactions (> 20%) included: thrombocytopenia, anemia, diarrhea, fatigue, respiratory tract infection, cough, and

hypertension (Table 13). Serious adverse events were reported in 56% of the patients in the KdD arm and 46% of the patients in the Kd arm. The most common serious adverse reactions occurred with ≥ 2% incidences in either treatment arm were: pneumonia, urinary tract infection, influenza, sepsis, pyrexia, pulmonary embolism, dyspnea, cardiac failure, acute kidney injury, anemia, and plasma cell myeloma. Grade ≥ 3 adverse events occurred in 82% of patients in the KdD arm as compared with 74% in the Kd arm. Discontinuation of any study treatment due to any adverse events occurred in 22% of patients in the KdD arm versus 25% in the Kd arm. The most common adverse reactions leading to discontinuation of any study drug were cardiac failure (n = 6, 2%) and fatigue (n = 6, 2%) in the KdD arm and cardiac failure (n = 3, 2%), hypertension (n = 3, 2%) and acute kidney injury (n = 3, 2%) in the Kd arm. The most common reactions leading to discontinuation of KYPROLIS were cardiac failure (n = 6, 2%) and fatigue (n = 6, 2%) in the KdD arm and cardiac failure (n = 3, 2%), hypertension (n = 3, 2%) and acute kidney injury (n = 3, 2%) in the Kd arm. The most common reaction leading to discontinuation of daratumumab was pneumonia (n = 4, 1%). Additionally, deaths due to adverse events within 30 days of the last dose of any study treatment occurred in 30/308 (10%) patients in the KdD arm compared with 8/153 (5%) patients in the Kd arm. The most common causes of death occurring in patients (%) in the two arms (KdD vs. Kd) was infections 14 (5%) vs. 4 (3%). The risk of fatal treatment-emergent adverse events was higher among patients ≥ 65 years of age (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

In the IKEMA Study, which compared IsaKd vs. Kd, the most frequent adverse reactions (in ≥ 20% of patients who received IsaKd) were upper respiratory tract infection (66.7%), infusion reactions (45.8%), fatigue (41.8%), hypertension (37.3%), pneumonia (36.2%), diarrhea (36.2%), dyspnea (28.8%), insomnia (23.7%), bronchitis (23.7%), and back pain (22.0%). Serious adverse reactions occurred in 59.3% of patients receiving IsaKd and in 57.4% of patients receiving Kd. The most frequent serious adverse reactions (in > 5% of patients) were pneumonia (24.9% with IsaKd vs 18.0% with Kd) and upper respiratory tract infections (9.0% with IsaKd vs 8.2% with Kd). Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients in the IsaKd group and in 3.3% of patients in the Kd group (those occurring in more than 1% of patients were pneumonia and cardiac failure both occurring in 1.1% of patients in the IsaKd group and in 0.8% of patients in the Kd group). Permanent discontinuation of treatment because of adverse reactions was reported in 8.5% of patients treated with IsaKd and in 13.9% of patients treated with Kd. The most frequent adverse reactions requiring permanent discontinuation in patients who received IsaKd were infections (2.8%). Isatuximab alone was discontinued in 0.6% of patients due to infusion-related reactions. Isatuximab dose interruptions due to an adverse reaction occurred in 32.8% of patients. The most frequent adverse reaction requiring isatuximab dose interruption was infusion-related reaction (29.9%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

KYPROLIS in Combination with Lenalidomide and Dexamethasone (KRd)

The safety of KYPROLIS has been evaluated in the ASPIRE study. The safety population includes open-label randomized Phase 3 pivotal study of patients with relapsed multiple myeloma receiving at least one dose of KYPROLIS in combination with lenalidomide and dexamethasone (N = 392) vs. patients receiving at least one dose of lenalidomide and dexamethasone (N = 389) (see 14 CLINICAL TRIALS). The median overall duration of treatment with any study drug in the KRd and Rd arms were 88.0 and 57.0 weeks, respectively; each treatment cycle was 4 weeks (28 days). In the KRd arm, the median number of cycles of KYPROLIS initiated were 18.0 (the maximum number of cycles allowed per protocol in that study after which patients in that arm continued on treatment with Rd). Adverse reactions that occurred in ≥ 5% of patients are presented in Table 10.

Table 10. Adverse Reactions that Occurred in ≥ 5% of Patients in the ASPIRE Study

	KRd (N = 392)		Rd (N = 389)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥ Grade 3 n (%)**	**All Grades n (%)**	**≥ Grade 3 n (%)**
Blood and lymphatic system disorders				
Anemia[a]	173 (44.1%)	75 (19.1%)	161 (41.4%)	69 (17.7%)
Neutropenia[b]	170 (43.4%)	132 (33.7%)	150 (38.6%)	114 (29.3%)
Thrombocytopenia[c]	128 (32.7%)	79 (20.2%)	102 (26.2%)	58 (14.9%)
Leukopenia[d]	38 (9.7%)	15 (3.8%)	28 (7.2%)	17 (4.4%)
Cardiac disorders				
Cardiac failure[e]	20 (5.1%)	9 (2.3%)	13 (3.3%)	6 (1.5%)
Eye disorders				
Cataract	44 (11.2%)	20 (5.1%)	37 (9.5%)	17 (4.4%)
Vision blurred	24 (6.1%)	0	15 (3.9%)	1 (0.3%)
Gastrointestinal disorders				
Diarrhea	174 (44.4%)	18 (4.6%)	145 (37.3%)	17 (4.4%)
Nausea	82 (20.9%)	3 (0.8%)	56 (14.4%)	4 (1.0%)
Constipation	81 (20.7%)	1 (0.3%)	70 (18.0%)	2 (0.5%)
Vomiting	49 (12.5%)	1 (0.3%)	33 (8.5%)	2 (0.5%)
Abdominal pain[f]	58 (14.8%)	7 (1.8%)	38 (9.8%)	5 (1.3%)
Dyspepsia	24 (6.1%)	0	22 (5.7%)	2 (0.5%)
Toothache	20 (5.1%)	1 (0.3%)	12 (3.1%)	0
General disorders and administration site conditions				
Fatigue	131 (33.4%)	32 (8.2%)	124 (31.9%)	26 (6.7%)
Pyrexia	117 (29.8%)	7 (1.8%)	84 (21.6%)	3 (0.8%)
Edema peripheral	78 (19.9%)	4 (1.0%)	66 (17.0%)	2 (0.5%)

Table 10. Adverse Reactions that Occurred in ≥ 5% of Patients in the ASPIRE Study

	KRd (N = 392)		Rd (N = 389)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥ Grade 3 n (%)**	**All Grades n (%)**	**≥ Grade 3 n (%)**
Asthenia	73 (18.6%)	15 (3.8%)	57 (14.7%)	8 (2.1%)
Chills	26 (6.6%)	0	9 (2.3%)	0
Infections and infestations				
Bronchitis	79 (20.2%)	8 (2.0%)	59 (15.2%)	12 (3.1%)
Pneumonia	91 (23.2%)	63 (16.1%)	66 (17.0%)	47 (12.1%)
Respiratory tract infection[g]	195 (49.7%)	28 (7.1%)	161 (41.4%)	17 (4.4%)
Urinary tract infection	38 (9.7%)	5 (1.3%)	22 (5.7%)	2 (0.5%)
Influenza	29 (7.4%)	2 (0.5%)	15 (3.9%)	3 (0.8%)
Viral infection	28 (7.1%)	0	11 (2.8%)	0
Gastroenteritis	20 (5.1%)	4 (1.0%)	13 (3.3%)	2 (0.5%)
Investigations				
Blood creatinine increased	27 (6.9%)	5 (1.3%)	20 (5.1%)	1 (0.3%)
Alanine aminotransferase increased	21 (5.4%)	9 (2.3%)	15 (3.9%)	3 (0.8%)
Metabolism and nutrition disorders				
Hypokalemia	116 (29.6%)	41 (10.5%)	58 (14.9%)	23 (5.9%)
Hypocalcemia	66 (16.8%)	13 (3.3%)	48 (12.3%)	7 (1.8%)
Hypophosphatemia	57 (14.5%)	35 (8.9%)	33 (8.5%)	20 (5.1%)
Hyperglycemia	50 (12.8%)	21 (5.4%)	39 (10.0%)	18 (4.6%)
Decreased appetite	47 (12.0%)	0	35 (9.0%)	2 (0.5%)
Hypomagnesemia	40 (10.2%)	4 (1.0%)	29 (7.5%)	3 (0.8%)
Hyperuricemia	22 (5.6%)	2 (0.5%)	10 (2.6%)	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	106 (27.0%)	5 (1.3%)	82 (21.1%)	4 (1.0%)
Back pain	73 (18.6%)	6 (1.5%)	83 (21.3%)	12 (3.1%)
Arthralgia	57 (14.5%)	2 (0.5%)	58 (14.9%)	2 (0.5%)
Pain in extremity	48 (12.2%)	4 (1.0%)	43 (11.1%)	6 (1.5%)
Bone pain	39 (9.9%)	2 (0.5%)	36 (9.3%)	5 (1.3%)
Muscular weakness	28 (7.1%)	5 (1.3%)	24 (6.2%)	7 (1.8%)
Musculoskeletal pain	25 (6.4%)	1 (0.3%)	36 (9.3%)	3 (0.8%)
Musculoskeletal chest pain	26 (6.6%)	1 (0.3%)	29 (7.5%)	2 (0.5%)
Myalgia	25 (6.4%)	0	22 (5.7%)	0

Table 10. Adverse Reactions that Occurred in ≥ 5% of Patients in the ASPIRE Study

	KRd (N = 392)		Rd (N = 389)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥ Grade 3 n (%)**	**All Grades n (%)**	**≥ Grade 3 n (%)**
Nervous system disorders				
Headache	56 (14.3%)	4 (1.0%)	32 (8.2%)	2 (0.5%)
Dizziness	53 (13.5%)	2 (0.5%)	44 (11.3%)	2 (0.5%)
Peripheral neuropathy[h]	57 (14.5%)	9 (2.3%)	54 (13.9%)	7 (1.8%)
Paresthesia	27 (6.9%)	1 (0.3%)	23 (5.9%)	1 (0.3%)
Psychiatric disorders				
Insomnia	81 (20.7%)	12 (3.1%)	65 (16.7%)	11 (2.8%)
Anxiety	33 (8.4%)	1 (0.3%)	17 (4.4%)	2 (0.5%)
Respiratory, thoracic, and mediastinal disorders				
Cough[i]	128 (32.7%)	2 (0.5%)	78 (20.1%)	0
Dyspnea	78 (19.9%)	10 (2.6%)	59 (15.2%)	7 (1.8%)
Oropharyngeal pain	28 (7.1%)	0	22 (5.7%)	0
Epistaxis	20 (5.1%)	1 (0.3%)	17 (4.4%)	1 (0.3%)
Skin and subcutaneous tissue disorders				
Rash	52 (13.3%)	5 (1.3%)	60 (15.4%)	6 (1.5%)
Erythema	30 (7.7%)	0	13 (3.3%)	0
Pruritus	31 (7.9%)	0	16 (4.1%)	1 (0.3%)
Hyperhidrosis	28 (7.1%)	0	18 (4.6%)	1 (0.3%)
Vascular disorders				
Hypertension	62 (15.8%)	21 (5.4%)	31 (8.0%)	9 (2.3%)
Deep vein thrombosis	26 (6.6%)	7 (1.8%)	15 (3.9%)	4 (1.0%)
Hypotension	26 (6.6%)	8 (2.0%)	24 (6.2%)	4 (1.0%)

[a] 'Anemia' includes Anemia PT, Hematocrit Decreased PT and Hemoglobin Decreased PT.
[b] 'Neutropenia' includes Neutrophil Count Decreased PT and Neutropenia PT.
[c] 'Thrombocytopenia' includes Platelet Count Decreased PT and Thrombocytopenia PT.
[d] 'Leukopenia' includes Leukopenia PT and White Blood Cell Count Decreased PT.
[e] 'Cardiac Failure' includes Cardiac Failure PT, and Cardiac Failure Congestive PT.
[f] 'Abdominal Pain' includes Abdominal Pain PT, and Abdominal Pain Upper PT.
[g] 'Respiratory Tract Infection' includes Respiratory Tract Infection PT, Lower Respiratory Tract Infection, Upper Respiratory Tract Infection PT and Viral Upper Respiratory Tract Infection.
[h] 'Peripheral Neuropathy' includes Peripheral Sensory Neuropathy PT and Neuropathy Peripheral PT.
[i] 'Cough' includes Productive Cough PT, and Cough PT.

KYPROLIS in Combination with Dexamethasone (Kd)

Kd Twice Weekly Dosing Regimen

The safety of KYPROLIS was evaluated in the ENDEAVOR study. The safety population includes open-label randomized Phase 3 study of patients with relapsed multiple myeloma receiving at least one dose of KYPROLIS and dexamethasone (Kd; N = 463) vs. patients receiving at least one dose of bortezomib and dexamethasone (Vd; N = 456). The median overall duration of treatment with Kd was 48.0 weeks (12 cycles) and with Vd was 27.0 weeks (8 cycles); the treatment cycle for Kd was 4 weeks (28 days), and the treatment cycle for Vd was 3 weeks (21 days). Adverse reactions that occurred in ≥ 5% of patients are presented in Table 11.

Table 11. Adverse Reactions that Occurred in ≥ 5% of Kd Patients in the ENDEAVOR Study

	Kd (N = 463)		Vd (N = 456)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥ Grade 3 n (%)**	**All Grades n (%)**	**≥ Grade 3 n (%)**
Blood and lymphatic system disorders				
Anemia	197 (42.5%)	76 (16.4%)	129 (28.3%)	46 (10.1%)
Thrombocytopenia[a]	147 (31.7%)	57 (12.3%)	123 (27.0%)	67 (14.7%)
Lymphopenia[b]	71 (15.3%)	50 (10.8%)	43 (9.4%)	23 (5.0%)
Neutropenia	28 (6.0%)	11 (2.4%)	26 (5.7%)	10 (2.2%)
Cardiac disorders				
Cardiac failure[c]	26 (5.6%)	13 (2.8%)	5 (1.1%)	3 (0.7%)
Palpitations	23 (5.0%)	0	6 (1.3%)	0
Tachycardia	23 (5.0%)	0	10 (2.2%)	0
Eye disorders				
Cataract	32 (6.9%)	11 (2.4%)	17 (3.7%)	9 (2.0%)
Gastrointestinal disorders				
Diarrhea	168 (36.3%)	18 (3.9%)	185 (40.6%)	39 (8.6%)
Nausea	109 (23.5%)	9 (1.9%)	91 (20.0%)	3 (0.7%)
Vomiting	77 (16.6%)	7 (1.5%)	45 (9.9%)	7 (1.5%)
Constipation	75 (16.2%)	2 (0.4%)	127 (27.9%)	8 (1.8%)
Abdominal pain[d]	51 (11.0%)	5 (1.1%)	68 (14.9%)	7 (1.5%)
Dyspepsia	35 (7.6%)	3 (0.6%)	25 (5.5%)	1 (0.2%)
General disorders and administration site conditions				
Pyrexia	150 (32.4%)	14 (3.0%)	70 (15.4%)	3 (0.7%)
Fatigue	149 (32.2%)	31 (6.7%)	140 (30.7%)	35 (7.7%)
Peripheral edema	116 (25.1%)	5 (1.1%)	87 (19.1%)	3 (0.7%)

Table 11. Adverse Reactions that Occurred in ≥ 5% of Kd Patients in the ENDEAVOR Study

System Organ Class Preferred Term	Kd (N = 463) All Grades n (%)	Kd (N = 463) ≥ Grade 3 n (%)	Vd (N = 456) All Grades n (%)	Vd (N = 456) ≥ Grade 3 n (%)
Asthenia	107 (23.1%)	21 (4.5%)	79 (17.3%)	14 (3.1%)
Chest pain	43 (9.3%)	3 (0.6%)	21 (4.6%)	3 (0.7%)
Chills	26 (5.6%)	0	12 (2.6%)	1 (0.2%)
Influenza like illness	24 (5.2%)	0	10 (2.2%)	0
Malaise	24 (5.2%)	0	8 (1.8%)	1 (0.2%)
Infections and infestations				
Respiratory tract infection[e]	166 (35.9%)	26 (5.6%)	121 (26.5%)	15 (3.3%)
Bronchitis	108 (23.3%)	13 (2.8%)	48 (10.5%)	4 (0.9%)
Nasopharyngitis	81 (17.5%)	1 (0.2%)	61 (13.4%)	1 (0.2%)
Pneumonia[f]	66 (14.3%)	50 (10.8%)	57 (12.5%)	41 (9.0%)
Urinary tract infection	39 (8.4%)	11 (2.4%)	30 (6.6%)	3 (0.7%)
Rhinitis	29 (6.3%)	0	10 (2.2%)	0
Gastroenteritis	23 (5.0%)	4 (0.9%)	16 (3.5%)	3 (0.7%)
Investigations				
Blood creatinine increased	53 (11.4%)	4 (0.9%)	28 (6.1%)	2 (0.4%)
Creatinine renal clearance decreased	29 (6.3%)	10 (2.2%)	18 (3.9%)	3 (0.7%)
Alanine aminotransferase increased	23 (5.0%)	6 (1.3%)	20 (4.4%)	3 (0.7%)
Metabolism and nutrition disorders				
Hypokalemia	60 (13.0%)	11 (2.4%)	51 (11.2%)	17 (3.7%)
Hyperglycemia	54 (11.7%)	22 (4.8%)	42 (9.2%)	17 (3.7%)
Decreased appetite	50 (10.8%)	4 (0.9%)	62 (13.6%)	6 (1.3%)
Hypophosphatemia	32 (6.9%)	15 (3.2%)	28 (6.1%)	6 (1.3%)
Hyperuricemia	31 (6.7%)	5 (1.1%)	8 (1.8%)	3 (0.7%)
Hypocalcemia	27 (5.8%)	6 (1.3%)	19 (4.2%)	1 (0.2%)
Musculoskeletal and connective tissue disorders				
Back pain	107 (23.1%)	10 (2.2%)	81 (17.8%)	14 (3.1%)
Muscle spasms	92 (19.9%)	1 (0.2%)	28 (6.1%)	3 (0.7%)
Arthralgia	60 (13.0%)	3 (0.6%)	52 (11.4%)	4 (0.9%)
Bone pain	55 (11.9%)	9 (1.9%)	40 (8.8%)	6 (1.3%)
Pain in extremity	55 (11.9%)	3 (0.6%)	50 (11.0%)	4 (0.9%)

Table 11. Adverse Reactions that Occurred in ≥ 5% of Kd Patients in the ENDEAVOR Study

System Organ Class Preferred Term	Kd (N = 463)		Vd (N = 456)	
	All Grades n (%)	≥ Grade 3 n (%)	All Grades n (%)	≥ Grade 3 n (%)
Muscular weakness	44 (9.5%)	8 (1.7%)	47 (10.3%)	8 (1.8%)
Musculoskeletal chest pain	39 (8.4%)	2 (0.4%)	20 (4.4%)	3 (0.7%)
Myalgia	28 (6.0%)	1 (0.2%)	18 (3.9%)	1 (0.2%)
Musculoskeletal pain	25 (5.4%)	3 (0.6%)	24 (5.3%)	3 (0.7%)
Nervous system disorders				
Headache	95 (20.5%)	4 (0.9%)	49 (10.7%)	3 (0.7%)
Peripheral neuropathy[g]	72 (15.6%)	7 (1.5%)	192 (42.1%)	33 (7.2%)
Paresthesia	43 (9.3%)	3 (0.6%)	76 (16.7%)	2 (0.4%)
Dizziness	42 (9.1%)	1 (0.2%)	70 (15.4%)	3 (0.7%)
Hypoesthesia	24 (5.2%)	1 (0.2%)	14 (3.1%)	0
Psychiatric disorders				
Insomnia	125 (27.0%)	12 (2.6%)	122 (26.8%)	12 (2.6%)
Renal and urinary disorders				
Renal failure acute	23 (5.0%)	12 (2.6%)	15 (3.3%)	7 (1.5%)
Respiratory, thoracic, and mediastinal disorders				
Dyspnea	149 (32.2%)	29 (6.3%)	62 (13.6%)	10 (2.2%)
Cough[h]	143 (30.9%)	0	80 (17.5%)	2 (0.4%)
Oropharyngeal pain	28 (6.0%)	0	19 (4.2%)	0
Epistaxis	24 (5.2%)	3 (0.6%)	14 (3.1%)	1 (0.2%)
Skin and subcutaneous tissue disorders				
Rash	41 (8.9%)	4 (0.9%)	35 (7.7%)	1 (0.2%)
Pruritus	34 (7.3%)	0	29 (6.4%)	0
Vascular disorders				
Hypertension	149 (32.2%)	67 (14.5%)	45 (9.9%)	15 (3.3%)
Hypotension	29 (6.3%)	5 (1.1%)	40 (8.8%)	8 (1.8%)
Flushing	24 (5.2%)	1 (0.2%)	7 (1.5%)	0

[a] 'Thrombocytopenia' includes Thrombocytopenia With Platelet Count Decreased preferred term (PT).
[b] 'Lymphopenia' includes Lymphopenia with Lymphocyte Count Decreased PT.
[c] 'Cardiac Failure' includes Cardiac Failure PT, and Cardiac Failure Congestive PT.
[d] 'Abdominal Pain' includes Abdominal Pain PT, and Abdominal Pain Upper PT.
[e] 'Respiratory Tract Infection' includes Respiratory Tract Infection PT, Lower Respiratory Tract Infection PT and Upper Respiratory Tract Infection PT.
[f] 'Pneumonia' includes Bronchopneumonia PT, and Pneumonia PT.
[g] 'Peripheral Neuropathy' includes Peripheral Sensory Neuropathy PT and Neuropathy Peripheral PT.
[h] 'Cough' includes Productive Cough PT, and Cough PT.

Kd Once Weekly Dosing Regimen

The safety of KYPROLIS as a once weekly dosing regimen was evaluated in the ARROW study (see 14 CLINICAL TRIALS). The safety population of the open-label Phase 3 ARROW study includes patients with relapsed and refractory multiple myeloma receiving at least one dose of KYPROLIS and dexamethasone as a once weekly dosing regimen (Kd 20/70 mg/m^2; N = 238) vs. patients receiving at least one dose of KYPROLIS and dexamethasone as a twice weekly dosing regimen (Kd 20/27 mg/m^2; N = 235). The twice weekly Kd 20/27 mg/m^2 regimen is not an authorized treatment. In the ARROW study, the median overall duration of treatment with the Kd once weekly dosing regimen was 38.0 weeks (9.5 cycles); the treatment cycle for Kd once weekly dosing in the ARROW study is 4 weeks (28 days). Adverse reactions that occurred in ≥ 5% of patients observed in the Kd once weekly arm in the ARROW study are presented in Table 12.

Table 12. Adverse Reactions That Occurred in ≥ 5% of Patients in Kd Once Weekly Arm in the ARROW Study

	Once Weekly Kd 20/70 mg/m^2 (N = 238)	
System Organ Class Preferred Term	**All Grades n (%)**	**≥ Grade 3 n (%)**
Blood and lymphatic system disorders		
Anemia[a]	64 (26.9%)	42 (17.6%)
Thrombocytopenia[b]	53 (22.3%)	26 (10.9%)
Neutropenia[c]	30 (12.6%)	21 (8.8%)
Gastrointestinal disorders		
Diarrhea	44 (18.5%)	2 (0.8%)
Nausea	34 (14.3%)	1 (0.4%)
Constipation	19 (8.0%)	0
Vomiting	19 (8.0%)	0
Abdominal pain[d]	12 (5.0%)	2 (0.8%)
General disorders and administration site conditions		
Pyrexia	55 (23.1%)	2 (0.8%)
Fatigue	48 (20.2%)	11 (4.6%)
Asthenia	24 (10.1%)	3 (1.3%)
Peripheral edema	18 (7.6%)	0 (0.0%)
Infections and infestations		
Respiratory tract infection[e]	70 (29.4%)	7 (2.9%)
Pneumonia	28 (11.8%)	24 (10.1%)
Bronchitis	27 (11.3%)	2 (0.8%)

Table 12. Adverse Reactions That Occurred in ≥ 5% of Patients in Kd Once Weekly Arm in the ARROW Study

System Organ Class Preferred Term	Once Weekly Kd 20/70 mg/m^2 (N = 238) All Grades n (%)	≥ Grade 3 n (%)
Influenza	12 (5.0%)	4 (1.7%)
Investigations		
Blood creatinine increased	14 (5.9%)	2 (0.8%)
Metabolism and nutrition disorders		
Hypokalemia	19 (8.0%)	6 (2.5%)
Decreased appetite	13 (5.5%)	1 (0.4%)
Musculoskeletal and connective tissue disorders		
Back pain	28 (11.8%)	2 (0.8%)
Muscle spasms	21 (8.8%)	0
Bone pain	20 (8.4%)	2 (0.8%)
Arthralgia	15 (6.3%)	0
Pain in extremity	15 (6.3%)	1 (0.4%)
Musculoskeletal pain	12 (5.0%)	0
Nervous system disorders		
Headache	25 (10.5%)	1 (0.4%)
Psychiatric disorders		
Insomnia	35 (14.7%)	2 (0.8%)
Renal and urinary disorders		
Acute kidney injury	15 (6.3%)	8 (3.4%)
Respiratory, thoracic, and mediastinal disorders		
Cough[f]	37 (15.5%)	2 (0.8%)
Dyspnea	23 (9.7%)	1 (0.4%)
Vascular disorders		
Hypertension	51 (21.4%)	13 (5.5%)

[a] 'Anemia' includes Anemia PT, Hematocrit Decreased PT and Hemoglobin Decreased PT.
[b] 'Thrombocytopenia' includes Platelet Count Decreased PT and Thrombocytopenia PT.
[c] 'Neutropenia' includes Neutrophil Count Decreased PT and Neutropenia PT.
[d] 'Abdominal Pain' includes Abdominal Pain PT, and Abdominal Pain Upper PT.
[e] 'Respiratory Tract Infection' includes Respiratory Tract Infection PT, Lower Respiratory Tract Infection, Upper Respiratory Tract Infection PT and Viral Upper Respiratory Tract Infection
[f] 'Cough' includes Productive Cough PT, and Cough PT.

KYPROLIS in Combination with Dexamethasone and Daratumumab (KdD)

The safety of 20/56 mg/m^2 twice weekly KYPROLIS in combination with dexamethasone and daratumumab (KdD) was evaluated in an open-label, randomized Phase 3 trial (CANDOR) (see 14 CLINICAL TRIALS).

Twice Weekly KdD

CANDOR evaluated patients with relapsed or refractory multiple myeloma. The safety population includes patients with relapsed or refractory multiple myeloma who received at least one dose of KYPROLIS in combination with dexamethasone and daratumumab (KdD; N = 308) vs. patients receiving at least one dose of Kd (N = 153). Patients received treatment with any study drug for a median duration of 70 weeks in the KdD arm and 40 weeks in the Kd arm. Patients received a median of 58 weeks of treatment with KYPROLIS in the KdD arm and 40 weeks in the Kd arm. Patients in the KdD group received a median of 68 weeks of treatment with daratumumab. Adverse reactions that occurred in ≥ 5% of patients are presented in Table 13.

Table 13. Adverse Reactions That Occurred in ≥ 5% of Patients in Either Kd or KdD Twice Weekly Arm in the CANDOR Study

	20/56 mg/m^2 KdD BIW (N = 308)		**20/56 mg/m^2 Kd BIW (N = 153)**	
System Organ Class Preferred Term	**Any Grade n (%)**	**≥ Grade 3 n (%)**	**Any Grade n (%)**	**≥ Grade 3 n (%)**
Blood and lymphatic system disorders				
Thrombocytopenia[a]	115 (37.3)	76 (24.7)	46 (30.1)	25 (16.3)
Anaemia[b]	101 (32.8)	51 (16.6)	48 (31.4)	22 (14.4)
Neutropenia[c]	45 (14.6)	28 (9.1)	15 (9.8)	9 (5.9)
Lymphopenia[d]	27 (8.8)	21 (6.8)	12 (7.8)	11 (7.2)
Leukopenia[e]	20 (6.5)	9 (2.9)	6 (3.9)	2 (1.3)
Cardiac disorders				
Cardiac failure[f]	15 (4.9)	7 (2.3)	8 (5.2)	7 (4.6)
Eye disorders				
Cataract	17 (5.5)	7 (2.3)	5 (3.3)	3 (2.0)
Gastrointestinal disorders				
Diarrhea	97 (31.5)	12 (3.9)	22 (14.4)	1 (0.7)
Nausea	56 (18.2)	0 (0.0)	20 (13.1)	1 (0.7)
Vomiting	37 (12.0)	0 (0.0)	13 (8.5)	0 (0.0)
Constipation	22 (7.1)	0 (0.0)	6 (3.9)	0 (0.0)
Abdominal pain[g]	20 (6.5)	0 (0.0)	11 (7.2)	2 (1.3)
General disorders and administration site conditions				
Fatigue	75 (24.4)	24 (7.8)	28 (18.3)	7 (4.6)
Pyrexia	60 (19.5)	6 (1.9)	23 (15.0)	1 (0.7)
Edema peripheral	33 (10.7)	0 (0.0)	14 (9.2)	1 (0.7)
Asthenia	30 (9.7)	9 (2.9)	17 (11.1)	5 (3.3)

Table 13. Adverse Reactions That Occurred in ≥ 5% of Patients in Either Kd or KdD Twice Weekly Arm in the CANDOR Study

	20/56 mg/m^2 KdD BIW (N = 308)		20/56 mg/m^2 Kd BIW (N = 153)	
System Organ Class Preferred Term	**Any Grade n (%)**	**≥ Grade 3 n (%)**	**Any Grade n (%)**	**≥ Grade 3 n (%)**
Chills	17 (5.5)	0 (0.0)	6 (3.9)	0 (0.0)
Infections and infestations				
Respiratory tract infection[h]	124 (40.3)	22 (7.1)	45 (29.4)	5 (3.3)
Pneumonia	55 (17.9)	41 (13.3)	19 (12.4)	13 (8.5)
Bronchitis	52 (16.9)	8 (2.6)	18 (11.8)	2 (1.3)
Influenza	34 (11.0)	11 (3.6)	10 (6.5)	1 (0.7)
Nasopharyngitis	27 (8.8)	1 (0.3)	13 (8.5)	1 (0.7)
Urinary tract infection	18 (5.8)	4 (1.3)	4 (2.6)	3 (2.0)
Injury, poisoning, and procedural complications				
Infusion related reaction	24 (7.8)	2 (0.6)	3 (2.0)	0 (0.0)
Metabolism and nutrition disorders				
Hyperglycemia	28 (9.1)	13 (4.2)	11 (7.2)	5 (3.3)
Decreased appetite	27 (8.8)	3 (1.0)	9 (5.9)	1 (0.7)
Hypokalemia	18 (5.8)	5 (1.6)	9 (5.9)	2 (1.3)
Musculoskeletal and connective tissue disorders				
Back pain	50 (16.2)	6 (1.9)	15 (9.8)	2 (1.3)
Muscle spasms	36 (11.7)	2 (0.6)	18 (11.8)	2 (1.3)
Arthralgia	26 (8.4)	2 (0.6)	8 (5.2)	1 (0.7)
Pain in extremity	19 (6.2)	1 (0.3)	10 (6.5)	1 (0.7)
Nervous system disorders				
Peripheral neuropathy[i]	45 (14.6)	0 (0.0)	7 (4.6)	0 (0.0)
Headache	41 (13.3)	2 (0.6)	18 (11.8)	1 (0.7)
Dizziness	23 (7.5)	2 (0.6)	4 (2.6)	0 (0.0)
Psychiatric disorders				
Insomnia	55 (17.9)	12 (3.9)	17 (11.1)	3 (2.0)
Renal and urinary disorders				
Acute kidney injury	12 (3.9)	7 (2.3)	9 (5.9)	7 (4.6)
Respiratory, thoracic, and mediastinal disorders				
Cough[j]	63 (20.5)	0 (0.0)	32 (20.9)	0 (0.0)
Dyspnea	61 (19.8)	12 (3.9)	34 (22.2)	4 (2.6)
Skin and subcutaneous tissue disorders				
Rash	17 (5.5)	0 (0.0)	10 (6.5)	1 (0.7)

Table 13. Adverse Reactions That Occurred in ≥ 5% of Patients in Either Kd or KdD Twice Weekly Arm in the CANDOR Study

	20/56 mg/m^2 KdD BIW (N = 308)		20/56 mg/m^2 Kd BIW (N = 153)	
System Organ Class Preferred Term	**Any Grade n (%)**	**≥ Grade 3 n (%)**	**Any Grade n (%)**	**≥ Grade 3 n (%)**
Vascular disorders				
Hypertension	94 (30.5)	54 (17.5)	42 (27.5)	20 (13.1)

K: KYPROLIS; d: dexamethasone; D: Daratumumab; BIW: twice weekly.
[a] 'Thrombocytopenia' includes Platelet Count Decreased PT and Thrombocytopenia PT.
[b] 'Anemia' includes Anemia PT, Hematocrit Decreased PT and Hemoglobin Decreased PT.
[c] 'Neutropenia' includes Neutrophil Count Decreased PT and Neutropenia PT.
[d] 'Lymphopenia' includes Lymphocyte Count Decreased PT and Lymphopenia PT.
[e] 'Leukopenia' includes Leukopenia PT and White Blood Cell Count Decreased PT.
[f] 'Cardiac Failure' includes Cardiac Failure PT, and Cardiac Failure Congestive PT.
[g] 'Abdominal Pain' includes Abdominal Pain PT, and Abdominal Pain Upper PT.
[h] 'Respiratory Tract Infection' includes Respiratory Tract Infection PT, Lower Respiratory Tract Infection, Upper Respiratory Tract Infection PT and Viral Upper Respiratory Tract Infection.
[i] 'Peripheral Neuropathy' includes Peripheral Sensory Neuropathy PT and Neuropathy Peripheral PT.
[j] 'Cough' includes Productive Cough PT, and Cough PT.

Of the 307 patients in the KdD arm with baseline CrCL data, 174 had CrCL ≥ 80 mL/min (normal renal function), 96 had CrCL ≥ 50 to < 80 mL/min (mild renal impairment), 32 had CrCL ≥ 30 to < 50 mL/min (moderate renal impairment), and 5 had CrCL ≥ 15 to < 30 mL/min (severe renal impairment). Serious adverse events were reported in 58.0%, 56.3%, 87.5% and 80.0% of patients with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment, respectively; fatal adverse events were reported in 9.2%, 7.3%, 18.8% and 20.0% of patients, respectively. Of the 293 patients in the KdD arm with baseline hepatic status (based on bilirubin and transaminase levels), 269 had normal hepatic function and 24 had mild hepatic impairment. Patients with moderate or severe hepatic impairment were excluded from the study. Serious adverse events were reported in 58.7% and 70.8% of patients with normal hepatic function and mild hepatic impairment, respectively; fatal adverse events were reported in 8.9% and 12.5% of patients, respectively (see 7 WARNINGS AND PRECAUTIONS, Renal Impairment and Hepatic Impairment).

KYPROLIS in Combination with Isatuximab and Dexamethasone (IsaKd)

Table 14 presents the adverse reactions observed during the treatment period of IKEMA in 299 patients with multiple myeloma, treated with isatuximab 10 mg/kg in combination with KYPROLIS and dexamethasone (IsaKd) or KYPROLIS and dexamethasone (Kd) (see 14 CLINICAL TRIALS).

Table 14. Adverse Reactions (≥ 10%) in Patients Receiving IsaKd in IKEMA

Adverse Reactions	IsaKd (N = 177)		Kd (N = 122)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections				
Upper respiratory tract infection[a]	67	9	57	7
Pneumonia[b]	36	22	30	18
Bronchitis[c]	24	2.3	13	0.8
General Disorders and Administration Site Conditions				
Infusion-related reaction[d]	46	0.6	3.3	0
Fatigue[e]	42	5	32	3.3
Vascular Disorders				
Hypertension[f]	37	21	32	20
Gastrointestinal Disorders				
Diarrhea	36	2.8	29	2.5
Vomiting	15	1.1	9	0.8
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnea[g]	29	5	24	0.8
Cough[h]	23	0	15	0

Isa-Kd = Kyprolis, isatuximab, and dexamethasone

[a] Upper respiratory tract infection includes acute sinusitis, chronic sinusitis, H1N1 influenza, H3N2 influenza, influenza, laryngitis, laryngitis viral, nasal herpes, nasopharyngitis, pharyngitis, pharyngotonsillitis, respiratory syncytial virus infection, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, tracheitis, upper respiratory tract infection, viral rhinitis, respiratory tract infection, respiratory tract infection viral, influenza like illness, parainfluenzae virus infection, respiratory tract infection bacterial, and viral upper respiratory tract infection.

[b] Pneumonia includes atypical pneumonia, lower respiratory tract infection, lower respiratory tract infection viral, pneumocystis jirovecii pneumonia, pneumonia, pneumonia influenzal, pneumonia legionella, pneumonia pneumococcal, pneumonia respiratory syncytial viral, pneumonia streptococcal, pneumonia viral, pulmonary sepsis, and pulmonary tuberculosis.

[c] Bronchitis includes bronchitis, bronchitis viral, respiratory syncytial virus bronchitis, bronchitis chronic, and tracheobronchitis.

[d] Infusion-related reaction includes infusion-related reaction, cytokine release syndrome, and hypersensitivity.

[e] Fatigue includes fatigue and asthenia.

[f] Hypertension includes hypertension, blood pressure increased, and hypertensive crisis.

[g] Dyspnea includes dyspnea and dyspnea exertional.

[h] Cough includes cough, productive cough, and allergic cough

Please refer to the isatuximab Product Monograph for further information regarding select adverse reactions.

8.3 Less Common Clinical Trial Adverse Reactions

Less Common Clinical Trial Adverse Reactions (< 5%)* in ASPIRE:

BLOOD AND LYMPHATIC SYSTEM DISORDERS: febrile neutropenia (3.6%), lymphopenia (3.3%)

CARDIAC DISORDERS: atrial fibrillation (4.6%), palpitations (3.6%), myocardial infarction (3.1%), tachycardia (2.3%), acute myocardial infarction (1.3%), cardiac arrest (0.5%), myocardial ischemia (0.5%), pericardial effusion (0.3%)

EAR AND LABYRINTH DISORDERS: tinnitus (1.5%)

GASTROINTESTINAL DISORDERS: gastrointestinal hemorrhage (0.3%)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: chest pain (3.8%), influenza like illness (3.8%), pain (3.8%), malaise (2.8%), infusion site reactions (2.0%), multi-organ dysfunction syndrome (0.5%)

HEPATOBILIARY DISORDERS: hyperbilirubinemia (4.1%)

IMMUNE SYSTEM DISORDERS: drug hypersensitivity (1.3%)

INFECTIONS AND INFESTATIONS: rhinitis (4.8%), nasopharyngitis (3.1%), *Clostridium difficile* colitis (1.8%), sepsis (1.8%), lung infection (1.3%)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: infusion related reaction (0.8%)

INVESTIGATIONS: C-reactive protein increased (4.1%), creatinine renal clearance decreased (3.3%), aspartate aminotransferase increased (2.3%), gamma-glutamyltransferase increase (1.8%), blood uric acid increased (1.3%)

METABOLISM AND NUTRITION DISORDERS: hyponatremia (4.6%), hyperkalemia (3.1%), hypoalbuminemia (2.6%), dehydration (1.5%), hypercalcemia (1.3%), tumour lysis syndrome (0.8%)

NERVOUS SYSTEM DISORDERS: hypoesthesia (4.6%), cerebrovascular accident (1.0%), intracranial hemorrhage (0.5%)

RENAL AND URINARY DISORDERS: acute kidney injury (4.3%), renal failure (2.6%), renal impairment (2.6%)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: dysphonia (4.8%), pulmonary embolism (3.6%), acute respiratory distress syndrome (1.0%), pulmonary edema (1.0%), pulmonary hemorrhage (0.3%), pneumonitis (0.5%), pulmonary hypertension (0.5%), acute respiratory failure (0.3%), interstitial lung disease (0.3%), wheezing (0.3%)

VASCULAR DISORDERS: flushing (3.3%), hypertensive crisis (0.5%), hemorrhage (0.3%)

* All adverse reactions < 5% based on the KYPROLIS arm.

Less Common Clinical Trial Adverse Reactions (< 5%)* in ENDEAVOR

BLOOD AND LYMPHATIC SYSTEM DISORDERS: leukopenia (3.7%), febrile neutropenia (1.1%), thrombotic microangiopathy (0.4%), thrombotic thrombocytopenic purpura (0.2%)

CARDIAC DISORDERS: atrial fibrillation (2.8%), myocardial infarction (1.3%), cardiac arrest (0.4%), pericardial effusion (0.4%)

EAR AND LABYRINTH DISORDERS: tinnitus (3.0%)

EYE DISORDERS: vision blurred (4.8%)

GASTROINTESTINAL DISORDERS: toothache (2.8%), gastrointestinal hemorrhage (0.9%)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: pain (3.5%), infusion site reactions (3.2%)

HEPATOBILIRARY DISORDERS: hyperbilirubinemia (1.5%), cholestasis (1.1%), hepatic failure (0.4%)

IMMUNE SYSTEM DISORDERS: drug hypersensitivity (1.1%)

INFECTIONS AND INFESTATIONS: influenza (4.5%), viral infection (2.6%), lung infection (1.7%), sepsis (1.5%)

INVESTIGATIONS: ejection fraction decreased (3.2%), gamma-glutamyltransferase increased (3.2%), aspartate aminotransferase increased (3.0%), C-reactive protein increased (1.9%), blood uric acid increased (1.7%)

METABOLISM AND NUTRITION DISORDERS: hyperkalemia (3.2%), hyponatremia (3.2%), dehydration (2.4%), hypercalcemia (1.7%), hypomagnesemia (1.7%), hypoalbuminemia (1.5%), tumour lysis syndrome (0.6%)

NERVOUS SYSTEM DISORDERS: cerebrovascular accident (0.9%), Posterior Reversible Encephalopathy Syndrome (0.4%)

PSYCHIATRIC DISORDERS: anxiety (4.1%)

RENAL AND URINARY DISORDERS: renal failure (3.0%), renal impairment (2.2%)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: pulmonary embolism (3.0%), dysphonia (3.0%), wheezing (2.6%), pulmonary hypertension (1.3%), pulmonary edema (1.1%), interstitial lung disease (0.6%), pneumonitis (0.4%), acute respiratory distress syndrome (0.4%), pulmonary hemorrhage (0.2%)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: erythema (4.3%), hyperhidrosis (2.6%)

VASCULAR DISORDERS: deep vein thrombosis (4.8%), hypertensive crisis (0.6%), hypertensive emergency (0.2%)

* All adverse reactions < 5% based on the KYPROLIS arm.

Less Common Clinical Trial Adverse Reactions (< 5%)* in ARROW

BLOOD AND LYMPHATIC SYSTEM DISORDERS: leukopenia (3.4%), febrile neutropenia (1.7%), lymphopenia (1.7%), thrombotic microangiopathy (0.4%)

CARDIAC DISORDERS: tachycardia (2.5%), palpitations (2.1%), cardiac failure (1.7%), atrial fibrillation (1.3%), myocardial infarction (0.4%), myocardial ischemia (0.4%), pericardial effusion (0.4%)

EAR AND LABYRINTH DISORDERS: tinnitus (0.4%)

EYE DISORDERS: cataract (4.6%), vision blurred (1.7%)

GASTROINTESTINAL DISORDERS: dyspepsia (1.7%), toothache (1.3%), gastrointestinal hemorrhage (0.4%)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: chest pain (4.6%), influenza like illness (2.5%), malaise (2.1%), infusion site reactions (1.7%), pain (1.7%), chills (0.8%)

HEPATOBILIRARY DISORDERS: cholestasis (0.4%), hyperbilirubinemia (0.4%)

INFECTIONS AND INFESTATIONS: rhinitis (4.2%), urinary track infection (4.2%), sepsis (2.5%), gastroenteritis (2.1%), lung infection (2.1%), nasopharyngitis (0.8%), clostridium difficile colitis (0.4%), viral infection (0.4%)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS: infusion related reaction (1.7%)

INVESTIGATIONS: gamma-glutamyltransferase increased (3.4%), C-reactive protein increased (2.1%), alanine aminotransferase increased (1.3%), aspartate aminotransferase increased (1.3%), blood uric acid increased (1.3%), creatinine renal clearance decreased (0.8%), ejection fraction decreased (0.8%)

METABOLISM AND NUTRITION DISORDERS: hyperglycemia (4.2%), hyperuricemia (3.8%), tumour lysis syndrome (2.9%), hyponatremia (2.5%), hypercalcemia (2.1%), hypophosphatemia (2.1%), hyperkalemia (1.7%), hypoalbuminemia (1.7%), hypocalcemia (1.7%), hypomagnesemia (1.7%), dehydration (0.8%)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: muscular weakness (2.9%), musculoskeletal chest pain (2.9%), myalgia (2.1%)

NERVOUS SYSTEM DISORDERS: peripheral neuropathy (3.8%), paresthesia (2.5%), dizziness (2.1%), hypoesthesia (0.8%), cerebrovascular accident (0.4%), intracranial hemorrhage (0.4%)

PSYCHIATRIC DISORDERS: anxiety (1.7%)

RENAL AND URINARY DISORDERS: renal failure (0.8%)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: epistaxis (3.8%), oropharyngeal pain (3.8%), pulmonary embolism (1.7%), wheezing (0.8%), pulmonary hypertension (1.3%), acute respiratory distress syndrome (0.4%), acute respiratory failure (0.4%), dysphonia (0.4%), interstitial lung disease (0.4%), pneumonitis (0.4%), pulmonary hemorrhage (0.4%)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: rash (2.9%), hyperhidrosis (2.1%), pruritus (1.7%), erythema (0.4%)

VASCULAR DISORDERS: flushing (1.7%), deep vein thrombosis (1.3%), hypotension (0.4%)

* All adverse reactions < 5% based on the KYPROLIS once weekly arm.

Less Common Clinical Trial Adverse Reactions (< 5%)* in CANDOR

BLOOD AND LYMPHATIC SYSTEM DISORDERS: febrile neutropenia (1.3%), thrombotic thrombocytopenic purpura (0.6%)

CARDIAC DISORDERS: cardiac failure (4.9%), tachycardia (4.2%), atrial fibrillation (2.9%), palpitations (2.9%), cardiac arrest (1.0%), myocardial infarction (1.0%), myocardial ischemia (0.6%), pericardial effusion (0.3%)

EAR AND LABYRINTH DISORDERS: tinnitus (1.6%)

EYE DISORDERS: vision blurred (2.6%)

GASTROINTESTINAL DISORDERS: dyspepsia (2.9%), toothache (1.6%), gastrointestinal hemorrhage (1.0%)

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: chest pain (4.2%), pain (4.2%), influenza like illness (3.6%), malaise (3.2%), infusion site reactions (0.6%)

HEPATOBILIARY DISORDERS: hyperbilirubinemia (1.9%), cholestasis (0.3%)

INFECTIONS AND INFESTATIONS: sepsis (3.9%), viral infection (3.9%), gastroenteritis (2.9%), lung infection (2.6%), rhinitis (2.6%), clostridium difficile colitis (0.3%)

INVESTIGATIONS: alanine aminotransferase increased (3.9%), blood creatinine increased (2.3%), aspartate aminotransferase increased (1.9%), gamma-glutamyltransferase increased (1.9%), C-reactive protein increased (1.3%), ejection fraction decreased (0.6%), creatinine renal clearance decreased (0.0%)

METABOLISM AND NUTRITION DISORDERS: hypocalcemia (4.9%), hypomagnesaemia (3.6%), hyperkalemia (1.9%), hyperuricemia (1.6%), hypoalbuminemia (1.3%), hyponatremia (1.3%), hypophosphatemia (1.3%), dehydration (1.0%), tumour lysis syndrome (1.0%), hypercalcemia (0.6%)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: myalgia (4.5%), musculoskeletal chest pain (4.2%), muscular weakness (3.6%), bone pain (2.9%), musculoskeletal pain (2.9%)

NERVOUS SYSTEM DISORDERS: hypoesthesia (1.6%), cerebrovascular accident (0.6%), posterior reversible encephalopathy syndrome (0.6%), intracranial hemorrhage (0.3%), paresthesia (0.3%)

PSYCHIATRIC DISORDERS: anxiety (1.9%)

RENAL AND URINARY DISORDERS: acute kidney injury (3.9%), renal impairment (1.3%), renal failure (1.0%)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: dysphonia (4.2%), oropharyngeal pain (3.9%), epistaxis (2.6%), pulmonary embolism (2.3%), pulmonary hypertension (1.6%), pulmonary edema (1.6%), interstitial lung disease (1.0%), wheezing (1.0%), pneumonitis (0.6%), pulmonary hemorrhage (0.6%), acute respiratory failure (0.0%)

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: pruritus (4.5%), erythema (1.6%), hyperhidrosis (1.6%)

VASCULAR DISORDERS: hypotension (4.2%), deep vein thrombosis (1.6%), flushing (0.6%), hypertensive crisis (0.0%)

* All adverse reactions < 5% based on the KdD twice weekly arm.

Other TEAEs of clinical relevance in the IsaKd arm in IKEMA include:

EYE DISORDERS: cataract

EAR AND LABYRINTH DISORDERS: vertigo

CARDIAC DISORDERS: angina pectoris

GASTROINTESTINAL DISORDERS: dyspepsia, gastroesophageal reflux disease, stomatitis

INVESTIGATIONS: weight decreased

METABOLISM AND NUTRITION DISORDERS: decreased appetite, hyperglycemia, fluid retention

NEOPLASM BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS): skin cancer, solid tumour other than skin cancer

NERVOUS SYSTEM DISORDER: paresthesia

PSYCHIATRIC DISORDERS: anxiety

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS: pulmonary hypertension

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: erythema, purpura

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Table 15 and Table 16 describe Grade 3-4 hematologic and laboratory abnormalities reported in the ASPIRE study.

Table 15. Abnormal Hematologic Findings in the ASPIRE Study*

	Grade 3 or 4 Laboratory Values	
	KRd (N = 392) n (%)	Rd (N = 389) n (%)
Absolute neutrophil count (ANC) decreased	184 (47.0%)	171 (44.0%)
Hemoglobin decreased	84 (21.4%)	97 (24.9%)
Lymphocyte count decreased	200 (51.0%)	147 (37.8%)
Platelet count decreased	119 (30.4%)	79 (20.4%)
Total white blood cell (WBC) count decreased	128 (32.7%)	94 (24.2%)

* Patients whose grade remained the same post baseline were excluded from this table.

Table 16. Abnormal Clinical Chemistry Findings in the ASPIRE Study*

	Grade 3 or 4 Laboratory Values	
	KRd (N = 392) n (%)	Rd (N = 389) n (%)
ALT increased	24 (6.1%)	13 (3.4%)
AST increased	17 (4.4%)	1 (0.3%)
Hypocalcemia	42 (10.7%)	30 (7.7%)
Hypercalcemia	16 (4.1%)	12 (3.0%)
Hypermagnesemia	23 (5.9%)	11 (2.9%)
Hypophosphatemia	154 (39.3%)	135 (34.7%)
Hypokalemia	73 (18.7%)	43 (11.1%)
Hyperkalemia	20 (5.1%)	19 (4.9%)
Serum creatinine increased	35 (8.9%)	24 (6.2%)
Hyponatremia	47 (12.0%)	34 (8.7%)
Total bilirubin increased	43 (11.0%)	14 (3.6%)

* Patients whose grade remained the same post baseline were excluded from this table.

Table 17 and Table 18 describe Grade 3-4 hematologic and laboratory abnormalities reported in the ENDEAVOR study.

Table 17. Abnormal Hematologic Findings in the ENDEAVOR Study

	Grade 3 or 4 Laboratory Values	
	Kd (N = 463) n (%)	Vd (N = 456) n (%)
Lymphocyte count decreased	377 (81.4%)	257 (56.4%)
Platelet count decreased	127 (27.4%)	106 (23.2%)
Hemoglobin decreased	103 (22.2%)	75 (16.4%)
Neutrophils decreased	54 (11.7%)	47 (10.3%)
Total white blood cell (WBC) count decreased	44 (9.5%)	37 (8.1%)

Table 18. Abnormal Clinical Chemistry Findings in the ENDEAVOR Study

	Grade 3 or 4 Laboratory Values	
	Kd (N = 463) n (%)	Vd (N = 456) n (%)
Uric acid increased	337 (72.7%)	237 (52.0%)
Hypophosphatemia	106 (22.9%)	86 (18.9%)
Creatinine clearance	92 (19.9%)	62 (13.6%)
Hyperkalemia	94 (20.3%)	33 (7.2%)
Hyponatremia	41 (8.9%)	43 (9.4%)
Hypocalcemia	43 (9.3%)	8 (1.8%)
Hypokalemia	28 (6.0%)	30 (6.6%)
Serum creatinine increased	21 (4.5%)	25 (5.5%)
Hypoglycemia	12 (2.6%)	9 (2.0%)
Hypercalcemia	9 (1.9%)	17 (3.7%)
Serum albumin decreased	9 (1.9%)	4 (0.9%)
ALT increased	9 (1.9%)	3 (0.7%)
AST increased	7 (1.5%)	3 (0.7%)
Serum alkaline phosphatase increased	3 (0.6%)	3 (0.7%)
Hypomagnesemia	3 (0.6%)	1 (0.2%)
Hypermagnesemia	1 (0.2%)	1 (0.2%)
Hypernatremia	0	1 (0.2%)
Total bilirubin increased	2 (0.4%)	1 (0.2%)

Table 19 and Table 20 describe Grade 3-4 hematologic and laboratory abnormalities reported in the ARROW study.

Table 19. Abnormal Hematologic Findings in the ARROW Study

	Grade 3 or 4 Laboratory Values
	Kd 20/70 mg/m^2 Once Weekly (N = 238) n (%)
Lymphocyte count decreased	102 (42.9%)
Platelet count decreased	52 (21.8%)
Hemoglobin decreased	38 (16.0%)
Leukocytes decreased	37 (15.5%)
Neutrophils decreased	32 (13.4%)

Table 20. Abnormal Clinical Chemistry Findings in the ARROW Study

	Grade 3 or 4 Laboratory Values Kd 20/70 mg/m^2 Once Weekly (N = 238) n (%)
Uric acid increased	30 (12.6%)
Hypophosphatemia	24 (10.1%)
Hyponatremia	18 (7.6%)
Hypokalemia	15 (6.3%)
Glucose increased	15 (6.3%)
Hypercalcemia	7 (2.9%)
Serum creatinine increased	4 (1.7%)
Hypocalcemia	4 (1.7%)
AST increased	3 (1.3%)
ALT increased	2 (0.8%)
Alkaline phosphatase increase	2 (0.8%)
Serum albumin decreased	1 (0.4%)
Hypomagnesemia	1 (0.4%)
Hypermagnesemia	1 (0.4%)

Table 21 and Table 22 describe Grade 3-4 hematologic and laboratory abnormalities reported in the CANDOR study.

Table 21. Abnormal Hematologic Findings in the CANDOR Study

	Grade 3 or 4 Laboratory Values	
	KdD (N = 308) n (%)	Kd (N = 153) n (%)
Absolute neutrophil count (ANC) decreased	31 (10.1)	13 (8.5)
Hemoglobin decreased	28 (9.1)	20 (13.1)
Lymphocyte count decreased	177 (57.5)	56 (36.6)
Platelet count decreased	59 (19.2)	16 (10.5)
Total white blood cell (WBC) count decreased	58 (18.8)	14 (9.2)

Table 22. Abnormal Clinical Chemistry Findings in the CANDOR Study

	Grade 3 or 4 Laboratory Values	
	KdD (N = 308) n (%)	Kd (N = 153) n (%)
ALT increased	7 (2.3)	1 (0.7)
AST increased	1 (0.3)	1 (0.7)
Hypocalcemia	6 (1.9)	1 (0.7)
Hypercalcemia	6 (1.9)	4 (2.6)
Hypokalemia	13 (4.2)	1 (0.7)
Hyperkalemia	5 (1.6)	0 (0.0)
Serum creatinine increased	7 (2.3)	2 (1.3)
Hyponatremia	8 (2.6)	8 (5.2)
Serum albumin decreased	1 (0.3)	3 (2.0)
Total bilirubin increased	1 (0.3)	0 (0.0)

Table 23. Treatment Emergent Laboratory Abnormalities in Patients Receiving IsaKd Treatment Versus Kd Treatment – IKEMA Study

	IsaKd (N = 177)			Kd (N = 122)		
Laboratory parameter	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Anemia	99.4%	22.0%	0%	99.2%	19.7%	0%
Lymphopenia	94.4%	52.0%	16.9%	95.1%	43.4%	13.9%
Thrombocytopenia	94.4%	18.6%	11.3%	87.7%	15.6%	8.2%
Neutropenia	54.8%	17.5%	1.7%	43.4%	6.6%	0.8%

The denominator used for the percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.
CTCAE version: 4.03

8.5 Post-Market Adverse Reactions

The following additional adverse reactions were reported in the post-marketing experience. This includes spontaneous case reports as well as adverse reactions from other clinical studies.

- **Blood and Lymphatic System Disorders:** hemolytic uremic syndrome (HUS)
- **Cardiac Disorders:** pericarditis, cardiomyopathy
- **Gastrointestinal Disorders:** gastrointestinal perforation, intestinal obstruction, acute pancreatitis
- **Infections and Infestations:** cytomegalovirus chorioretinitis, hepatitis B reactivation
- **Neurologic disorders:** progressive multifocal leukoencephalopathy
- **Respiratory, Thoracic, and Mediastinal Disorders:** laryngeal edema

9 DRUG INTERACTIONS

9.1 Serious Drug Interactions

No serious drug interactions at the time of authorization.

9.2 Drug-Interactions Overview

Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers (see 10 CLINICAL PHARMACOLOGY).

9.3 Drug-Behavioural Interactions

Drug-behavioural interactions have not been established.

9.4 Drug-Drug Interactions

Based on *in vitro* studies, carfilzomib is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6, therefore, it is not expected to influence exposure of other drugs that are substrates of these enzymes as a result of inhibition.

In vitro studies indicated that carfilzomib does not induce CYP3A4/5 at the highest concentration tested (2.5 µM) in cultured human hepatocytes. In an *in vitro* study using human liver microsomes, carfilzomib showed modest direct (Ki = 1.7 micromolar) and time-dependent inhibition (Ki = 11 micromolar) of human cytochrome CYP3A4/5.

An open-label, Phase 1, non-randomized, fixed-sequence, drug-drug interaction study enrolled 18 evaluable patients with solid tumours in order to assess the effects of KYPROLIS on the pharmacokinetics of the CYP3A substrate midazolam. Repeated administration of KYPROLIS (27 mg/m^2) did not result in a significant interaction on the pharmacokinetics of midazolam indicating that carfilzomib is not expected to inhibit the metabolism of CYP3A4/5 substrates and is not a CYP3A4 inducer in patients.

It is unknown whether carfilzomib is an inducer of CYP1A2, 2C8, 2C9, 2C19 and 2B6 at therapeutic concentrations. Caution should be observed when carfilzomib is combined with medicinal products that are substrates of these enzymes, including oral contraceptives.

In vitro, carfilzomib inhibited the efflux transport of P-glycoprotein (P-gp) substrate digoxin by 25% in a Caco-2 monolayer system when tested at 3 µM. Carfilzomib is a P-gp substrate. However, given that carfilzomib is administrated intravenously and is extensively metabolized, the pharmacokinetic profile of carfilzomib is unlikely to be affected by P-gp inhibitors or inducers.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established. When isatuximab is used in a therapy combination, consult its Product Monograph.

9.8 Drug-Lifestyle Interactions

Patients treated with KYPROLIS may experience fatigue, dizziness and a drop in blood pressure that could affect their ability to drive or operate machines.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Carfilzomib is a tetrapeptide epoxyketone 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. Carfilzomib has antiproliferative and proapoptotic activities in preclinical models. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumour growth in models of multiple myeloma, hematologic, and solid tumours. *In vitro*, carfilzomib was found to have minimal inhibition against a panel of twenty-one non-proteasomal proteases.

10.2 Pharmacodynamics

Intravenous carfilzomib administration resulted in suppression of proteasome chymotrypsin-like (CT-L) activity when measured in blood 1 hour after the first dose. Doses of $\geq$ 15 mg/m^2 inhibited the CT-L activity (≥ 80%) of the proteasome. In addition, carfilzomib administration at 20 mg/m^2 resulted in inhibition of the low molecular mass polypeptide 2 (LMP2) and multicatalytic endopeptidase complex-like 1 (MECL1) subunits of the immunoproteasome ranging from 26% to 32% and 41% to 49%, respectively. Proteasome inhibition (CT-L activity) in the blood and PBMC was maintained for ≥ 48 hours following the first dose of carfilzomib for each week of dosing. Combination dosing with lenalidomide and dexamethasone did not affect proteasome inhibition.

10.3 Pharmacokinetics

Absorption

The mean C_{max} and AUC following a 2- to 10- minute IV infusion of 15 mg/m^2, 20 mg/m^2 and 27 mg/m^{2}are shown in Table 24.

Table 24. Summary of Observed Carfilzomib PK Parameters Over 2- to 10-minute IV Infusion

	15 mg/m^2 (n = 8)	20 mg/m^2 (n = 30)	27 mg/m^2 (n = 5)
C_{max} (ng/mL)	2077 (91.4)	2390 (104)	4232 (48.8)
$AUC_{0\text{-last}}$ (ng·hr/mL)	187 (75.3)	251 (92.0)	379 (24.8)

Values presented are geometric mean (geometric CV%).

The mean C_{max} and AUC following a 30-minute IV infusion of 20 mg/m^2, 45 mg/m^2, 56 mg/m^2 and 70 mg/m^2 are shown in Table 25.

Table 25. Summary of Observed Carfilzomib PK Parameters Over 30-minute IV Infusion

	20 mg/m^2 (n = 30)	45 mg/m^2 (n = 4)	56 mg/m^2 (n = 12)	70 mg/m^2 (n = 21)
C_{max} (ng/mL)	722 (62.1)	1758 (25.8)	2079 (43.9)	2390 (30.7)
$AUC_{0\text{-last}}$ (ng·hr/mL)	269 (54.3)	740 (24.8)	948 (34.0)	1040 (21.7)

Values presented are geometric mean (geometric CV%).
C_{max} and $AUC_{0\text{-last}}$ values were calculated based on a single dose for twice weekly regimens (20, 45 and 56 mg/m^2) and once weekly regimen (70 mg/m^2).

At doses between 20 and 70 mg/m^2, carfilzomib administered as a 30-minute infusion resulted in dose-dependent increases in maximum plasma concentrations (C_{max}) and area under the concentration-time curve from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$). Following repeated administration of carfilzomib 70 mg/m^2, systemic exposure (AUC) and half-life were similar on Day 15 of cycles 1 and 2, suggesting there was no systemic carfilzomib accumulation. A 30-minute infusion resulted in a similar half-life and AUC, but 2- to 3-fold lower C_{max} compared to that observed with a 2- to 10-minute infusion of the same dose.

Distribution:

The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib on Day 1 of Cycle 1 was 28 L. When tested *in vitro*, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 µM.

Metabolism:

Carfilzomib is rapidly and extensively metabolized. Three predominant metabolites were identified in human plasma and urine. Two metabolites (M14 and M15) result from peptide hydrolysis of carfilzomib while the third metabolite (M16) of similar molecular mass to carfilzomib is formed by hydrolysis of the epoxyketone ring. The metabolites have no known biologic activity.

Elimination

Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour consistent with its rapid metabolism and distribution to tissues. Carfilzomib is eliminated primarily via metabolism with subsequent excretion of the metabolites in urine.

Special Populations and Conditions

- **Age**

  Population pharmacokinetic analyses indicate there are no effects of age on the pharmacokinetics of carfilzomib.

- **Sex**

  Population pharmacokinetic analyses indicate there are no effects of gender on the pharmacokinetics of carfilzomib.

- **Ethnic Origin**

  Population pharmacokinetic analyses indicate there are no effects of race on the pharmacokinetics of carfilzomib.

- **Hepatic Insufficiency**

  Reduce the dose of KYPROLIS by 25% in patients with baseline mild or moderate hepatic impairment. Dosing recommendation cannot be made for patients with baseline severe hepatic function (see 4 DOSAGE AND ADMINISTRATION**,** Patients with Hepatic Impairment).

  The pharmacokinetics and safety of carfilzomib was studied in 46 patients with relapsed or progressive advanced malignancies (solid tumours; n = 43 or hematologic malignancies; n = 3) who had normal hepatic function (n = 11), mild hepatic impairment (bilirubin > 1 to 1.5×ULN or AST > ULN, n = 17), moderate hepatic impairment (bilirubin > 1.5 to 3×ULN, n = 14), or severe hepatic impairment (bilirubin > 3 x ULN, n=4). Pharmacokinetic data was not collected in patients with severe hepatic impairment. KYPROLIS, was administered intravenously over 30 minutes at 20 mg/m^2 on Days 1 and 2 and at 27 mg/m^2 on Days 8, 9, 15 and 16 of cycle 1. If tolerated, patients received 56 mg/m^2 starting in cycle 2. The geometric mean ratio (%) in carfilzomib AUC_{last} at the 27 mg/m^2 dose for mild and moderate impairment vs. normal hepatic function were 144% and 126%, respectively; and at the 56 mg/m^2 dose were 145% and 121%. Systemic exposure to M15 and M16 metabolites was approximately 60%-80% elevated in patients with moderate hepatic impairment compared to patients with normal hepatic function. These metabolites have no known biological activities.

  In patients with baseline mild, moderate, or severe hepatic impairment, there was a higher subject incidence of hepatic function abnormalities, ≥ grade 3 adverse events and serious adverse events compared with patients with normal hepatic function.

- **Renal Insufficiency**

  No starting dose adjustment is required in patients with baseline renal impairment.

  The pharmacokinetics of carfilzomib was studied in two dedicated renal impairment studies.

  The first study was conducted in 50 multiple myeloma patients with normal renal function (CrCL > 80 mL/min, n = 12), mild (CrCL 50-80 mL/min, n = 12), moderate (CrCL 30-49 mL/min, n = 10), and severe (CrCL < 30 mL/min, n = 8) renal impairment, and patients on chronic dialysis (n = 8). KYPROLIS, as a single agent, was administered intravenously over 2 to 10 minutes at doses up to 20 mg/m^2. Pharmacokinetic data were collected from patients following the 15 mg/m^2 dose in cycle 1 and the 20 mg/m^2 dose in cycle 2. The second study was conducted in 23 relapsed multiple myeloma patients with CrCL ≥ 75 mL/min (n = 13) and patients with end stage renal disease (ESRD) requiring dialysis (n = 10). Pharmacokinetic data were collected from patients following administration of a 27 mg/m^2 dose as a 30-minute infusion on cycle 1, Day 16 and the 56 mg/m^2 dose on cycle 2, Day 1.

  Results from both studies show that renal function status had no marked effect on the exposure of carfilzomib following single or repeat-dose administration. The geometric mean ratio (%) in AUC_{last} at the 15 mg/m^2 dose for mild, moderate, severe renal impairment and chronic dialysis vs. normal renal function were 124%, 111%, 85% and 122%, respectively. The geometric mean ratios in AUC_{last} at the 27 mg/m^2 and 56 mg/m^2 dose for ESRD vs. normal renal function were 140% and 133%, respectively.

Compared to patients with normal renal function, patients with ESRD showed elevated systemic exposure to the M14 metabolite by approximately 4- to 7-fold, and elevated systemic exposure to the M15 metabolite by approximately 2-fold. These metabolites have no known biological activities.

In the Phase 3 ENDEAVOR study, serious adverse events related to worsening renal function were more common in patients with baseline renal dysfunction.

- **Cardiac Electrophysiology**

  Analyses of ECG effects of carfilzomib via collection of triplicate ECG and central blind reading have been conducted in 2 clinical studies from 154 patients with advanced malignancies, including multiple myeloma. The effect of carfilzomib on cardiac repolarization using the QT interval with Fridericia's correction (QTcF interval) and the analysis of concentration-QTc relationships show no clear signal of any dose-related effect. The upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcF at C_{max} was 4.8 msec. With Bazett's correction (QTcB interval), the upper bound of one-sided 95% confidence interval (CI) for predicted effect on QTcB at C_{max} was 5.9 msec.

11 STORAGE, STABILITY AND DISPOSAL

Unopened vials should be stored refrigerated (2°C to 8°C). Retain in original package to protect from light. It is not necessary to protect the reconstituted or diluted product from light during administration.

Unopened vials of KYPROLIS are stable until the date indicated on the package when stored in the original package at 2°C to 8°C.

Reconstituted Solution:

The elapsed time from reconstitution to administration should not exceed 24 hours. Store reconstituted solutions in the vial, syringe, or IV bag refrigerated (2°C to 8°C) up to 24 hours or at room temperature (15°C to 30°C) for up to 4 hours.

12 SPECIAL HANDLING INSTRUCTIONS

Not Applicable

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

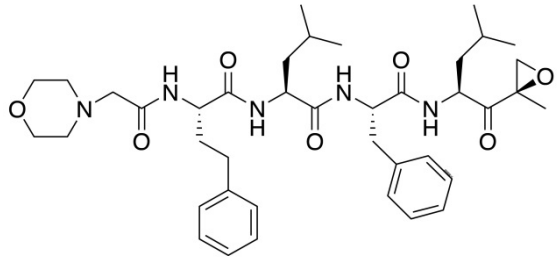
Drug Substance

Proper name: carfilzomib

Chemical name: (2S)-N-[(1S)-1-benzyl-2-[[(1S)-3-methyl-1-[[(2R)-2-methyloxiran-2-yl]carbonyl]butyl]amino]-2-oxoethyl]-4-methyl-2-[[(2S)-2-[(morpholin-4-ylacetyl)amino]-4-phenylbutanolyl]amino]pentamide

Molecular formula and molecular mass: $C_{40}H_{57}N_5O_7$; 719.9 g/mol

Structural formula:



Physicochemical properties: KYPROLIS is a sterile, white to off-white lyophilized powder for solution for injection. Carfilzomib is practically insoluble in water, and very slightly soluble in acidic conditions.

Product Characteristics: Carfilzomib is a modified tetrapeptidyl epoxide, isolated as the crystalline free base.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The efficacy and safety of KYPROLIS in combination with dexamethasone alone (the Kd regimen), dexamethasone and daratumumab (the KdD regimen), or lenalidomide and dexamethasone (the KRd regimen) in the treatment of patients with relapsed multiple myeloma, have been evaluated in open-label, active-controlled Phase 3 studies as described in Table 26.

Table 26. Summary of Pivotal Clinical Trials to Support KYPROLIS in Relapsed Multiple Myeloma

Study #	Trial design	Dosage, route of administration and duration	Study patients (n = number)	Mean age (Range)	Gender (male/female)
ASPIRE	Randomized, open-label, active-controlled; Phase 3	KRd: KYP (IV 10 min) 20/27 mg/m^2 in 28-day cycles[a] for up to 12 cycles then on D1, 2, 15 and 16 in Cycles 13−18 for up to 18 cycles; LEN 25 mg on D1–21 and DEX 40 mg on D1, 8, 15, 22 until PD *or* Rd: LEN 25 mg on D1–21 and DEX 40 mg on D1, 8, 15, 22 until PD	N = 792 (n = 396 KRd; n = 396 Rd)	64.0 (38-87) KRd 65.0 (31-91) Rd	215/181 KRd 232/164 Rd
ENDEAVOR	Randomized, open-label, active-controlled; Phase 3	Kd: KYP (IV 30 min) 20/56 mg/m^2 in 28-d cycles[a]; DEX 20 mg on D1, 2, 8, 9, 15, 16, 22, 23 of 28-d cycles until PD *or* Vd: BOR 1.3 mg/m^2 on D1, 4, 8, 11 of 21-day cycles; DEX 20 mg on D1, 2, 4, 5, 8, 9, 11, 12 of 21-day cycles until PD	N = 929 (n = 464 Kd; n = 465 Vd)	65.0 (35-89) Kd 65.0 (30-88) Vd	240/224 Kd 229/236 Vd
ARROW	Randomized, open-label, active-controlled; Phase 3	Kd: KYP (IV 30 min) 20/70 mg/m^2 in 28-d cycles[b]; DEX 40 mg on D1, 8, 15, 22 for first 9 cycles. DEX is omitted on D22 for cycle 10 on *or* Kd: KYP (IV 10 min) 20/27 mg/m^2 in 28-d cycles[a]; DEX 40 mg on D1, 8, 15, 22 for first 9 cycles. DEX is omitted on D22 for cycle 10 on	N = 473 (n = 238 Kd QW; n = 235 Kd BIW)	65.5 (39-85) Kd QW 64.8 (35-83) Kd BIW	132/108 Kd QW 128/110 Kd BIW

Table 26. Summary of Pivotal Clinical Trials to Support KYPROLIS in Relapsed Multiple Myeloma

Study #	Trial design	Dosage, route of administration and duration	Study patients (n = number)	Mean age (Range)	Gender (male/female)
CANDOR	Randomized, open-label, active-controlled; Phase 3	KdD: KYP (IV 30 min) 20/56 mg/m^2 in 28-d cycles DEX 40 mg on D1, 8, 15, 22; DARA 16 mg/kg (Cycles 1-2: D1, 8, 15, 22, Cycles 3-6: every 2 weeks, Cycle 7+ every 4 weeks) *or* Kd: KYP (IV 30 min) 20/56 mg/m^2 in 28-d cycles DEX 40 mg on D1, 8, 15, 22	N = 466 n = 312 KdD	64 (29, 84) KdD	177/135 KdD
			n = 154 Kd	65 (35, 83) Kd	91/63 Kd
IKEMA (EFC15246)	Multicenter, multinational, randomized, open-label, 2-arm study in patients with relapsed and/or refractory multiple myeloma who had received one to three prior therapies; Phase 3	IsaKd: ISA (10 mg/Kg IV)[c] + KYP IV[d] + DEX (20 mg IV/PO)[e] Kd: KYP IV[d] + DEX (20 mg IV/PO)[e] 28-day cycle	N = 302 n = 179 IsaKd n = 123 Kd	63.1 (33-90)	169/133

KYP = KYPROLIS; KRd = KYPROLIS, lenalidomide, and dexamethasone; D = day; DARA = daratumumab; DEX = dexamethasone; LEN = lenalidomide; Rd = lenalidomide and dexamethasone; Kd = KYPROLIS and dexamethasone; KdD = KYPROLIS, dexamethasone, and daratumumab; Vd = bortezomib and dexamethasone; BOR = bortezomib; PD = progressive disease; ISA = isatuximab; IsaKd = KYPROLIS, isatuximab, and dexamethasone; IV = intravenous; PO = taken orally

[a] KYPROLIS administered in 28-day cycles on Days 1, 2, 8, 9, 15, and 16. Stepped-up dosing occurs in Cycle 1 on Day 8.

[b] KYPROLIS administered in 28-day cycles on Days 1, 8, and 15. Stepped-up dosing occurs in Cycle 1 on Day 8.

[c] administered as an IV weekly in the first cycle and every two weeks thereafter

[d] 20 mg/m² on days 1 and 2; 56 mg/m² on days 8, 9, 15 and 16 of cycle 1; and at the dose of 56 mg/m² on days 1, 2, 8, 9, 15 and 16 for subsequent cycles of each 28-day cycle

[e] IV on the days of isatuximab and/or KYPROLIS infusions, and PO the other days; given on days 1, 2, 8, 9, 15, 16, 22 and 23 for each 28-day cycle

KYPROLIS in Combination with Lenalidomide and Dexamethasone (KRd) for the Treatment of Patients with Relapsed Multiple Myeloma (the ASPIRE Study)

The safety and efficacy of KYPROLIS were evaluated in a randomized, open-label, multicenter Phase 3 study of 792 patients with relapsed multiple myeloma who had received 1 to 3 prior lines of therapy (median of 2), which evaluated the combination of KYPROLIS with lenalidomide and dexamethasone (KRd) vs. lenalidomide and dexamethasone alone (Rd), randomized 1:1.

The primary efficacy endpoint was progression-free survival (PFS) as determined by an Independent Review Committee (IRC) using standard objective International Myeloma Working Group (IMWG)/European Blood and Marrow Transplantation (EBMT) response criteria. Key secondary efficacy endpoints included overall survival (OS) and overall response rate (ORR).

Important exclusion criteria included: creatinine clearance rates < 50 mL/min, disease progression during the treatment with a bortezomib-containing regimen, progression during the first 3 months of initiating treatment with lenalidomide and dexamethasone, or progression at any time during treatment with lenalidomide and dexamethasone if this was the patient's most recent line of therapy. Intolerance to bortezomib was not an exclusion criterion. KYPROLIS treatment was administered for a maximum of 18 cycles unless discontinued early for disease progression or unacceptable toxicity. Lenalidomide and dexamethasone administration could continue until progression or unacceptable toxicity.

The demographics and disease and baseline characteristics for the ASPIRE study are summarized in Table 27.

Table 27. Demographic, Disease and Other Baseline Characteristics

Characteristic	KRd Arm (N = 396)	Rd Arm (N = 396)
Age, years		
Median (min, max)	64.0 (38, 87)	65.0 (31, 91)
Age group, years, n (%)		
≥ 75	43 (10.9)	53 (13.4)
Males	215 (54.3)	232 (58.6)
ECOG Performance Status, n (%)		
0	165 (41.7)	175 (44.2)
1	191 (48.2)	186 (47.0)
2	40 (10.1)	35 (8.8)
ISS stage, n (%)		
III	73 (18.4)	82 (20.7)
Measurable disease category, n (%)		
UPEP disease	97 (24.5)	98 (24.7)
Genetic mutations, n (%)		
High-risk genetic mutations[a]	48 (12.1)	52 (13.1)
Standard risk genetic mutations	147 (37.1)	170 (42.9)
Unknown genetic mutations	201 (50.8)	174 (43.9)
CrCL, mL/min median (min, max)	78.6 (38.7, 211.9)	79.2 (30.0, 207.8)
30 to < 50, n (%)[b]	19 (4.8)	32 (8.1)
50 to < 80, n (%)	185 (46.7)	170 (42.9)
≥ 80, n (%)	192 (48.5)	194 (49.0)

Table 27. Demographic, Disease and Other Baseline Characteristics

Characteristic	KRd Arm (N = 396)	Rd Arm (N = 396)
Hemoglobin, g/L median (min, max)	114.0 (71.0, 154.0)	111.0 (57.0, 166.0)
ANC, 10^9/L median (min, max)	2.6 (0.6, 11.8)	2.7 (0.7, 28.2)
Platelet count, 10^9/L median (min, max)	185.0 (32.0, 540.0)	192.5 (25.0, 597.0)
History of neuropathy, n (%)	199 (50.3)	188 (47.5)
Serum beta-2 microglobulin, mg/L median (min, max)	3.5 (1.3, 13.0)	3.6 (1.5, 31.7)
Heavy chain, n (%)		
IgG	275 (69.4)	281 (71.0)
Light chain, n (%)		
Kappa	271 (68.4)	256 (64.6)
Lambda	124 (31.3)	139 (35.1)

ECOG = Eastern Cooperative Oncology Group; ANC = absolute neutrophil count; CrCL = creatinine clearance; IgG = immunoglobulin G; ISS = International Staging System; KRd = KYPROLIS, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone; UPEP = urine protein electrophoresis

[a] The results were based on fluorescent in situ hybridization (FISH) analysis performed by a central laboratory, and the high-risk group consisted of the genetic subtypes t(4;14), t(14;16), or deletion 17p in ≥ 60% of plasma cells, based on IMF criteria.

[b] All but 2 patients had > 50 mL/min CrCL at screening (as per inclusion criteria) and their reduced renal function was assessed prior to dosing. Half of these patients had a CrCL > 50 mL/min within the first two cycles.

Patients in the KYPROLIS, lenalidomide, and dexamethasone (KRd) arm demonstrated improved progression-free survival (PFS) compared with those in the lenalidomide and dexamethasone (Rd) arm (HR = 0.69, with 1-sided p-value < 0.0001). This represents a 45% improvement in PFS or a 31% reduction in the risk of disease progression or death. The median PFS was 26.3 months in the KRd arm vs. 17.6 months in the Rd arm (see Table 28 and Figure 1).

The PFS benefit of KRd was consistently observed in all subgroups including those defined according to age, cytogenetic risk and number of prior lines of therapy.

A pre-planned overall survival (OS) analysis was performed after 246 deaths in the KRd arm and 267 deaths in the Rd arm. The median follow-up was approximately 67 months. A statistically significant advantage in OS was observed in patients in the KRd arm compared to patients in the Rd arm. Patients in the KRd arm had a 21% reduction in the risk of death compared with those in the Rd arm (HR = 0.79; 95% CI: 0.67, 0.95; p-value = 0.0045). The median OS improved by 7.9 months in patients in the KRd arm compared with those in the Rd arm (see Table 28 and Figure 2). The overall response rate (ORR) was higher in the KRd arm vs. the Rd arm (87.1% vs. 66.7%; 1-sided p-value < 0.0001).

Patients treated with KRd reported a statistically significant improvement in global health status, with higher Global Health Status/Quality of Life (QoL) scores compared with Rd over 18 cycles of treatment measured with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), an instrument validated in multiple myeloma.

Table 28. Summary of Efficacy Analysis

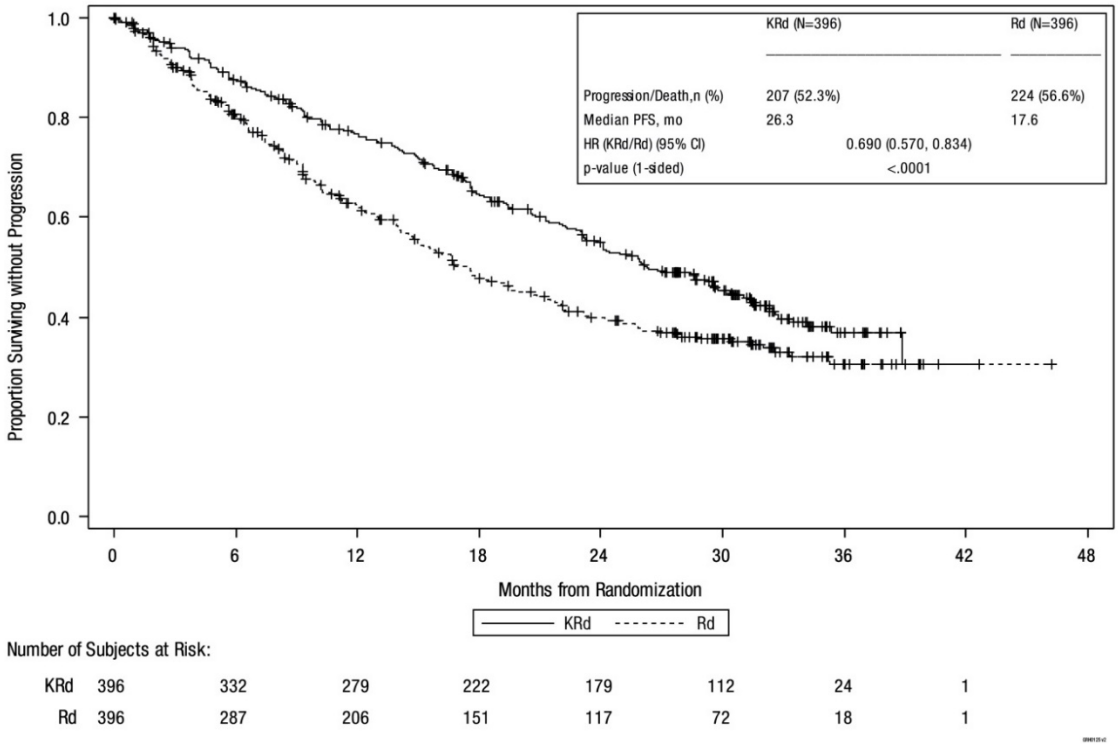
	KRd Arm[a] (N = 396)	Rd Arm[a] (N = 396)
PFS months median (95% CI)	26.3 (23.3, 30.5)	17.6 (15.0, 20.6)
HR (95% CI); 1-sided p-value[b]	0.69 (0.57, 0.83); < 0.0001	
OS months median (95% CI)	48.3 (42.4, 52.8)	40.4 (33.6, 44.4)
HR (95% CI); 1-sided p-value	0.79 (0.67, 0.95); 0.0045	
ORR n (%)	345 (87.1)	264 (66.7)
sCR	56 (14.1)	17 (4.3)
CR	70 (17.7)	20 (5.1)
VGPR	151 (38.1)	123 (31.1)
PR	68 (17.2)	104 (26.3)
Odds Ratio (95% CI)	3.47 (2.41, 5.00)	

CI = confidence interval; CR = complete response; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; KRd = KYPROLIS, lenalidomide, and dexamethasone; NE = not estimable; OS = overall survival; ORR = overall response rate; PR = partial response; PFS = progression-free survival; Rd = lenalidomide and dexamethasone; sCR = stringent complete response; VGPR = very good partial response

[a] As determined by an Independent Review Committee using standard objective IMWG/EBMT response criteria.

[b] Statistically significant.

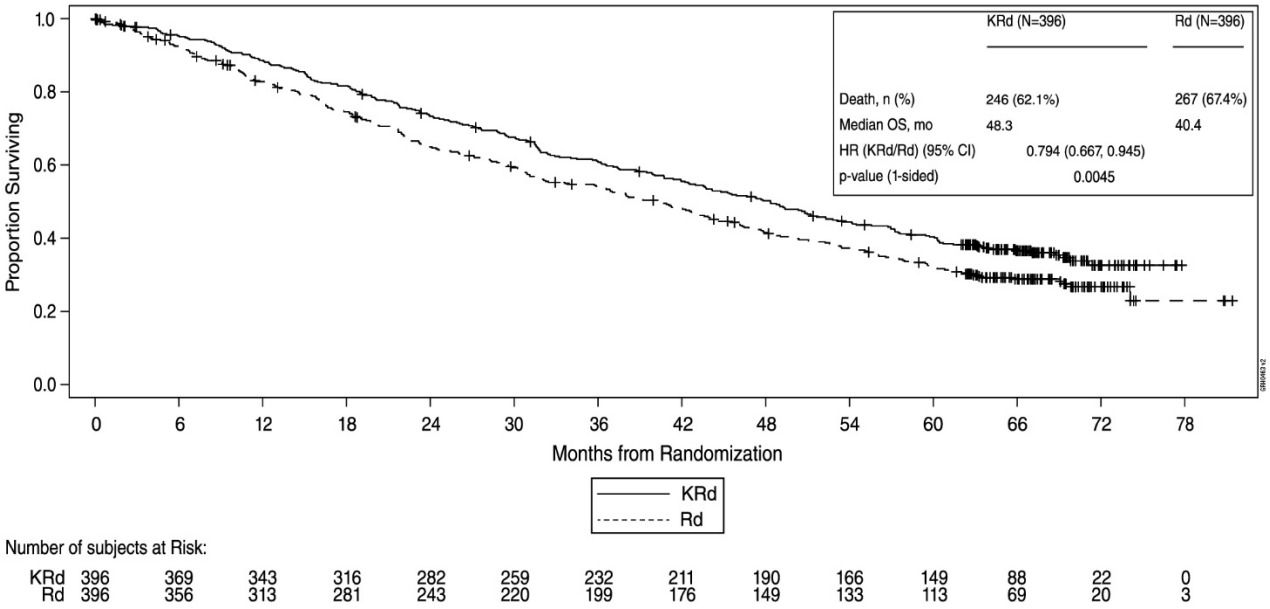
Figure 1. Kaplan-Meier Plot of Progression-Free Survival in the ASPIRE Study



CI = confidence interval; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; KRd = KYPROLIS, lenalidomide, and dexamethasone; mo = months; PFS = progression-free survival; Rd = lenalidomide and dexamethasone arm

Note: The response and PD outcomes were determined using standard objective IMWG/EBMT response criteria.

Figure 2. Kaplan-Meier Plot of Overall Survival in the ASPIRE Study[a]



Number of subjects at Risk:

KRd	396	369	343	316	282	259	232	211	190	166	149	88	22	0
Rd	396	356	313	281	243	220	199	176	149	133	113	69	20	3

CI = confidence interval; HR = hazard ratio; KRd = KYPROLIS, lenalidomide, and dexamethasone; mo = months; OS = overall survival; Rd = lenalidomide and dexamethasone

[a] Study PX-171-009

KYPROLIS in Combination with Dexamethasone (Kd) for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (the ENDEAVOR Study) (Twice Weekly Dosing Regimen)

The safety and efficacy of KYPROLIS 56 mg/m^2 twice weekly were evaluated in a Phase 3, randomized, open-label, multicenter study of KYPROLIS and dexamethasone (Kd) vs. bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. A total of 929 patients were enrolled and randomized (464 in the Kd arm; 465 in the Vd arm). This study evaluated KYPROLIS at an initial dose of 20 mg/m^2, which was increased to 56 mg/m^2 on Cycle 1, Day 8, administered twice weekly as a 30-minute infusion until disease progression or unacceptable toxicity.

The primary efficacy endpoint was progression-free survival (PFS) as determined by an Independent Review Committee (IRC) using standard objective International Myeloma Working Group (IMWG)/European Blood and Marrow Transplantation (EBMT) response criteria. Secondary efficacy endpoints included overall survival (OS), overall response rate (ORR), and duration of response (DOR).

Patients enrolled on study must have received at least one but not more than 3 prior treatment regimens. Patients were required to have a documented partial response (PR) to at least one line of prior therapy. Prior therapy with bortezomib or KYPROLIS was allowed as long as the patient had at least a PR to a previous treatment with these proteasome inhibitors.

The demographics and disease and baseline characteristics are summarized in Table 29.

Table 29. Demographic, Disease and Other Baseline Characteristics

Characteristic	Kd Arm (N = 464)	Vd Arm (N = 465)
Age, years		
Median (min, max)	65.0 (35.0, 89.0)	65.0 (30.0, 88.0)
Age Group, years, n (%)		
< 65	223 (48.1)	210 (45.2)
65–74	164 (35.3)	189 (40.6)
≥ 75	77 (16.6)	66 (14.2)
Sex, n (%)		
Female	224 (48.3)	236 (50.8)
Male	240 (51.7)	229 (49.2)
ECOG Performance Status, n (%)		
0	221 (47.6)	232 (49.9)
1	210 (45.3)	203 (43.7)
2	33 (7.1)	30 (6.5)
Creatinine Clearance Reported (mL/min)		
Median (min, max)	73.0 (14.0, 185.0)	72.0 (12.0, 208.0)
< 30, n (%)	28 (6.0)	28 (6.0)
30 – < 50, n (%)	57 (12.3)	71 (15.3)
50 – < 80, n (%)	186 (40.1)	177 (38.1)
≥ 80, n (%)	193 (41.6)	189 (40.6)
Absolute Neutrophils Count (10^9/L)		
Median (min, max)	2.8 (0.5, 16.1)	2.9 (0.6, 14.9)
< 1.5, n (%)	28 (6.0)	48 (10.3)
≥ 1.5, n (%)	436 (94.0)	417 (89.7)
FISH, n (%)		
High-risk Group[a]	97 (20.9)	113 (24.3)
Standard-risk Group	284 (61.2)	291 (62.6)
Unknown-risk Group	55 (11.9)	30 (6.5)
Prior Therapies, n (%)	464 (100.0)	465 (100.0)
Prior Proteasome Inhibitor Therapy	252 (54.3)	253 (54.4)
KYPROLIS	2 (0.4)	1 (0.2)
Bortezomib	250 (53.9)	252 (54.2)
Prior Transplant for Multiple Myeloma	266 (57.3)	272 (58.5)
Prior Thalidomide	212 (45.7)	249 (53.5)
Prior Lenalidomide	177 (38.1)	178 (38.3)

ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization;
Kd = KYPROLIS and dexamethasone; Vd = bortezomib and dexamethasone

[a] The results were based on fluorescent in situ hybridization (FISH) analysis performed by a central laboratory, and the high-risk group consisted of the genetic subtypes t(4;14) or t(14;16) in 10% or more of screened plasma cells or deletion 17p in ≥ 20% of plasma cells

The study showed a significant improvement in PFS for patients in the Kd arm over those in the Vd arm (HR: 0.53, 95% CI: 0.44, 0.65 [p-value < 0.0001]), with a difference in median PFS of 9.3 months (18.7 months [95 % CI: 15.6, NE] in the Kd arm vs. 9.4 months [95% CI: 8.4, 10.4] in the Vd arm) (see Table 30 and Figure 3).

The PFS benefit of Kd over Vd was consistently observed in all subgroups including those defined according to age, cytogenetic risk, prior bortezomib therapy and number of prior lines of therapy.

The pre-planned OS analysis was performed after 189 deaths in the Kd arm and 209 deaths in the Vd arm. The median follow-up was approximately 37 months. A statistically significant advantage in OS was observed in patients in the Kd arm compared to patients in the Vd arm (HR = 0.79; 95% CI: 0.65, 0.96; p-value = 0.010) (see Table 30 and Figure 4). The results of the secondary efficacy endpoints of ORR and DOR are also presented in Table 30.

Table 30. Summary of Key Results

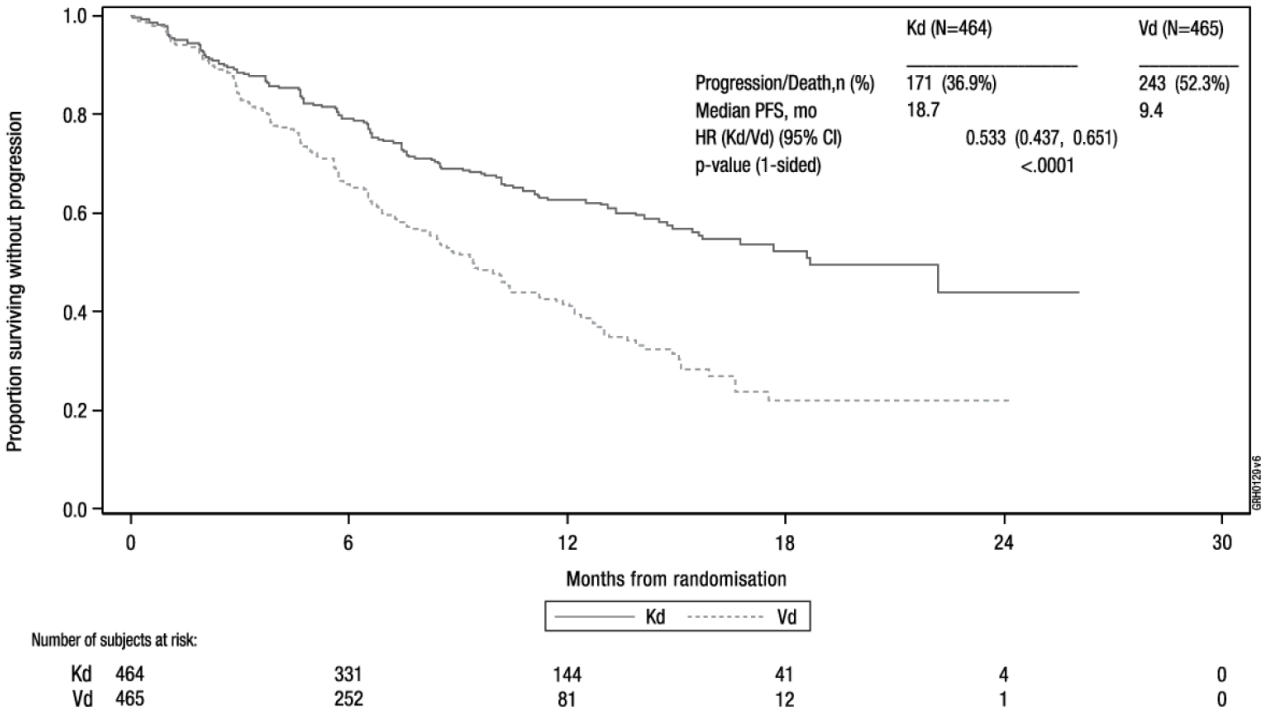
	Kd Arm[a] (N = 464)	**Vd Arm[a] (N = 465)**
PFS months median (95% CI)	18.7 (15.6, —)	9.4 (8.4, 10.4)
HR (95% CI); 1-sided p-value[b]	0.53 (0.44, 0.65); < 0.0001	
OS months median (95% CI)	47.6 (42.5, —)	40.0 (32.6, 42.3)
HR (95% CI); 1-sided p-value[b]	0.79 (0.65, 0.96); 0.010	
ORR n (%) (95% CI)	357 (76.9) (72.8, 80.7)	291 (62.6) (58.0, 67.0)
sCR	8 (1.7)	9 (1.9)
CR	50 (10.8)	20 (4.3)
VGPR	194 (41.8)	104 (22.4)
PR	104 (22.4)	157 (33.8)
Odds Ratio (95% CI)	2.03 (1.52, 2.72)	
DOR, median (months)	21.3 (21.3, —)	10.4 (9.3, 13.9)

CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; Kd = KYPROLIS and dexamethasone; ORR = overall response rate; OS = overall survival; PR = partial response; PFS = progression-free survival; sCR = stringent complete response; Vd = bortezomib and dexamethasone; VGPR = very good partial response

[a] As determined by an Independent Review Committee using standard objective IMWG/EBMT response criteria.

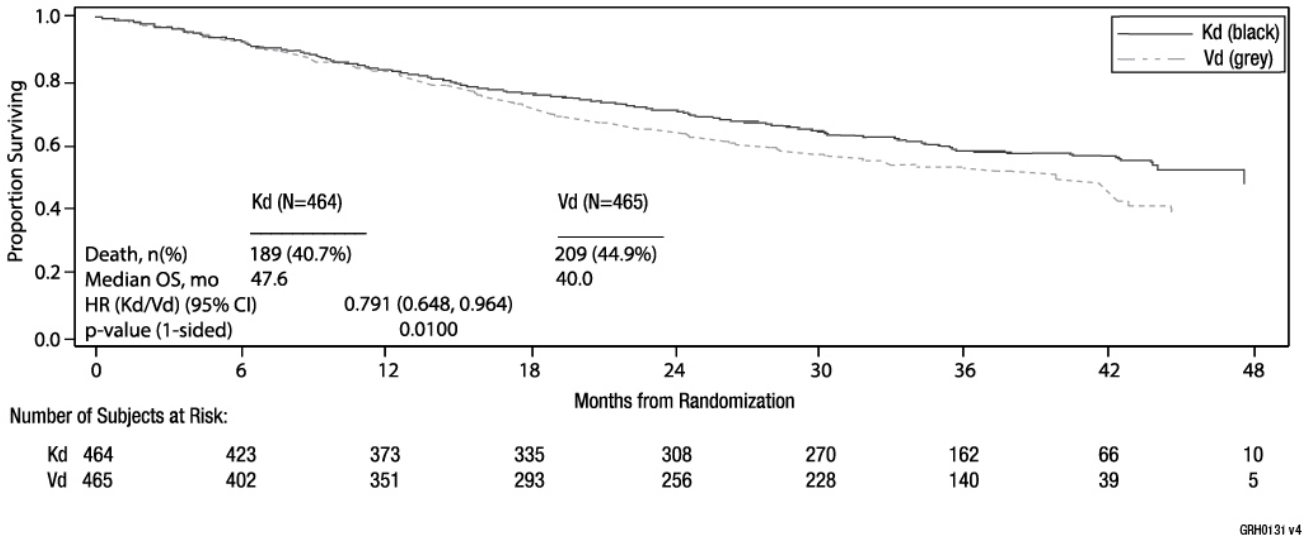
[b] Statistically significant.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival in the ENDEAVOR Study



HR = hazard ratio; Kd = KYPROLIS and dexamethasone; mo = months; PFS = progression-free-survival; Vd = bortezomib and dexamethasone

Figure 4. Kaplan-Meier Plot of Overall Survival in the ENDEAVOR Study



CI = confidence interval; HR = hazard ratio; Kd = KYPROLIS and dexamethasone; mo = months; OS = overall survival; Vd = bortezomib and dexamethasone

KYPROLIS in Combination with Dexamethasone (Kd) for the Treatment of Patients with Relapsed and Refractory Multiple Myeloma (the ARROW Study) (Once Weekly Dosing Regimen)

The safety and efficacy of KYPROLIS 70 mg/m^2 once weekly were evaluated in a Phase 3, randomized, open-label, multicenter study of Kd 70 mg/m^2 once weekly vs. Kd 27 mg/m^2 twice weekly in patients with relapsed and refractory multiple myeloma who had received 2 to 3 prior lines of therapy. A total of 478 patients were enrolled and randomized (240 in the Kd 70 mg/m^2 arm; 238 in the Kd 27 mg/m^2 arm). This study evaluated KYPROLIS at an initial dose of 20 mg/m^2, which was increased to 70 mg/m^2 on Cycle 1, Day 8, administered once weekly as a 30-minute infusion until disease progression or unacceptable toxicity. The twice weekly Kd 20/27 mg/m^2 regimen is not an authorized therapy.

The primary efficacy endpoint was progression-free survival (PFS), and secondary efficacy endpoints included overall response rate (ORR).

Eligible patients had previous exposure to a proteasome inhibitor and an immunomodulatory agent, and were required to have at least partial response to at least one prior line of therapy. Patients were also required to have left ventricular ejection fraction (LVEF) of 40% or higher, have adequate organ and bone marrow function within 21 days prior to randomization, and have measurable disease per International Myeloma Working Group (IMWG) diagnostic criteria. Important exclusion criteria included: prior treatment with carfilzomib, active congestive heart failure, uncontrolled hypertension or diabetes mellitus, and active infection requiring systemic treatment or significant neuropathy (≥ Grade 3) within 14 days prior to randomization.

The demographics and baseline characteristics are summarized in Table 31 and Table 32. The efficacy of Kd once weekly is summarized in Table 33.

Table 31. Demographics

Demographics	Kd 20/70 mg/m^2 Once Weekly Arm (N =240)
Age, years	
Median (min, max)	66 (39, 85)
Age Group, years, n (%)	
< 65	104 (43.3)
65–74	90 (37.5)
≥ 75	46 (19.2)
Sex, n (%)	
Female	108 (45.0)
Male	132 (55.0)
Race, n (%)	
White	200 (83.3)
Black	3 (1.3)
Asian	30 (12.5)
Other or Missing	7 (3.0)

Table 31. Demographics

Demographics	Kd 20/70 mg/m^2 Once Weekly Arm (N =240)
Geographic Region, n (%)	
Europe	192 (80.0)
North America	16 (6.7)
Asia Pacific	32 (13.3)

Kd = KYPROLIS and dexamethasone

Table 32. Baseline Characteristics

Characteristic	Kd 20/70 mg/m^2 Once Weekly Arm (N = 240)
ECOG Performance Status, n (%)	
0	118 (49.2)
1	121 (50.4)
2	1 (0.4)
Creatinine Clearance Reported, mL/min	
Median (min, max)	70.80 (27.6, 211.8)
< 30, n (%)	2 (0.8)
30 – < 50, n (%)	48 (20.0)
50 – < 80, n (%)	91 (37.9)
≥ 80, n (%)	99 (41.3)
Absolute Neutrophils Count, 10^9/L	
Median (min, max)	2.31 (0.6, 7.3)
< 1.5, n (%)	39 (16.3)
≥ 1.5, n (%)	201 (83.8)
FISH, n (%)	
High-risk Group[a]	34 (14.2)
Standard-risk Group	47 (19.6)
Unknown-risk Group	159 (66.3)
Prior Therapies, n (%)	
Bortezomib	236 (98.3)
Transplantation	146 (60.8)
Thalidomide	119 (49.6)
Lenalidomide	207 (86.3)

ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization; Kd = KYPROLIS and dexamethasone

[a] Fluorescent in situ hybridization (FISH) data were historical and captured if available, and the high-risk group consisted of the genetic subtypes t(4;14), t(14;16), or deletion 17p.

In the Kd 70 mg/m^2 once weekly arm, median PFS was 11.3 months (95% CI: 8.6, 13.2) and ORR was 63.8% (95% CI: 57.3, 69.8) (see Table 33 and Figure 5).

Table 33. Summary of Key Results

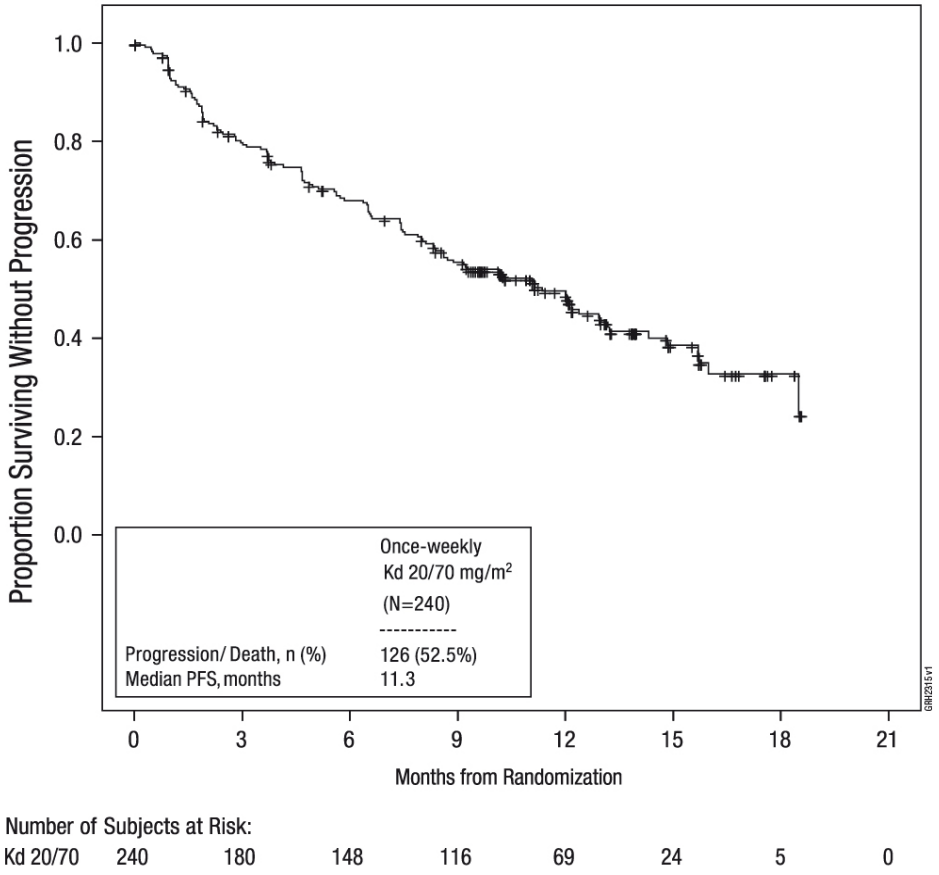
	Kd 70 mg/m^2 Once Weekly Arm[a] (N = 240)
PFS months median (95% CI)	11.3 (8.6, 13.2)
ORR[b], n (%)	153 (63.8)
sCR	4 (1.7)
CR	10 (4.2)
VGPR	70 (29.2)
PR	69 (28.8)

CI = confidence interval; CR = complete response; Kd = KYPROLIS and dexamethasone; ORR = overall response rate; PR = partial response; sCR = stringent complete response; VGPR = very good partial response

[a] As assessed by Independent Review Committee using International Myeloma Working Group (IMWG)/European Blood and Marrow Transplantation (EBMT) response criteria.

[b] Overall response is defined as achieving a best overall response of PR, VGPR, CR or sCR.

Figure 5. Kaplan-Meier Plot of Progression-Free Survival in the ARROW Study[a]



Kd = KYPROLIS and dexamethasone; PFS = progression-free survival

[a] As determined by Independent Review Committee

KYPROLIS in Combination with Dexamethasone and Daratumumab (KdD) in Multiple Myeloma (the CANDOR Study)

CANDOR was a randomized, open-label, multicenter superiority trial of KYPROLIS with dexamethasone and daratumumab (KdD) twice weekly (20/56 mg/m^2) vs. KYPROLIS and dexamethasone (Kd) twice weekly (20/56 mg/m^2) in patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. Patients were excluded if they had known moderate or severe persistent asthma within the past 2 years, known chronic obstructive pulmonary disease (COPD) with a FEV1 < 50% of predicted normal, and active congestive heart failure. A total of 466 patients were enrolled and randomized in a 2:1 randomization (312 in KdD arm and 154 in Kd arm). Randomization was stratified by the ISS (stage 1 or 2 vs stage 3) at screening, prior proteasome inhibitor exposure (yes vs no), number of prior lines of therapy (1 vs ≥ 2), and prior cluster differentiation antigen 38 (CD38) antibody therapy (yes vs no).

In the KdD and Kd arms, KYPROLIS was evaluated at a starting dose of 20 mg/m^2, which was increased to 56 mg/m^2 on Cycle 1, Day 8 onward. KYPROLIS was administered twice weekly as a 30-minute infusion on Days 1, 2, 8, 9, 15 and 16 of each 28 day cycle. In the KdD arm, daratumumab was evaluated at a 16 mg/kg split dose of 8 mg/kg in Cycle 1 on Days 1 and 2. Thereafter, daratumumab was administered 16 mg/kg once weekly on Days 8, 15 and 22 of Cycle 1 and Days 1, 8 and 15 and 22 of Cycle 2, then every 2 weeks for 4 cycles (cycles 3 to 6) and then every 4 weeks for the remaining cycles or until disease progression. In both arms, dexamethasone 20 mg was administered on Days 1, 2, 8, 9, 15 and 16 and then 40 mg by mouth or intravenously on Day 22 of each 28-day cycle. The demographics and baseline characteristics are summarized in Table 34.

Table 34. Demographics and Baseline Characteristics

Characteristic	KdD Arm (N = 312)	Kd Arm (N = 154)
Age at randomization (years)		
Median (min, max)	64 (29,84)	65 (35,83)
Age group – n (%)		
18 – 64 years	163 (52.2)	77 (50.0)
65 – 74 years	121 (38.8)	55 (35.7)
75 years and older	28 (9.0)	22 (14.3)
Sex – n (%)		
Male	177 (56.7)	91 (59.1)
Female	135 (43.3)	63 (40.9)
Race – n (%)		
Asian	46 (14.7)	20 (13.0)
Black or African American	7 (2.2)	2 (1.3)
White	243 (77.9)	123 (79.9)
Other	16 (5.1)	9 (5.8)
Geographic region – n (%)		
North America	21 (6.7)	12 (7.8)
Europe	207 (66.3)	103 (66.9)
Asia Pacific	84 (26.9)	39 (25.3)
ECOG performance status – n (%)	295 (94.6)	147 (95.5)
0 or 1	15 (4.8)	7 (4.5)
2	2 (0.6)	0 (0.0)
Risk group as determined by fluorescent in situ hybridization – n (%)		
High risk	48 (15.4)	26 (16.9)
Standard risk	104 (33.3)	52 (33.8)
Unknown	160 (51.3)	76 (49.4)

Table 34. Demographics and Baseline Characteristics

Characteristic	KdD Arm (N = 312)	Kd Arm (N = 154)
ISS stage per IxRS at screening – n (%)		
I or II	252 (80.8)	127 (82.5)
III	60 (19.2)	27 (17.5)
Number of prior regimens – n (%)		
1	144 (46.2)	70 (45.5)
2	99 (31.7)	46 (29.9)
3	69 (22.1)	37 (24.0)
Prior Therapies – n (%)		
Lenalidomide	123 (39.4)	74 (48.1)
Refractory to lenalidomide	99 (31.7)	55 (35.7)
Bortezomib	287 (92)	134 (87)
Carfilzomib	7 (2.2)	2 (1.3)
Prior CD38 antibody therapy	1 (0.3)	0 (0.0)
Prior stem cell transplant (ASCT)	195 (62.5)	75 (48.7)

ECOG = eastern cooperative oncology group; ISS = international staging system; Kd = KYPROLIS and dexamethasone; KdD = KYPROLIS, dexamethasone, and daratumumab

* Subjects with number of prior regimens > 3 was 0 in the KdD arm and 1 in Kd arm.

The primary efficacy endpoint of the CANDOR study was PFS determined by a Blinded Independent Review Committee using IMWG Uniform Response Criteria. Key secondary efficacy endpoints were overall response rate, minimal residue disease-negative complete response (MRD [-] CR) rate at 12 months and overall survival. The trial demonstrated an improvement in PFS in the KdD arm as compared to the KD arm; the median PFS has not been reached in the KdD arm vs. 15.8 months in the Kd arm (hazard ratio [HR]=0.630; 95% CI: 0.464, 0.854; p=0.0014) representing a 37% reduction in the risk of disease progression or death in patients treated with KdD.

Table 35. Summary of Efficacy Analysis

	Twice Weekly KdD 20/56 mg/m^2 Arm (N = 312)	Twice weekly Kd 20/56 Kd Arm (N = 154)
PFS[a]		
Number of events, n (%)	110 (35.3)	68 (44.2)
Median, Months (95% CI)	NE (NE, NE)	15.8 (12.1, NE)
Hazard Ratio (95% CI)	0.630 (0.46, 0.85)	
p-value (1-sided)	0.0014	
Overall Response[b]		
N with Response	263	115
ORR (%) (95% CI)	84.3 (79.8, 88.1)	74.7 (67.0, 81.3)
Odds Ratio (95% CI)	1.925 (1.18, 3.13)	
p-value (1-sided)	0.0040	
CR n (%)	89 (28.5)	16 (10.4)
VGPR n (%)	127 (40.7)	59 (38.3)
PR n (%)	47 (15.1)	40 (26.0)
MRD [-] CR at 12 months (at a 10^{-5} level)[b,c]		
MRD[-]CR rate (%) (95% CI)	12.5 (9.0, 16.7)	1.3 (0.2, 4.6)
Odds Ratio (95% CI)	11.329 (2.70, 47.48)	
p-value (1-sided)	< 0.0001	

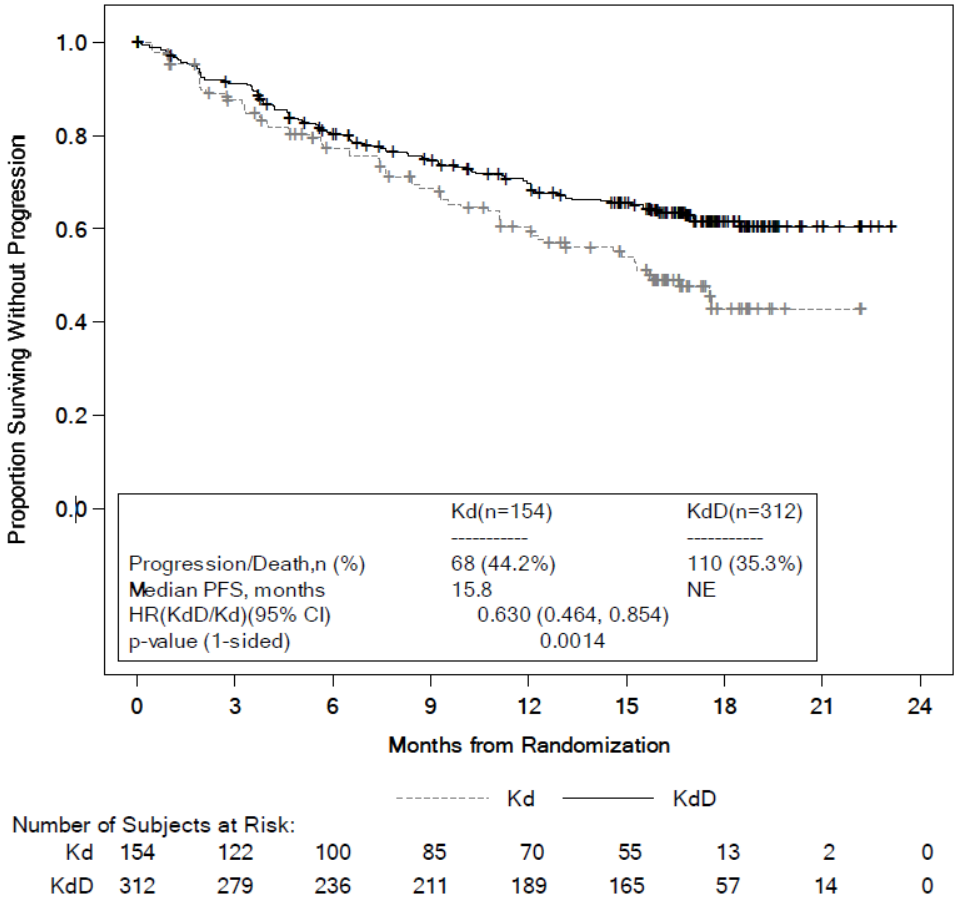
CI = confidence interval; CR = complete response; Kd = KYPROLIS and dexamethasone; KdD = KYPROLIS, dexamethasone and daratumumab; MRD[-]CR = minimal residual disease negative-complete response; NE = not estimable; ORR = overall response rate; PR = partial response; PFS = progression-free survival; VGPR = very good partial response
Stratification factors used in the analyses include (as assessed at randomization): International Staging System (ISS) stage (Stage 1 or 2 vs Stage 3) at screening; prior proteasome inhibitor exposure (yes vs no); number of prior lines of therapy (1 vs ≥ 2).

[a] Hazard ratio and 95% CI were estimated using stratified Cox proportional hazards model; 1-sided p-value was calculated using log-rank test stratified by the randomization stratification factors at level of 0.025 (1-sided); medians were estimated using the Kaplan-Meier method. 95% CIs for medians were estimated using the method by Klein and Moeschberger (1997) with log-log transformation.

[b] Odds ratio and 95% CI were estimated by a stratified analysis using the Mantel-Haenszel method; 1-sided p-values were calculated using Cochran-Mantel-Haenszel Chi-Square test controlling for the stratification factors at level of 0.025(1-sided); 95% CIs for proportions were estimated using the Clopper-Pearson method.

[c] MRD[-]CR at 12-month is defined as achievement of CR or better per IMWG-URC and MRD[-] status as assessed by NGS at 12 months landmark (from 8 months to 13 months window).

Figure 6. Kaplan-Meier Plot of Progression-Free Survival



Overall survival data were not mature. The median duration of response was not estimable for the KdD arm and was 16.6 months (13.9, NE) for the Kd arm. The median time to response was 1 (range: 1, 14) months for the KdD arm and 1 (range: 1,10) months for the Kd arm.

KYPROLIS in Combination with Isatuximab and Dexamethasone (IsaKd) in Multiple Myeloma (the IKEMA Study)

The efficacy and safety of KYPROLIS in combination with isatuximab and dexamethasone were evaluated in IKEMA, a multicenter, multinational, randomized, open-label, 2-arm, phase 3 study in patients with relapsed and/or refractory multiple myeloma. Patients had received one to three prior lines of therapy. Patients were eligible for inclusion if they had an ECOG status of 0-2, platelets ≥ 50,000 cells/mm^3, absolute neutrophil count ≥ 1 × 10^9/L, creatinine clearance ≥ 15 mL/min/1.73 m^2 (MDRD formula), AST ≤ 3 × ULN, and ALT ≤ 3 × ULN. Patients were excluded if they had primary refractory disease or were refractory to previous anti-CD38 monoclonal antibody treatment.

A total of 302 patients were randomized in a 3:2 ratio to receive either KYPROLIS in combination with isatuximab and dexamethasone (IsaKd, 179 patients) or KYPROLIS and dexamethasone (Kd, 123 patients). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. Isatuximab 10 mg/kg was administered as an intravenous infusion weekly in the first cycle and every two weeks thereafter. KYPROLIS was administered as an intravenous infusion at a dose of 20 mg/m^2 on days 1 and 2; 56 mg/m^2 on days 8, 9, 15, and 16 of cycle 1; and at a dose of 56 mg/m^2 on days 1, 2, 8, 9, 15, and 16 for subsequent cycles of each 28-day cycle. Dexamethasone (intravenously on the days of isatuximab and/or KYPROLIS infusions, and orally on the other days) 20 mg was given on days 1, 2, 8, 9, 15, 16, 22, and 23 for each 28-day cycle. On the days where both KYPROLIS and isatuximab were administered, dexamethasone was administered first, followed by isatuximab infusion, then followed by KYPROLIS infusion.

Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 64 years (range 33-90), 9% of patients were ≥ 75 years, 71% were White, 17% Asian, and 3% Black or African American. The proportion of patients with renal impairment (eGFR < 60 mL/min/1.73 m^2) was 24% in the IsaKd group versus 15% in the Kd group. The International Staging System (ISS) stage at study entry was I in 53%, II in 31%, and III in 15% of patients. Overall, 24% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14), t(14;16) were present in 11%, 14%, and 2% of patients, respectively. In addition, gain(1q21) was present in 42% of patients.

The median number of prior lines of therapy was 2 (range 1-4) with 44% of patients who received 1 prior line of therapy. Overall, 90% of patients received prior proteasome inhibitors, 78% received prior immunomodulators (including 43% who received prior lenalidomide), and 61% received prior stem cell transplantation. Overall, 33% of patients were refractory to prior proteasome inhibitors, 45% were refractory to prior immunomodulators (including 33% refractory to lenalidomide), and 21% were refractory to both a proteasome inhibitor and an immunomodulator.

The median duration of treatment was 80 weeks for the IsaKd group compared to 61 weeks for the Kd group.

Efficacy was based upon PFS. PFS results were assessed by an Independent Response Committee based on central laboratory data for M-protein and central radiologic imaging review using the IMWG criteria. The improvement in PFS represented a 46.9% reduction in the risk of disease progression or death in patients treated with IsaKd compared to patients treated with Kd.

Efficacy results are presented in Table 36 and Figure 7.

Table 36. Efficacy of KYPROLIS in Combination with Isatuximab and Dexamethasone (IsaKd) versus KYPROLIS and Dexamethasone (Kd) in the Treatment of Multiple Myeloma (IKEMA)[a]

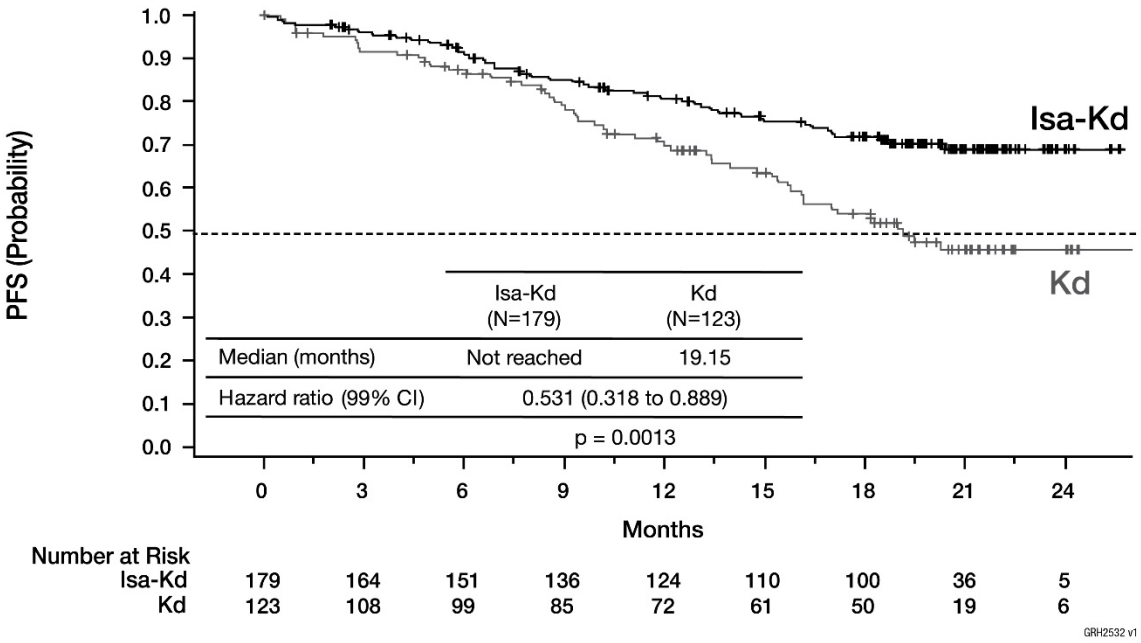
Endpoint	IsaKd N = 179	Kd N = 123
Progression-Free Survival[b]		
Median (months)	NR	19.15
[95% CI]	[NR- NR]	[15.77- NR]
Hazard ratio[c] [95% CI]	0.531 [0.318-0.889]	
p-value (stratified log-rank test)[c]	0.0013	
Overall Response Rate[d]		
Responders (sCR+CR+VGPR+PR) n (%) [95% CI][e]	155 (86.6) [0.8071-0.9122]	102 (82.9) [0.7509-0.8911]
p-value (stratified Cochran-Mantel-Haenszel)[c]	0.3859	
Complete Response (CR) n (%)	71 (39.7)	34 (27.6)
Very Good Partial Response (VGPR) n (%)	59 (33.0)	35 (28.5)
Partial Response (PR) n (%)	25 (14.0)	33 (26.8)

NR: not reached.
[*] Median follow-up time 20.7 months.
[a] Results are based on a prespecified interim analysis.
[b] PFS results were assessed by the IRC based on central laboratory data for M-protein and central radiologic imaging review using the IMWG criteria. A comparison is considered statistically significant if the *p*-value is < 0.008 (efficacy boundary).
[c] Stratified on number of previous lines of therapy (1 versus > 1) and R-ISS (I or II versus III versus not classified) according to IRT.
[d] sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria.
[e] Estimated using Clopper-Pearson method.

The percentage of patients achieving a best overall response of VGPR or better, defined as patients with sCR, CR, or VGPR by the IRC using the IMWG response criteria, was 72.6% in the IsaKd group and 56.1% in the Kd group.

Subgroup analyses based on PFS hazard ratio were consistent across the pre-specified subgroups including patients with high-risk cytogenetics, ≥ 65 years of age, with baseline eGFR (MDRD) < 60 mL/min/1.73 m², with > 1 prior line of therapy, or with ISS stage III at study entry.

Figure 7. Kaplan-Meier Plot of Progression-Free Survival (Intent-to-Treat Population) in the IKEMA Study



15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

The potential impact of infusion length on carfilzomib tolerability and toxicity was assessed in a single-dose administration study in rats. Bolus administration of 8 mg/kg (48 mg/m^2) resulted in mortality in 14 of 32 animals. The same dose administered as a 30-minute infusion resulted in no mortality in 24 animals; and when administered as a 10-minute infusion mortality was seen in 1 of 8 animals. When higher doses of carfilzomib, 10 and 12 mg/kg (60 and 72 mg/m^2), were given as a 30-minute infusion, mortality was noted in 1 of 6 and 4 of 6 animals, respectively. Moreover, bolus administration of carfilzomib at 8 mg/kg (48 mg/m^2) resulted in ruffled fur, dyspnea, lethargy, and pale ears in nearly all animals. A 30-minute infusion of the same dose resulted in fewer and less severe clinical observations that were limited to slightly ruffled fur in the animals. At 24 hours post-dose, bolus administration of carfilzomib at 8 mg/kg resulted in clinical chemistry changes consisting of an approximately 4-fold increase in blood urea nitrogen (BUN), 2-fold increase in creatinine, and 4-fold increase in alanine aminotransferase (ALT); the 30-minute infusion of carfilzomib at the same dose resulted in an approximately 2-fold increase in BUN, no changes in creatinine levels, and 2-fold increase in ALT. Clinical chemistry changes resolved by 72 hours.

Acute Dose Toxicity

Carfilzomib was toxic following single bolus injections in rats and monkeys at similar or lower exposures (based on AUC) achieved clinically in humans receiving 27 mg/m^2. Rats administered ≥ 7 mg/kg showing signs of lethargy and piloerection at 1 and 4 hours after the bolus injection, respectively, with deaths reported in animals administered 9 mg/kg. Single carfilzomib doses of 4 mg/kg in monkeys resulted in considerable toxicity including deaths. Signs of nephrotoxicity and changes consistent with an acute phase response (APR) including increased C-reactive protein (CRP), neutrophils, monocytes and fibrinogen and decreased albumin in rats and pericardial effusion in monkeys along with congestion of the livers and kidneys and discolouration of the GI tract were observed. The toxicities were more severe in the rat than in the monkey, possibly owing to higher exposures of carfilzomib in these animals.

Repeat Dose Toxicity

Repeat-dose toxicity studies of 4-weeks and 3/6-months in rats and of 1, 4-weeks and 9-months in monkeys were conducted. The 3/6-month study in rats and 9-month study in monkeys used dosing schedules (Days 1, 2, 8, 9, 15 and 16 of a 28-day cycle) similar to those used clinically. Intravenous administration of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys, approximating human equivalent exposures of ≥ 0.3 and 0.1 times, respectively (based on AUC_{last}), resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac hemorrhage/ degeneration), gastrointestinal (necrosis/hemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (hemorrhage/ inflammation) systems. Carfilzomib achieved higher systemic concentrations in rats compared to monkeys at similar starting doses (based on mg/kg) and mortalities generally occurred earlier in rats than in monkeys.

Carcinogenicity

Carcinogenicity studies have not been conducted with KYPROLIS.

Carfilzomib was clastogenic in the *in vitro* chromosomal aberration test in peripheral blood lymphocytes. Carfilzomib was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) test (Table 37).

Table 37. Summary of Mutagenicity Studies

Study Title	Species/Number of Animals	Dosage/Route	Principal Findings
Carfilzomib: Bacterial Reverse Mutation Test	*S. typhimurium*: TA1535, TA1537, TA98, TA100; *E. coli*: WP *uvr*A (pKM101)	In vitro 5 to 5000 µg/plate	Carfilzomib showed no mutagenic potential
Carfilzomib: In Vitro Chromosome Aberration Test in Human Lymphocytes	Human lymphocytes	In vitro 0.001 to 2500 µg/mL	Carfilzomib caused an increase in the frequency of structural chromosome aberrations.
Carfilzomib: Mouse Micronucleus Test	CD-1 Mice/5 sex/group	IV injections at 0.31 to 7 mg/kg	Carfilzomib showed no evidence for causing an increase in the induction of micronucleated polychromatic erythrocytes or of causing bone marrow cell toxicity

Reproductive and Developmental Toxicology

Fertility studies with carfilzomib have not been conducted. No effects on reproductive tissues were noted during 28-day repeat-dose rat and monkey toxicity studies or in 6-month rat and 9-month monkey chronic toxicity studies. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Carfilzomib administered to pregnant rats during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day, which is approximately half the recommended dose in humans of 27 mg/m^2 based on body surface area (see Table 38).

Table 38. Summary of Embryo Fetal Development Studies

Study Title	Species/Number of Animals	Dosage/Route	Principal Findings
Carfilzomib: An Intravenous Embryo-fetal Toxicity Study in Rats (GLP)	Time-mated Sprague-Dawley rats/ 22 females/group for controls, 28/group for carfilzomib groups	Daily IV from gestation day 6 to 17 inclusive at 0, 0.5, 1.0, 2.0 mg/kg	Mortality at 2 mg/kg (2 females) on gestation day (GD) 9 and GD 15. Thin fluid in the thoracic cavities, distended colon, discoloured jejunal serosa, small spleen, and enlarged heart at necropsy. At ≥ 1 mg/kg, there was decreased activity, anogenital staining, pallor, and labored breathing ↓ body weight gain was associated with ↓ food consumption from GD 6 through 18 with recovery and increased body weight gain from GD 18 through GD20 at ≥ 1 mg/kg. There were no effects on percent pre- or post-implantation loss, on placental or fetal weight, or on the incidence of external, visceral, or skeletal malformations. The maternal NOAEL was 0.5 mg/kg and the NOAEL for embryo-fetal toxicity was 2 mg/kg.
Carfilzomib: Preliminary Intravenous Embryo-fetal Toxicity Study in Rabbits (Non-GLP)	Time-mated New Zealand White rabbits/8 females/group	Daily IV from gestation day 6 to 19 inclusive at 0, 0.2, 0.4, 0.8 mg/kg	Mortality at 0.8 mg/kg (one female) preceded by ↓ food consumption and accumulation of thin, red fluid in the thoracic and pericardial cavities, edema in the pericardium and thymus, and enlarged mediastinal lymph node at necropsy. ↓ body weight, ↓body weight gain, food consumption, and/or fecal volume from GD 6 through 29 at 0.8 mg/kg. At 0.4 mg/kg, there was transient ↓ body weight and food consumption that were toxicologically insignificant. At scheduled necropsy, at 0.8 mg/kg one female had 60% post-implantation loss, signs of fetal toxicity and possible early abortion or premature delivery on GD 29. ↓fetal body weight at 0.8 mg/kg may have been secondary to the severe maternal toxicity. A NOAEL for embryo-fetal toxicity was established at 0.4 mg/kg/day, based on decreased fetal body weight at 0.8 mg/kg/day that were considered, in part, secondary to maternal toxicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrKyprolis®

carfilzomib for injection

Read this carefully before you start taking **KYPROLIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KYPROLIS**.

Your cancer will be treated with KYPROLIS in combination with other medicines. Read the leaflets for the other drugs as well as this one. This will help you understand the information related to those medicines.

Serious Warnings and Precautions

KYPROLIS should be prescribed and managed by a healthcare professional experienced in the use of anticancer drugs.

If you are given the 56 mg/m^2 or 70 mg/m^2 dose of KYPROLIS, it must be given over 30 minutes. If you are given the 27 mg/m^2 dose of KYPROLIS, it must be given over at least 10 minutes.

KYPROLIS may cause serious side effects, which can cause death. These include:

- Heart problems
- Breathing problems
- Liver problems
- Blood clots in the veins (deep vein thrombosis) and lungs (pulmonary embolism)
- Blood clots in small blood vessels (thrombotic microangiopathies)
- Swelling in the back of the brain (Posterior Reversible Encephalopathy Syndrome [PRES])
- Bleeding into your organs, eg, the brain, lungs or gastrointestinal tract (stomach or bowel)

What is KYPROLIS used for?

KYPROLIS is used to treat patients with multiple myeloma who have received 1 to 3 previous treatments. Multiple myeloma is a cancer of plasma cells (a type of white blood cell in the bone marrow that produces antibodies).

KYPROLIS can be used together with the following medicines:

- dexamethasone alone,
- lenalidomide plus dexamethasone,
- daratumumab plus dexamethasone,
- isatuximab plus dexamethasone

How does KYPROLIS work?

KYPROLIS is a proteasome inhibitor. Proteasomes play an important role in cells by breaking down proteins that are damaged or no longer needed. KYPROLIS blocks proteasomes, which can lead to a build-up of proteins within cells. KYPROLIS can cause cell death, especially in multiple myeloma cells because they contain a higher amount of abnormal proteins.

What are the ingredients in KYPROLIS?

Medicinal ingredient: carfilzomib

Non-medicinal ingredients: anhydrous citric acid, sodium hydroxide (for pH adjustment), and sulfobutylether beta-cyclodextrin

KYPROLIS comes in the following dosage forms:

Powder for solution: 10, 30, or 60 mg/vial

Do not use KYPROLIS if:

- You are allergic to carfilzomib or any other ingredients in KYPROLIS.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KYPROLIS. Talk about any health conditions or problems you may have, including if you:

- have or have had heart problems, including a history of chest pain (angina), heart attack, irregular heartbeat, high blood pressure or if you have ever taken a medicine for your heart
- have or have had lung problems, including a history of shortness of breath at rest or with activity (dyspnea)
- have or have had kidney problems, including kidney failure or if you have ever received dialysis
- have or had liver problems, including a history of hepatitis, fatty liver, or if you have ever been told your liver is not working properly
- have or had unusual bleeding, including easy bruising, bleeding from an injury, such as a cut that does not stop bleeding in a normal amount of time, or internal bleeding, which can indicate you have low platelets
- have or had blood clots in your veins
- have or have had any other major medical problem for which you were hospitalized or received medication
- are pregnant or plan to become pregnant
- are male and are considering fathering a child
- are breast-feeding or plan to breast-feed
- are on a controlled sodium diet

Other warnings you should know about:

- **Check-ups and testing**

  Your healthcare professional will examine you and review your full medical history before starting treatment with KYPROLIS. You will be followed closely during treatment.

  Your healthcare professional may:

  - Do blood and/or urine tests before and during treatment with KYPROLIS. This is to make sure you have enough blood cells and your liver and kidneys are working properly.
  - Check your blood pressure. If your blood pressure is too high, it may need to be lowered before you begin treatment with KYPROLIS.
  - Check if you are getting enough fluids before starting treatment with KYPROLIS.

- **Infections**

  - Infections have occurred in patients treated with KYPROLIS. In some cases, these infections have been serious and some people have died from them.
  - Your healthcare professional will monitor you for signs and symptoms of an infection. If you develop an infection, your healthcare professional will treat your infection right away.

- **Hepatitis B Reactivation**
  - Cases of Hepatitis B reactivation have been reported in patients receiving KYPROLIS. This is when a previous viral infection of the liver becomes active again. It is a serious condition and can cause death.
  - Before you start KYPROLIS, your healthcare professional will do tests to find out if you have Hepatitis B. If you do have this virus, you may need to take antiviral medications before initiating KYPROLIS treatments and continue during your treatment and for at least 6 months after your last dose.
  - During treatment with KYPROLIS, your healthcare professional will monitor you for signs of Hepatitis B reactivation. If this virus becomes active during your treatment, you may need to stop taking KYPROLIS. If this happens, your healthcare professional will decide if you can restart KYPROLIS once your infection is under control.
- **Progressive Multifocal Leukoencephalopathy (PML)**
  - Cases of PML have been reported in patients treated with KYPROLIS who have had or are currently taking other medicines that weakens your immune system (immunosuppressive medicines). PML is a rare brain disorder caused by an infection. PML can cause death.
  - Your healthcare professional will monitor you for any signs and symptoms of PML. If PML is suspected, your healthcare professional will interrupt your treatment and refer you to a specialist for additional tests. If PML is confirmed, your healthcare professional will stop your treatment with KYPROLIS.

- **Pregnancy, breast-feeding and birth control**

  For women taking KYPROLIS:

  - KYPROLIS should not be taken if you are pregnant, think you may be pregnant or if you are trying to become pregnant.
  - During KYPROLIS treatment and for 30 days after stopping treatment, you should use an effective method of birth control to ensure you do not become pregnant. You should talk to your healthcare professional about effective methods of birth control.
  - Tell your healthcare professional right away if you become pregnant while taking KYPROLIS, or within 30 days after stopping KYPROLIS.
  - If you are breast-feeding, you should not take KYPROLIS. It is not known if KYPROLIS passes into breast milk in humans. Talk to your healthcare professional on the best way to feed your baby during treatment.

  For men taking KYPROLIS:

  - While taking KYPROLIS and for 90 days after stopping treatment, you should use an effective method of birth control to ensure your partner does not become pregnant. You should talk to your healthcare professional about effective methods of birth control.
  - Tell your healthcare professional right away if your partner becomes pregnant while you are taking KYPROLIS or within 90 days after stopping treatment.

- **Asian Population**

  Heart failure occurs more often in Asian patients who take KYPROLIS.

- **Children and adolescents**

  KYPROLIS is NOT recommended for use in patients under the age of 18 years.

- **Driving and Using Machines**

  Treatment with KYPROLIS may cause fatigue, dizziness and a drop in blood pressure that could affect your ability to drive or operate machines. Do not drive or perform tasks which may require special attention until you know how KYPROLIS affects you.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with KYPROLIS:

- Certain types of birth control methods
  - KYPROLIS may stop certain types of birth control methods (eg, oral hormonal methods) from working.
  - There may be a higher risk of blood clots when KYPROLIS is used together with certain types of birth control methods (eg, hormonal methods).

How to take KYPROLIS:

- KYPROLIS will be given to you by a healthcare professional. The KYPROLIS powder will first be mixed into a solution. This solution will then be given through a tube placed in your vein. This is called an intravenous (IV) infusion. KYPROLIS will be infused over 10 or 30 minutes.
- KYPROLIS is given in treatment cycles that each last 28 days. For each treatment cycle, KYPROLIS is given once or twice each week for the first three weeks. This is followed by one week without treatment.
- KYPROLIS will be given with other medicines. These medicines will be given to you according to one of the following schedules:

1. KYPROLIS with lenalidomide and dexamethasone:

- KYPROLIS:
  - Cycles 1-12: KYPROLIS will be given on Days 1, 2, 8, 9, 15, and 16.
  - Cycle 13 and onwards: KYPROLIS will only be given on Days 1, 2, 15 and 16.
- Lenalidomide: you will take daily on Days 1-21 of each cycle.
- Dexamethasone: you will take on Days 1, 8, 15 and 22 of each cycle.

Or

2. KYPROLIS and dexamethasone (<u>twice</u> a week treatment):

- KYPROLIS: will be given on Days 1, 2, 8, 9, 15, and 16 of each cycle.
- Dexamethasone: you will take on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each cycle.

Or

3. KYPROLIS and dexamethasone (<u>once</u> a week treatment):

- KYPROLIS: will be given on Days 1, 8, and 15 of each cycle.
- Dexamethasone:
  - Cycles 1-9: you will take dexamethasone on Days 1, 8, 15, and 22.
  - Cycle 10 and onwards: you will only take dexamethasone on Days 1, 8 and 15.

Or

4. KYPROLIS with dexamethasone and daratumumab:

- KYPROLIS: will be given on Days 1, 2, 8, 9, 15 and 16 of each cycle.
- Dexamethasone: you will take on Days 1, 2, 8, 9, 15, 16 and 22 of each cycle.
- Daratumumab:
  - Cycle 1: daratumumab will be given on Days 1, 2, 8, 15 and 22.
  - Cycle 2: daratumumab will be given on Days 1, 8, 15 and 22.
  - Cycles 3-6: daratumumab will be given on Days 1 and 15.
  - Cycle 7 and onwards: daratumumab will only be given on Day 1 of each cycle.

Or

5. **KYPROLIS with isatuximab and dexamethasone:**
    - KYPROLIS: will be given on Days 1, 2, 8, 9, 15 and 16 of each cycle.
    - Isatuximab:
        - Cycle 1: you will take isatuximab on Days 1, 8, 15 and 22.
        - Cycle 2 and onwards: you will only take isatuximab on Days 1 and 15.
    - Dexamethasone: you will take on Days 1, 2, 8, 9, 15, 16, 22 and 23 of each cycle.

You and your healthcare professional will decide the schedule that is right for you. Your healthcare professional will also decide for how long you should receive KYPROLIS.

Most patients will receive treatment until their disease gets worse. Your healthcare professional may stop your KYPROLIS treatment if you experience side effects that cannot be managed.

Usual Dose:

- Your healthcare professional will decide how much KYPROLIS you should receive. This will be based on your height and weight.
- The starting dose of KYPROLIS is 20 mg/m^2. The dose may be increased to either 27 mg/m^2, 56 mg/m^2 or 70 mg/m^2. This will depend on how well you tolerated the starting dose and the dosing schedule you are following.

Overdose:

If you think you, or a person you are caring for, have been given too much KYPROLIS, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important for you to keep all your appointments to receive KYPROLIS. If you miss an appointment, ask your healthcare professional when you should schedule your next dose.

What are possible side effects from using KYPROLIS?

These are not all the possible side effects you may have when taking KYPROLIS. If you experience any side effects not listed here, tell your healthcare professional.

- Fatigue, weakness, general feeling of illness or discomfort
- Diarrhea, nausea, constipation, vomiting, digestion problems, stomach pain, decreased appetite, dehydration
- Pain, redness, irritation or swelling where you received the injection into your vein (infusion site reaction)
- Fever, chills, common cold, the flu, bronchitis
- Headache, dizziness
- Numbness, tingling, or decreased sensation in hands and/or feet
- Nose bleed
- Change in voice or hoarseness, pain in the throat

- Blurred vision
- Ringing in the ears (tinnitus)
- Toothache
- Trouble sleeping, anxiety
- Rash, itchy skin
- Reddening of the skin on neck, upper chest or face
- Increased sweating, feeling too hot
- Back pain, joint pain, pain in legs, arms, hands, or feet, bone pain, muscle pain, muscle spasms, muscle weakness, aching muscles

KYPROLIS may alter your blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Thrombocytopenia (decreased platelets): bruising or bleeding	X		
Pneumonia, pneumonitis (lung infection/inflammation): cough, bloody or coloured mucus, fever, shortness of breath		X	
Dyspnea, interstitial lung disease (breathing problems): difficulty breathing, including shortness of breath at rest or with activity, rapid breathing, wheezing or cough		X	
COMMON			
Deep vein thrombosis (blood clot in the leg): leg swelling or pain			X
Pulmonary embolism (blood clot in the lungs): chest pain or shortness of breath			X
Heart failure/heart attack, atrial fibrillation, palpitations, tachycardia, pericardial effusion, cardiomyopathy (heart problems): chest pain (angina), shortness of breath, rapid, strong or irregular heartbeat or if there is swelling of your ankles and feet			X
Bleeding events: coughing up blood, vomiting up blood, dark tarry stools, or bright red blood in your stools			X

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Kidney problems/kidney failure: swollen ankles, feet or hands, loss of appetite, passing less urine, or abnormal blood test results			X
Infusion reactions/drug hypersensitivity: fever, chills or shaking, joint pain, flushing or swelling, swelling of the throat, shortness of breath, low blood pressure	X		
Pulmonary hypertension (high blood pressure in the arteries of the lungs): shortness of breath with everyday activities or at rest, irregular heartbeat, fast pulse, tiredness, dizziness, and fainting spells			X
Urinary tract infection: pain or burning sensation while urinating, frequent urination	X		
Sepsis (infection of the blood) and/or septic shock (a life-threatening form of sepsis): fever or dizziness	X		
Infection of the stomach and intestine: severe and persistent diarrhea and/or pain in the abdomen	X		
Peripheral edema: leg or arm swelling		X	
Acute Respiratory Distress Syndrome, acute respiratory failure (lung failure): severe difficulty breathing, including shortness of breath at rest or with activity, rapid breathing, wheezing or coughing			X
UNCOMMON			
Tumour lysis syndrome (symptoms caused by the sudden, rapid death of cancer cells due to the treatment): irregular heartbeat, muscle spasms or twitching, passing less urine and abnormal blood tests due to rapid breakdown of cancer cells			X
Liver problems (including reactivation of Hepatitis B infection): yellowing of your skin and eyes, stomach pain or swelling, nausea or vomiting			X

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Hypertensive crisis: very high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea and vomiting, or severe anxiety			X
Stroke (bleeding or blood clot in the brain): sudden numbness, weakness or tingling of the face, arm, or leg, particularly on one side of the body, sudden headache, blurry vision, difficulty swallowing or speaking, or lethargy			X
Posterior reversible encephalopathy syndrome (PRES) (a rare neurological disorder): headaches, confusion, seizures, speech and visual loss, and high blood pressure due to swelling in the back of the brain			X
Thrombotic microangiopathies (damage to the smallest blood vessels inside your body's main organs causing clots): bleeding, bruising, weakness, confusion, fever, nausea, vomiting, diarrhea, and acute kidney failure due to blood clots in small vessels			X
Inflammation of the colon: diarrhea resulting from inflammation of the colon caused by bacteria called *Clostridium difficile*	X		
Multi-organ dysfunction syndrome (failure of multiple organs): failure of multiple organs (eg, lung, kidney, heart) at the same time including passing less urine, difficulty breathing (including shortness of breath at rest or with activity), rapid breathing, wheezing or cough; yellowing of your skin and eyes, stomach pain or swelling, nausea or vomiting; chest pain (angina), shortness of breath, rapid, strong or irregular heartbeat, or if there is swelling of your ankles and feet			X
Intestinal obstruction (blockage that stop or impairs passage of contents of the intestines): nausea, vomiting, bloating, inability to pass gas, severe abdominal pain, pain that comes and goes, loss of appetite, constipation or diarrhea			X

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Pancreatitis (inflammation of the pancreas): upper abdominal pain, fever, rapid pulse, nausea, vomiting, and tenderness when touching the abdomen			X
RARE			
Cytomegalovirus (infection in the back of the eye): floaters in the eye, flashes in the eye, blurred vision, blind spot in vision, and loss of peripheral vision		X	
VERY RARE			
Progressive Multifocal Leukoencephalopathy (PML) (central nervous system infection): blurred or double vision, vision loss, difficulty speaking, weakness in an arm or a leg, a change in the way you walk, problems with your balance, persistent numbness, decreased sensation or loss of sensation, memory loss or confusion		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

KYPROLIS will be stored and managed by healthcare professionals. The information below on how to store KYPROLIS is meant for your healthcare professional.

Unopened vials:

- Store refrigerated (2°C to 8°C).
- Keep in the original carton to protect from light. Protection from light is not necessary during administration.

Reconstituted solution:

- Reconstituted solutions in the vial, syringe or IV bag can be stored refrigerated (2°C to 8°C) for up to 24 hours, or at room temperature (15°C to 30°C) for up to 4 hours.

Keep out of reach and sight of children.

If you want more information about KYPROLIS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.amgen.ca, or by calling 1-866-50-AMGEN (1-866-502-6436).

This leaflet was prepared by Amgen Canada Inc.

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