PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

KYPROLIS® 60 mg/50 ml powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use 50 ml vial contains 60 mg of carfilzomib.

After reconstitution, 1 ml contains 2 mg of carfilzomib.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile, white to off-white lyophilized powder for solution for infusion.

The reconstituted product should be a clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

KYPROLIS® in combination with either dexamethasone and daratumumab, lenalidomide and dexamethasone or with dexamethasone alone is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy (see section 5.1).

KYPROLIS®, as a single medicine, is indicated for the treatment of patients with relapsed and refractory multiple myeloma who have received at least 2 prior therapies that included bortezomib and an immunomodulatory therapy (see section 5.1).

4.2. Posology and Method of Administration

KYPROLIS® treatment should be supervised by a healthcare professional experienced in the use of anti-cancer therapy.

Posology:

KYPROLIS® is an intravenous (IV) infusion that can be administered once or twice weekly based on the selected regimen. (see Table 1). Treatment may be continued until disease progression or until unacceptable toxicity occurs.

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® Monotherapy	20 mg/m^2	27 mg/m^2 twice weekly	10 minutes
KYPROLIS®, Lenalidomide, and Dexamethasone	20 mg/m^2	27 mg/m^2 twice weekly	10 minutes
KYPROLIS® plus Dexamethasone	20 mg/m^2	56 mg/m^2 twice weekly	30 minutes
	20 mg/m^2	70 mg/m^2 once weekly	30 minutes
KYPROLIS® Dexamethasone and Daratumumab	20 mg/m^2	56 mg/m^2 twice weekly	30 minutes
		70 mg/m^2 once weekly	30 minutes

[a] Infusion time remains consistent throughout each regimen.

The dose is calculated 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 body surface area of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20 %.

KYPROLIS® Monotherapy

Twice weekly (27 mg/m^2)

KYPROLIS® is administered at a starting dose of 20 mg/m2 in Cycle 1 on Days 1 and 2 If tolerated, the dose should be increased to 27 mg/m^2 on Day 8 of Cycle 1. KYPROLIS® is omitted on Days 8 and 9 of Cycles 13 and higher. KYPROLIS® 20/27 mg/m^2 is administered as a 10-minute IV infusion 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.

Table 2: KYPROLIS® Monotherapy 20/27 mg/m^2 Twice Weekly (10-Minute Infusion)

	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	Days 22–28
KYPROLIS® (mg/m^2)[a]	20	20	-	27	27	-	27	27	-	-
	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	Days 22–28
KYPROLIS® (mg/m²)	27	27	-	27	27	-	27	27	-	-
	Cycles 13 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	Days 22–28
KYPROLIS® (mg/m²)	27	27	-	-	-	-	27	27	-	-
[a] Dexamethasone premedication is required for each KYPROLIS® dose in Cycle 1, (See Section 4.2 Dexamethasone Premedication for KYPROLIS® Monotherapy).										

KYPROLIS® as monotherapy in Combination with Lenalidomide and Dexamethasone

KYPROLIS® is administered at a starting dose of 20 mg/m² in Cycle 1 on Days 1 and 2. If tolerated, the dose should be increased to 27 mg/m² on Day 8 of Cycle 1. KYPROLIS® is omitted on Days 8 and 9 of Cycles 13 and higher.

KYPROLIS® 27 mg/m² is administered IV 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.

If administered in combination with lenalidomide and dexamethasone, 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 to the recommendations in the lenalidomide Prescribing Information, for example, for patients with baseline renal impairment. Dexamethasone should be administered 30 minutes to 4 hours before KYPROLIS®.

Table 3: KYPROLIS® Twice Weekly (10-Minute Infusion) in Combination with Lenalidomide and Dexamethasone

	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/m²)	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	Day 17–21	Day 22	Days 23-28
KYPROLIS® (mg/m²)	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/m²)	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.

KYPROLIS® in Combination with Dexamethasone

Twice Weekly Dosing (56 mg/m^2)

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 56 mg/m^2 on Day 8 of Cycle 1.

KYPROLIS® 20/56 mg/m^2 is administered as a 30-minute IV infusion 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.

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®.

Table 4: KYPROLIS® Twice Weekly (30-Minute Infusion) in Combination with Dexamethasone

	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	-

Once Weekly Dosing-(70 mg/m^2)

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 20/70 mg/m^2 on Day 8 of Cycle 1. KYPROLIS® 70 mg/m^2 is administered as a 30-minute 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. Dexamethasone is administered as 40 mg orally or IV on Days 1, 8, and 15 of all cycles and on Day 22 of Cycles 1 to 9.

Dexamethasone should be administered 30 minutes to 4 hours before KYPROLIS®.

Table 5: KYPROLIS® Once Weekly (30-Minute Infusion) in Combination with Dexamethasone

	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	-	-	-	-	-

KYPROLIS® in Combination with Dexamethasone plus IV Daratumumab

For the combination regimen with dexamethasone plus daratumumab, administer KYPROLIS® intravenously once weekly or twice weekly as a 30-minute infusion as described in Table 6 & 7 below.

Once weekly 20/70 mg/m^2 regimen by 30-minute infusion

KYPROLIS® is administered intravenously as a 30-minute infusion each week for three weeks followed by a 13-day rest period as shown in Table 6. Each 28-day period is considered one treatment cycle. Administer KYPROLIS® at a starting dose of 20 mg/m^2 in Cycle 1 on Day 1. If tolerated, escalate the dose to 70 mg/m^2 on Day 8 of Cycle 1 and thereafter. Dexamethasone is administered orally or intravenously at a dose of 20 mg in Cycle 1 and 2 on Days 1, 2, 8, 9, 15, 16, 22 and 23. In cycles 3-6, Dexamethasone is taken at a dose of 20 mg on Days 1, 2, 15 and 16 and at a dose of 40 mg on Day 8 and 22. In cycles 7 and thereafter, Dexamethasone is administered at a dose of 20 mg on Days 1 and 2 and at a dose of 40 mg on Days 8, 15, and 22.
or patients >75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week.
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.

Table 6: KYPROLIS® Once Weekly (30-Minute IV Infusion) in Combination with Dexamethasone plus IV Daratumumab

	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)*	20	20	-	20	20	-	20	20	-	20	20	-
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)	70	-	-	70	-	-	70	-	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	20	20	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
**For patients > 75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week.												

Treatment may be continued until disease progression or unacceptable toxicity occurs. Refer to the dexamethasone and daratumumab Prescribing Information for other information on that product.

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 7. 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.

Table 7: KYPROLIS® Twice Weekly (30-Minute Infusion) in Combination with Dexamethasone and Daratumumab

	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/m²)	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/m²)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	16	-	-	16	-	-	16	-	-
	Cycles 3-6											
	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/m²)	56	56	-	56	56	-	56	56	-	-	-	-
Dexamethasone (mg)*	20	20	-	20	20	-	20	20	-	40	-	-
Daratumumab (mg/kg)	16	-	-	-	-	-	16	-	-		-	-

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

Refer to the daratumumab and dexamethasone Prescribing Information for additional details on administration and concomitant medications.

Dexamethasone pre-medication prior to KYPROLIS®

When KYPROLIS® is administered as monotherapy, pre-medicate with dexamethasone 4 mg orally or intravenously at least 30 minutes but no more than 4 hours prior to all doses of KYPROLIS® during Cycle 1 to reduce the incidence and severity of infusion reactions (see section 4.4). Reinstate dexamethasone co-medication if these symptoms develop or reappear during subsequent cycles.

Concomitant medicine

Consider antiviral prophylaxis in patients being treated with KYPROLIS® to decrease the risk of herpes zoster reactivation (see section 4.8).

Refer to the lenalidomide and dexamethasone professional information for other concomitant medications such as the use of antacid prophylaxis, refer to the current lenalidomide and dexamethasone summary of product characteristics.

Thromboprophylaxis is recommended in patients being treated with Kyprolis in combination With daratumumab and dexamethasone, with lenalidomide and dexamethasone, or with dexamethasone alone and should be based on an assessment of the patient's underlying risks and clinical status.

In patients treated with Kyprolis in combination with daratumumab and dexamethasone, pre-infusion medications should be administered to reduce the risk of infusion-related reactions with daratumumab.

Hydration, fluid and electrolyte 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 risk for cardiac failure (see section 4.4). 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. Monitor serum potassium levels regularly during treatment with KYPROLIS®.

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

Recommended dose modifications

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

Dose level reductions are presented in Table 9.

Table 8: Dose Modifications during KYPROLIS® Treatment

Haematologic Toxicity	**Recommended Action**
Absolute Neutrophil Count (ANC) < 0,5 x 10^9/l (see section 4.4).	• Stop dose • If recovered to ≥ 0,5 x 10^9/l, continue at the same dose level • For subsequent drops to < 0,5 x 10^9/l, follow the same recommendations as above and consider 1 dose level reduction when restarting KYPROLIS®[a]
Febrile neutropenia ANC < 0,5 x 10^9/l and an oral temperature > 38,5 °C or two consecutive readings of > 38,0 °C for 2 hours	• Stop dose • If ANC returns to baseline grade and fever resolves, resume at the same dose level.
Platelets < 10 x 10^9/l or evidence of bleeding with Thrombocytopenia (see section 4.4).	• Stop dose • If recovered to ≥ 10 x 10^9/l and/or bleeding is controlled, continue at the same dose level • For subsequent drops to < 10 x 10^9/l, follow the same recommendations as above and consider 1 dose level reduction when restarting KYPROLIS®[a]
Non-Haematologic Toxicity (Renal)	**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 (see section 4.4).	• Stop 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[a] • 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-haematologic Toxicity	**Recommended Action**
All other Grade 3 or 4 non-haematological toxicities (see section 4.4).	• Stop KYPROLIS® until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction[a] • If tolerated, the reduced dose may be increased to the previous dose at the discretion of the physician
ANC = absolute neutrophil count [a]see Table 9 for dose level reductions.	

Table 9: Dose Level Reductions for KYPROLIS®

Regimen	**Dose**	**First Dose Reduction**	**Second Dose Reduction**	**Third Dose Reduction**
Monotherapy	27 mg/m^2	20 mg/m^2	15 mg/m^{2a}	-
KYPROLIS®, lenalidomide, and dexamethasone	27 mg/m^2	20 mg/m^2	15 mg/m^{2a}	-
KYPROLIS®, Dexamethasone, and Daratumumab	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^{2a}
	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^{2a}
KYPROLIS® plus dexamethasone	56 mg/m^2	45 mg/m^2	36 mg/m^2	27 mg/m^2
	70 mg/m^2	56 mg/m^2	45 mg/m^2	36 mg/m^2
Note: Infusion times remain unchanged during dose reduction(s). [a]If symptoms do not resolve, discontinue KYPROLIS® treatment.				

Special Populations

Renal Impairment

No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis (see section 5.2). Since dialysis clearance of KYPROLIS® concentrations has not been studied, the medicine should be administered after the dialysis procedure.

Cardiac Impairment

Patients with New York Heart Association Class III and IV heart failure were excluded from clinical trials. Safety and efficacy in this population have not been evaluated.

Hepatic Impairment

No starting dose adjustment is required in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The pharmacokinetics of KYPROLIS® has not been evaluated in patients with severe (Child-Pugh class C) hepatic impairment (see section 5.2)

Elderly Patients

Overall, the subject incidence of certain adverse events (including cardiac failure) in clinical trials was higher for patients who were ≥ 75 years of age compared to patients who were < 75 years of age (see section 4.4). In a phase 3 randomized open-label, multicentre superiority trial of Kyprolis with daratumumab plus dexamethasone (KdD) versus Kyprolis plus dexamethasone (Kd) for the treatment of patients with relapsed refractory multiple myeloma (CANDOR), 47% of the 308 patients who received KdD 20/56mg/m^2 twice weekly were ≥ 65 years of age. In the KdD arm of the study, 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 section 4.8).

Paediatric population

The safety and efficacy of KYPROLIS® have not yet been established in paediatric population.

Method of Administration

Administer intravenously 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.

Reconstituted KYPROLIS® for injection should not be diluted into a 0,9 % sodium chloride IV bag for IV administration only.

KYPROLIS® vials contain no antimicrobial preservatives and are intended for single use

Proper aseptic technique must be observed.

Any unused medicinal product or waste material should be disposed of.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Women who are breast feeding (see section 4.6).

As KYPROLIS® is administered in combination with other medicinal products, refer to their professional information for additional contraindications.

4.4. Special Warnings and Precautions for Use

As KYPROLIS® is administered in combination with other medicinal products, the summary of product characteristics of these other medicinal products must be consulted prior to initiation of treatment with KYPROLIS®. As lenalidomide may be used in combination with KYPROLIS®, particular attention to the lenalidomide pregnancy testing and prevention requirements is needed (see section 4.6).

<u>Cardiac disorders</u>

New or worsening cardiac failure (e.g., congestive cardiac failure, pulmonary oedema) decreased ejection fraction) myocardial ischaemia 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. 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 risk for cardiac failure (see section 4.2).

Stop KYPROLIS® for Grade 3 or 4 cardiac events until recovery and consider whether to restart KYPROLIS® at 1 dose level reduction based on a benefit/risk assessment (see section 4.2).

The risk of cardiac failure is increased in elderly patients (≥ 75 years). The risk of cardiac failure is also increased in Asian patients. It should be noted
that patients with New York Heart Association (NYHA) Class III and IV heart failure, recent myocardial infarction, cardiac conduction abnormalities, angina pectoris or dysrhythmias uncontrolled by medications were excluded from the clinical trials.

These patients may be at greater risk for cardiac complications and should have a comprehensive cardiological assessment (particularly, blood pressure control and volume of fluids management) prior to starting treatment with KYPROLIS®. Subsequently these patients should be treated with caution and remain under close follow up.

Electrocardiographic changes

There have been cases of QT interval prolongation reported in clinical studies and post-marketing. Cases of ventricular tachycardia have been reported in patients receiving KYPROLIS®.

Pulmonary toxicity

Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in patients receiving KYPROLIS®.

Some of these events have been fatal. KYPROLIS® should be discontinued in these cases (see section 4.2).

Pulmonary hypertension

Pulmonary hypertension has been reported commonly in patients treated with KYPROLIS®. Some of these events have been fatal. Evaluate as appropriate. Stop KYPROLIS® for pulmonary hypertension until resolved or returned to baseline and consider whether to restart KYPROLIS® based on a benefit/risk assessment (see Section 4.2).

Dyspnoea

Dyspnoea was reported very commonly in patients treated with KYPROLIS®.

Evaluate dyspnoea to exclude cardiopulmonary conditions including cardiac failure and Pulmonary syndromes.

Stop KYPROLIS® for Grade 3 and 4 dyspnoea until resolved or returned to baseline and consider whether to restart KYPROLIS® based on a benefit/risk assessment (see sections 4.2 and 4.8)

Hypertension

Hypertension occurred very commonly and included cases of hypertensive crisis and hypertensive emergency.

Some of these events have been fatal. Hypertension was reported more frequently in patients who received Kyprolis® in combination with daratumumab.

It is recommended to control hypertension prior to starting KYPROLIS®.

All patients should be routinely evaluated for hypertension while on KYPROLIS® and treated as needed. If the hypertension cannot be controlled, KYPROLIS® dose should be discontinued until resolved.

In case of hypertensive crisis, KYPROLIS® should be discontinued (see section 4.2).

Acute renal failure

Cases of acute renal failure have been reported in patients who received KYPROLIS®.

Some of these events have been fatal. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received KYPROLIS® monotherapy.

This incidence was increased in patients with a lower baseline creatinine clearance, than among subjects with higher baseline creatinine clearance.

Renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance should be monitored.

Reduce or stop KYPROLIS® as appropriate (see section 4.2).

Tumour lysis syndrome

Cases of tumour lysis syndrome (TLS), including fatal outcome, have been reported in

patients who received KYPROLIS®. 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 medicines should be considered in patients at high risk for TLS. Monitor for evidence of TLS during treatment including regular measurement of serum electrolytes, and manage promptly. Interrupt KYPROLIS® until TLS is resolved (see section 4.2).

Infusion reactions

Infusion reactions, including life-threatening reactions, have been reported in patients who received KYPROLIS®. Signs and symptoms may include fever, chills, arthralgia, myalgia, facial flushing, facial oedema, laryngeal oedema, vomiting, weakness, shortness of breath, hypotension, syncope, bradycardia, chest tightness, or angina pectoris. These reactions can occur immediately following or up to 24 hours after administration of KYPROLIS®. Dexamethasone should be administered prior to KYPROLIS® to reduce the incidence and severity of reactions (see section 4.2).

Haemorrhage and Thrombocytopenia

Cases of haemorrhage (e.g. gastrointestinal, pulmonary and intracranial haemorrhage) have been reported in patients treated with KYPROLIS®, often associated with thrombocytopenia. Some of these events have been fatal (see section 4.8).
KYPROLIS® causes thrombocytopenia with platelet nadirs observed on Day 8 or Day 15 of each 28 day cycle usually with recovery to baseline platelet count by the start of the next cycle (see section 4.8). Monitor platelet counts frequently during treatment with KYPROLIS®. Reduce or stop dose as appropriate (see section 4.2).

Venous thromboembolic events

Cases of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism with fatal out-comes, have been reported in patients who received KYPROLIS®. Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored.
Thromboprophylaxis should be considered based on an individual benefit/risk assessment. Caution should be used in the concomitant administration of other products that may increase the risk of thrombosis (e.g. erythropoietic medicines or hormone replacement

therapy). Patients and physicians are advised to observe for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, haemoptysis, arm or leg swelling or pain.

Hepatic toxicity

Cases of hepatic failure, including fatal cases, have been reported. KYPROLIS® can cause elevations of serum transaminases (see section 4.8). Monitor liver enzymes regularly, regardless of baseline values. Reduce or stop dose as appropriate (see section 4.2).

Thrombotic microangiopathy

Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura and haemolytic uremic syndrome (TTP/HUS) have been reported in patients who received KYPROLIS®.

Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop KYPROLIS® and evaluate patients for possible TTP/HUS. If the diagnosis of TTP/HUS is excluded, KYPROLIS® can be restarted. The safety of reinitiating KYPROLIS® therapy in patients previously experiencing TTP/HUS is not known.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES), formerly termed reversible Posterior leukoencephalopathy syndrome (RPLS), is a neurological disorder, which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro radiological imaging.

Cases of PRES have been reported in patients receiving KYPROLIS®.

Discontinue KYPROLIS® if PRES is suspected. The safety of reinitiating KYPROLIS® therapy in patients previously experiencing PRES is not known.

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. Carriers of HBV who require treatment with KYPROLIS® should be closely monitored for signs and symptoms of active HBV infection 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.

Progressive Multifocal Leukoencephalopathy

Cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in patients treated with KYPROLIS® who have had prior or concurrent immunosuppressive therapy. The causal relationship with KYPROLIS® is unknown. Patients should be monitored for any new or worsening neurologic, cognitive or behavioural signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders. If PML is suspected, further Kyprolis administration must be suspended and the patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue KYPROLIS® if PML diagnosis is confirmed.

Increased Incidence of Fatal and Serious Adverse Events in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Multiple Myeloma Patients

In a clinical trial of 955 transplant ineligible patients with newly diagnosed multiple myeloma randomized to KYPROLIS® (20/36 mg/m^2 by 30 minute infusion twice weekly for four weeks of each six week cycle), melphalan and 8.5 %) prednisone (KMP) or bortezomib, melphalan and prednisone (VMP), a higher incidence of fatal adverse events (6.5 % versus 4.3 %), a higher incidence of serious adverse events (49.6 % versus 42.1 %) and a higher incidence of any grade adverse events involving cardiac failure (10.8 % versus 4.3 %), hypertension (24.7 % versus 8.1 %), acute renal failure (13.9 % versus 6.2 %), and dyspnoea (18.1 % versus were observed in patients in the KMP arm compared to patients in the VMP arm. This study did not meet its primary outcome measure of superiority in progression free survival (PFS) for the KMP arm. KYPROLIS® in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma.

Contraception

Females of childbearing potential and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with KYPROLIS®.

Sodium content

Kyprolis 60 mg powder for solution for infusion

This medicinal product contains 216 mg sodium per 60 mg vial which is equivalent to 11% of The WHO recommended maximum daily intake of 2 g sodium for an adult.

Cyclodextrin content

Kyprolis 60 mg powder for solution for infusion

This medicinal product contains 3 000 mg of cyclodextrin (Betadex Sulfobutyl ether sodium) Per 60 mg vial which is equivalent to 88 mg/kg for a 70 kg adult.

4.5. Interaction with other Medicines and other forms of Interaction

Carfilzomib, as found in KYPROLIS®, is primarily metabolised 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. Carfilzomib is not expected to influence exposure of other medicines (see section 5.2). Based on in vitro and in vivo data, carfilzomib is not expected to inhibit CYP3A4/5 activities and/or affect the exposure to CYP3A4/5 substrates. A clinical trial using oral midazolam as a CYP3A probe demonstrated that the pharmacokinetics of midazolam were unaffected by concomitant carfilzomib administration.

Carfilzomib is a P glycoprotein (P-gp) substrate but not a BCRP substrate. However, given that carfilzomib is administrated intravenously and is extensively metabolised, the pharmacokinetic profile of carfilzomib is unlikely ~~to be~~ to be affected by P-gp or BCRP inhibitors or inducers.

In vitro, at concentrations (3 µm) lower than those expected at therapeutic doses, carfilzomib inhibits the efflux transport of digoxin, a P-gp substrate, by 25%. Caution should be observed when carfilzomib is combined with substrates of P-gp (e.g. digoxin, colchicine).

4.6. Fertility, Pregnancy and Lactation

Women of childbearing potential / Contraception in males and females

Females and males of reproductive potential should be advised to avoid conceiving/fathering a child while being treated with KYPROLIS®. Females patients of child bearing potential treated with KYPROLIS® and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with KYPROLIS® (see Section 5.).

Male patients treated with KYPROLIS® 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.

If pregnancy occurs during this time, patients should be apprised of the potential hazard to the foetus. It is not known if KYPROLIS® will reduce the efficacy of oral contraceptives.

Due to an increased risk of venous thrombosis associated with KYPROLIS®, patients currently using oral contraceptives or a hormonal method of contraception associated with a risk of thrombosis should consider an alternative method of effective contraception (see sections 4.4 and 4.8).

Pregnancy*:*

There are no data on the use of KYPROLIS® in pregnant women. KYPROLIS® caused embryo-foetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose (see section 5.3).

KYPROLIS® should only be used during pregnancy if the potential benefits to the mother outweigh the potential risks to the foetus.

Breastfeeding*:*

Mothers should not breastfeed their infants as KYPROLIS® is present in human breast milk.

Fertility*:*

No fertility studies have been performed (see section 5.3).

4.7. Effects on ability to drive and use machines

No studies on the effects of KYPROLIS® on the ability to drive or use machines have been performed. Fatigue, dizziness, fainting and/or a drop in blood pressure have been observed in clinical trials. Patients being treated with KYPROLIS® should, therefore, be advised not to drive or operate machinery if they experience any of these symptoms.

4.8. Undesirable Effects

Summary of safety profile

Serious adverse reactions that may occur during KYPROLIS® treatment include: cardiac failure, myocardial infarction, cardiac arrest, myocardial ischemia, interstitial lung disease, pneumonitis, acute respiratory distress syndrome, acute respiratory failure, pulmonary hypertension, dyspnoea, hypertension including hypertensive crisis, acute kidney injury, tumour lysis syndrome, infusion related reaction, gastrointestinal haemorrhage, intracranial haemorrhage, pulmonary haemorrhage, thrombocytopenia, hepatic failure, hepatitis B virus reactivation, PRES and thrombotic microangiopathy.
The most common adverse reactions (occurring in > 20 % of patients) were: anaemia, thrombocytopenia, neutropenia, nausea diarrhoea, fatigue, pyrexia, respiratory tract infection, dyspnoea, and cough.

Combination with Dexamethasone and Daratumumab

In CANDOR, in which Kyprolis 20/56 mg/m^2 twice weekly was administered in both trial arms, deaths due to adverse events within 30 days of the last dose of any study treatment occurred in 30/308 (10 %) patients in the carfilzomib-dexamethasone-daratumumab (KdD) arm compared with 8/153 (5 %) patients in the carfilzomib-dexamethasone (Kd) arm.
The most common cause of death occurring in patients (%) in the two arms (KdD versus Kd) was infections 14 (5 %) *versus* 4 (3 %).
The risk of fatal treatment-emergent adverse events was higher among subjects ≥ 65 years of age. 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 events reported in the KdD arm as compared with the Kd arm were anaemia (2 % *versus* 1 %), diarrhoea (2 % *versus* 0 %), pyrexia (4 % *versus* 2 %), pneumonia (12 % *versus* 9 %), influenza (4 % *versus* 1 %), sepsis (4 % *versus* 1 %) and bronchitis (2 % *versus* 0 %). Grade ≥ 3 adverse events occurred in 82 % of patients in the KdD arm as compared with 74 % in the Kd arm. The most frequently reported (occurring in ≥ 10 % of subjects in either treatment group [KdD, Kd]) grade ≥ 3 adverse events included thrombocytopenia (24 %, 16 %), hypertension (18 %, 13 %), anaemia (17 %, 14 %), and pneumonia (13 %, 9 %). 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.

Table 10: Summary of Subject Incidence of Treatment-emergent Adverse Events (in the Kd and KdD Arms Safety Population)

	Kd (N = 153) n (%)	KdD (N = 308) n (%)
All treatment-emergent adverse events	147 (96.1)	306 (99.4)
Grade ≥ 3	113 (73.9)	253 (82.1)
Serious adverse events	70 (45.8)	173 (56.2)
Fatal adverse events	8 (5.2)	30 (9.7)

K = KYPROLIS, d = dexamethasone, D = daratumumab

Treatment-emergent adverse events are defined as any adverse event with an onset after the administration of the first dose and within 30 days of the last dose of any investigational product. Adverse events were coded using MedDRA (version 22.0) and graded using NCI-CTCAE (version 4.03).

Tabulated list of adverse reactions

Adverse reactions are presented in Table 11 by system organ class and frequency category. Frequency categories were determined from the crude incidence rate reported for each adverse reaction in a dataset of pooled clinical studies (N = 3 878).

Incidence of adverse reactions are listed below by system organ class and frequency.

Frequencies are defined as: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 11: Tabulated Summary of Adverse Reactions

System Organ Class	**Adverse Reaction Preferred Term**	**Frequency**	**Overall Subject Incidence (N = 3 878) n (%)**
Blood and Lymphatic System Disorders	Anaemia[a]	Very common	1613 (41.6)
	Thrombocytopenia[a]	Very common	1263 (32.6)
	Neutropenia[a]	Very common	828 (21.4)
	Lymphopenia[a]	Very common	419 (10.8)
	Leukopenia[a]	Very common	390 (10.1)
	Febrile neutropenia	Common	67 (1.7)

	Thrombotic microangiopathy	Uncommon	7 (0.2)
	Thrombotic thrombocytopenic purpura	Uncommon	6 (0.2)
Cardiac Disorders	Cardiac failure[a]	Common	186 (4.8)
	Tachycardia	Common	134 (3.5)
	Palpitations	Common	114 (2.9)
	Atrial fibrillation	Common	99 (2.6)
	Myocardial infarction[a]	Common	46 (1.2)
	Cardiac arrest	Uncommon	16 (0.4)
	Cardiomyopathy	Uncommon	15 (0.4)
	Myocardial ischaemia	Uncommon	14 (0.4)
	Pericardial effusion	Uncommon	7 (0.2)
Ear and labyrinth disorders	Tinnitus	Common	54 (1.4)
Eye Disorders	Blurred vision	Common	150 (3.9)
	Cataract	Common	149 (3.8)
Gastrointestinal Disorders	Nausea	Very common	1120 (28.9)
	Diarrhoea	Very common	1163 (30.0)
	Vomiting	Very common	665 (17.1)
	Constipation	Very common	585 (15.1)
	Abdominal pain[a]	Common	363 (9.4)
	Dyspepsia	Common	204 (5.3)
	Toothache	Common	77 (2.0)
	Gastrointestinal haemorrhage[a]	Uncommon	33 (0.9)
	Pancreatitis acute[a]	Uncommon	9 (0.2)
	Intestinal obstruction	Uncommon	4 (0.1)
General Disorders and Administration Site Conditions	Fatigue	Very common	1346 (34.7)
	Pyrexia	Very common	1085 (28.0)
	Oedema peripheral	Very common	664 (17.1)

	Asthenia	Very common	519 (13.4)
	Chills	Common	340 (8.8)
	Pain	Common	192 (5.0)
	Chest pain	Common	178 (4.6)
	Infusion site reactions[a]	Common	110 (2.8)
	Malaise	Common	104 (2.7)
	Influenza like illness	Common	111 (2.9)
	Multi-organ dysfunction syndrome	Uncommon	12 (0.3)
Hepatobiliary Disorders	Hyperbilirubinemia	Common	59 (1.5)
	Hepatic failure	Uncommon	8 (0.2)
	Cholestasis	Uncommon	9 (0.2)
Immune System Disorders	Drug hypersensitivity	Uncommon	17 (0.4)
Infections and Infestations	Respiratory tract infection[a]	Very common	1071 (27.6)
	Pneumonia	Very common	552 (14.2)
	Nasopharyngitis	Very common	404 (10.4)
	Bronchitis	Very common	424 (10.9)
	Urinary tract infection	Common	275 (7.1)
	Influenza	Common	188 (4.8)
	Rhinitis	Common	99 (2.6)
	Viral infection	Common	87 (2.2)
	Sepsis	Common	87 (2.2)
	Gastroenteritis	Common	81 (2.1)
	Lung infection	Common	32 (0.8)
	Septic shock	Uncommon	25 (0.6)
	Clostridium difficile colitis	Uncommon	6 (0.2)
	Hepatitis B Virus Reactivation[a]	Uncommon	-
Injury, Poisoning and	Infusion related reaction	Common	89 (2.3)

Procedural Complications			
Investigations	Serum creatinine increased	Very common	439 (11.3)
	Alanine aminotransferase increased	Common	196 (5.1)
	Aspartate aminotransferase increased	Common	183 (4.7)
	Creatinine ~~renal~~ clearance decreased	Common	90 (2.3)
	Serum uric acid increased	Common	93 (2.4)
	Gamma-glutamyltransferase increased	Common	62 (1.6)
	C-reactive protein increased	Common	52 (1.3)
	Cardiac ejection fraction decreased	Uncommon	36 (0.9)
Metabolism and Nutrition Disorders	Decreased appetite	Very common	513 (13.2)
	Hypokalaemia	Very common	486 (12.5)
	Hyperglycaemia	Common	385 (9.9)
	Hypocalcaemia	Common	277 (7.1)
	Hypophosphatemia	Common	237(6.1)
	Hypomagnesemia	Common	227 (5.9)
	Hyponatremia	Common	199 (5.1)
	Hyperuricemia	Common	201 (5.2)
	Hyperkalaemia	Common	157 (4.0)
	Hypercalcemia	Common	155 (4.0)
	Dehydration	Common	127 (3.3)
	Hypoalbuminemia	Common	122 (3.1)
	Tumour lysis syndrome	Uncommon	35 (0.9)
Musculoskeletal and Connective	Back pain	Very common	689 (17.8)
	Muscle spasms	Very common	513 (13.2)

Tissue Disorders	Arthralgia	Very common	453 (11.7)
	Pain in extremity	Very common	420 (10.8)
	Musculoskeletal chest pain	Common	263 (6.8)
	Musculoskeletal pain	Common	264 (6.8)
	Bone pain	Common	267 (6.9)
	Muscular weakness	Common	227 (5.9)
	Myalgia	Common	188 (4.8)
Nervous System Disorders	Headache	Very common	691 (17.8)
	Dizziness	Very common	390 (10.1)
	Peripheral neuropathy[a]	Very common	428 (11.0)
	Paraesthesia	Common	232 (6.0)
	Hypoesthesia	Common	183 (4.7)
	Cerebrovascular accident	Uncommon	19 (0.5)
	Intracranial haemorrhage[a]	Uncommon	17 (0.4)
	PRES	Uncommon	4 (0.1)
Psychiatric Disorders	Insomnia	Very common	696 (17.9)
	Anxiety	Common	196 (5.1)
Renal and Urinary Disorders	Acute kidney injury	Common	226 (5.8)
	Renal failure	Common	117 (3.0)
	Renal impairment	Common	57 (1.5)
Respiratory, Thoracic, and Mediastinal Disorders	Dyspnoea	Very common	939 (24.2)
	Cough[a]	Very common	945 (24.4)
	Epistaxis	Common	216 (5.6)
	Oropharyngeal pain	Common	215 (5.5)
	Wheezing	Common	85 (2.2)
	Dysphonia	Common	96 (2.5)
	Pulmonary embolism	Common	76 (2.0)
	Pulmonary oedema	Common	49 (1.3)
	Pulmonary hypertension	Common	52 (1.3)

	Pulmonary haemorrhage[a]	Uncommon	30 (0.8)
	Pneumonitis	Uncommon	19 (0.5)
	Acute respiratory distress syndrome	Uncommon	9 (0.2)
	Acute respiratory failure	Uncommon	9 (0.2)
	Interstitial lung disease	Uncommon	12 (0.3)
Skin and Subcutaneous Tissue Disorders	Rash	Common	292 (7.5)
	Pruritus	Common	231 (6.0)
	Erythema	Common	129 (3.3)
	Hyperhidrosis	Common	120 (3.1)
Vascular Disorders	Hypertension	Very common	803 (20.7)
	Hypotension	Common	195 (5.0)
	Deep vein thrombosis	Common	112 (2.9)
	Flushing	Common	90 (2.3)
	Hypertensive crisis	Uncommon	15 (0.4)
	Haemorrhage	Uncommon	5 (0.1)
	Hypertensive emergency	Rare	2 (< 0.1)

Note: The frequency is calculated based on Carfilzomib treated subjects (N = 3878) in Study PX-171-001, PX-171-002, PX-171-003, PX-171-004, PX-171-005, PX-171-006, PX-171-007, PX-171-008, PX171009 (ASPIRE), PX171-010, PX-171-011 (FOCUS), 2011-002 (C-MAP), 2011-003 (ENDEAVOR), 2012-002, 2012-003, 2012-005 (CLARION), CFZ-001, CFZ-002, CFZ004, 20140355 (ARROW), and 20160275 (CANDOR PA). CANDOR data cutoff: 14Jul2019.

PRES = posterior reversible encephalopathy syndrome

[a] - 'Anaemia' includes Anaemia, Haematocrit decreased, and Haemoglobin decreased

- 'Thrombocytopenia' includes Platelet count decreased and Thrombocytopenia

- 'Neutropenia' includes Neutrophil count decreased and Neutropenia

- 'Lymphopenia' includes Lymphocyte count decreased and Lymphopenia

- 'Leukopenia' includes Leukopenia and White blood cell count decreased

- 'Cardiac failure' includes Cardiac failure and Congestive Cardiac failure

- 'Myocardial infarction' includes Myocardial infarction and Acute myocardial infarction

- 'Abdominal pain' includes Abdominal pain and Abdominal pain upper

- ‘Gastrointestinal haemorrhage’ includes Gastrointestinal haemorrhage, Gastric haemorrhage, Upper gastrointestinal haemorrhage, and Lower gastrointestinal haemorrhage.

- Pancreatitis acute’ includes Pancreatitis and Acute Pancreatitis

- ‘Infusion site reactions’ includes Infusion site inflammation, Infusion site erythema, Infusion site reaction, and Infusion site pain

- ‘Respiratory tract infection’ includes Respiratory tract infection, Lower respiratory tract infection, Upper respiratory tract infection, and Viral upper respiratory tract infection

- 'Hepatitis B Reactivation' includes Acute Hepatitis B PT, Hepatitis Acute PT, Hepatitis B PT, Hepatitis B DNA Assay Positive PT, Hepatitis B DNA Increased PT, Hepatitis B Reactivation PT, Hepatitis Viral PT.

- ‘Peripheral neuropathy’ includes Peripheral sensory neuropathy and Neuropathy peripheral

- ‘Intracranial haemorrhage’ includes Haemorrhage intracranial, Cerebral haemorrhage, Subarachnoid haemorrhage and Subdural hematoma

- ‘Cough’ includes Productive cough and Dry cough

- ‘Pulmonary haemorrhage’ includes Pulmonary haemorrhage, Pulmonary alveolar haemorrhage, and Haemoptysis

Post Marketing Experience

Frequency is provided by CIOMS category (e.g., Very Common (≥ 10 %), Common (≥ 1 % and < 10 %), uncommon (≥ 0.1 % and < 1 %), rare (≥ 0.01 % and < 0.1 %), very rare (< 0.01 %)).

System Organ Class	**Preferred Term**	**Frequency**
Blood and Lymphatic System Disorders	Haemolytic Uraemic Syndrome	Rare
Cardiac Disorders	Pericarditis	Rare
Gastrointestinal Disorders	Gastrointestinal Perforation	Rare
Infections and Infestations	Cytomegalovirus Chorioretinitis	Rare
Respiratory, Thoracic and Mediastinal Disorders	Laryngeal Oedema	Rare

The maximum frequency for these adverse drug reactions can be estimated from the upper limit of 95 % confidence interval for the point estimate, i.e. 3/3878 = 0.08 %. (see section 4.4)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04

Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Alternatively, suspected adverse events can be reported to:

Amgen South Africa (Pty) Ltd.

Tel: +27 (0)11 100 5300

Email: safety-south-africa@amgen.com

4.9. Overdose

Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia, and lymphopenia have been reported following a dose of 200 mg of KYPROLIS® administered in error. There is no known specific antidote for carfilzomib overdose. In the event of an overdose, the patient should be monitored, specifically for the side effects and/or adverse medicine reactions (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

A26 Cytostatic Agent

5.1. Pharmacodynamic Properties

Mechanism of Action

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that selectively and irreversibly binds to the N terminal threonine containing active sites of the 20S tumours. proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib had antiproliferative and proapoptotic activities in preclinical models in solid and haematologic tumours.

Pharmacodynamic Effects

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 ≥ 15 mg/m^2 consistently induced an (≥ 80 %) inhibition of the CT-L activity 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 immunoproteasome ranging from 26 % to 32 % and 41 % to 49 %, respectively. 1 (MECL1) subunits of the Proteasome inhibition 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.

Clinical efficacy and safety

KYPROLIS® in Combination with Dexamethasone and Daratumumab in Multiple Myeloma

The safety of 20/56 mg/m^2 twice weekly KYPROLIS® in combination with dexamethasone plus intravenous daratumumab (KdD) was evaluated in an open-label randomized Phase 3 trial (CANDOR). Additionally, the safety of 20/70 mg/m^2 once weekly KYPROLIS® in combination with intravenous daratumumab was evaluated in an open-label multi-cohort non-randomized trial (EQUULEUS),and in combination with subcutaneous daratumumab and hyaluronidase-fihj in a multi-cohort open-label trial (PLEIADES). CANDOR was a randomized, open-label, multicentre superiority trial of KYPROLIS® with dexamethasone plus daratumumab (KdD) twice weekly (20/56 mg/m^2) versus KYPROLIS® plus 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 orally or intravenously on Day 22 of each 28-day cycle.

The efficacy of KYPROLIS® was evaluated by PFS using IMWG response criteria. 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 versus 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.

Other endpoints included ORR. ORR was 84.3 % for patients in the KdD arm and 74.7 % in the Kd arm (see Table 12). Overall survival data (see Figure 2) were not mature, however, there was a trend toward longer OS in the KdD arm compared with Kd arm. The median duration of response was not estimable for the KdD arm and was 16.6 months (13.9, NE) for the Kd group. The median time to response was 1.0 (1, 14) months for the KdD arm and 1.0 (1,10) months for the Kd arm.

Table 12: 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		
Number of events, (n %)	110 (35.3)	68 (44.2)
Median, Months (95 % CI)	NE (NE,NE)	15.8 (12.1, NE)
Hazard Ratio	0.630 (0.464, 0.854)	
p-value (1-sided)	0.0014	
Lenalidomide refractory		
Median, Months (95 % CI)	NE (18.5, NE)	11.1 (7.4, 14.9)
Hazard Ratio (KdD/Kd)	0.453 (0.279,0.737)	
Lenalidomide Exposed		
Median, Months (95 % CI)	NE (18.5, NE)	12.1 (8.4, 15.3)
Hazard Ratio	0.521 (0.339, 0.802)	
Overall Response		
N with Response	263	115
ORR (%) (95 % CI)	84.3 (79.8, 88.1)	74.7 (67.0, 81.3)
Odds Ratio	1.925 (1.184, 3.129)	
p-value (1-sided)	0.0040	
MRD [-] CR at 12 months	12.5 (9.0, 16.7)	1.3 (0.2, 4.6)

Odds Ratio	11.329 (2.703, 47.476)	
p-value (1-sided)	<0.0001	
Response category, n(%)		
MRD – rate		
Complete Response (CR)	89 (28.5)	16 (10.4)
MRD [-] CR	43 (13.8)	5 (3.2)
VGPR	127 (40.7)	59 (38.3)
PR	47 (15.1)	40 (26.0)

Figure 1: Kaplan-Meier Plot of Progression-Free Survival

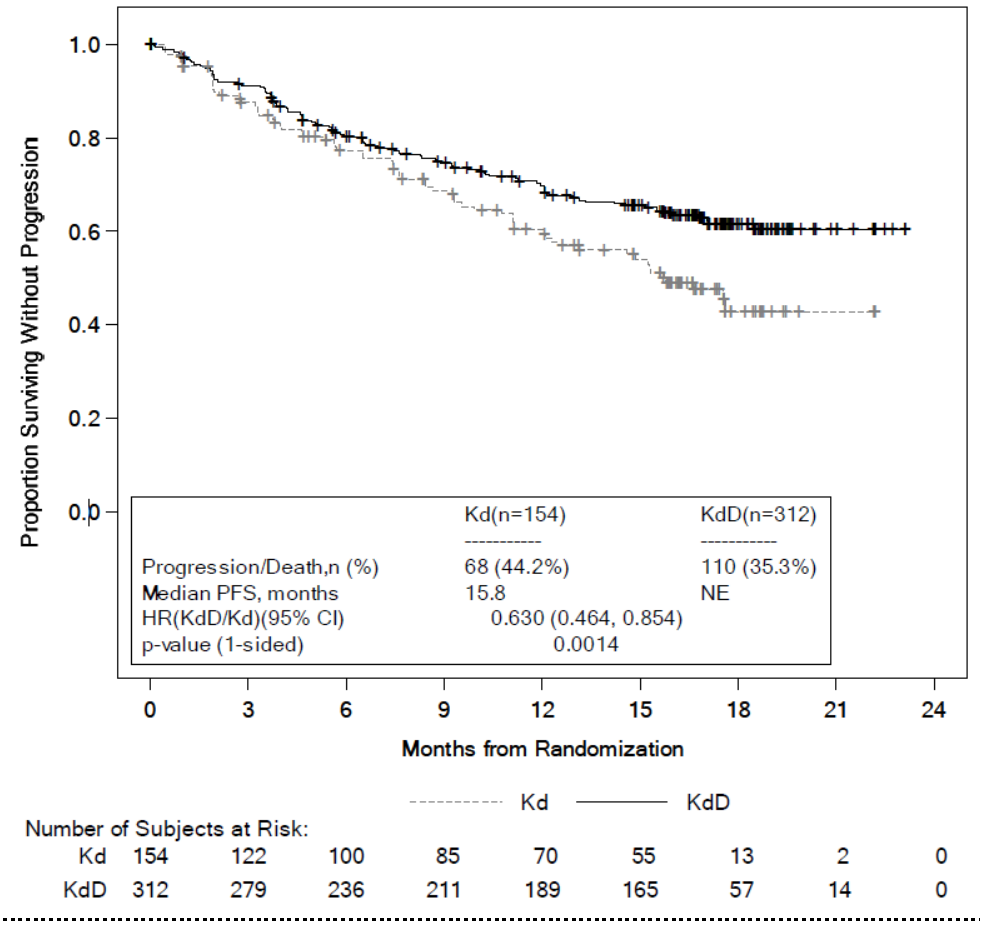
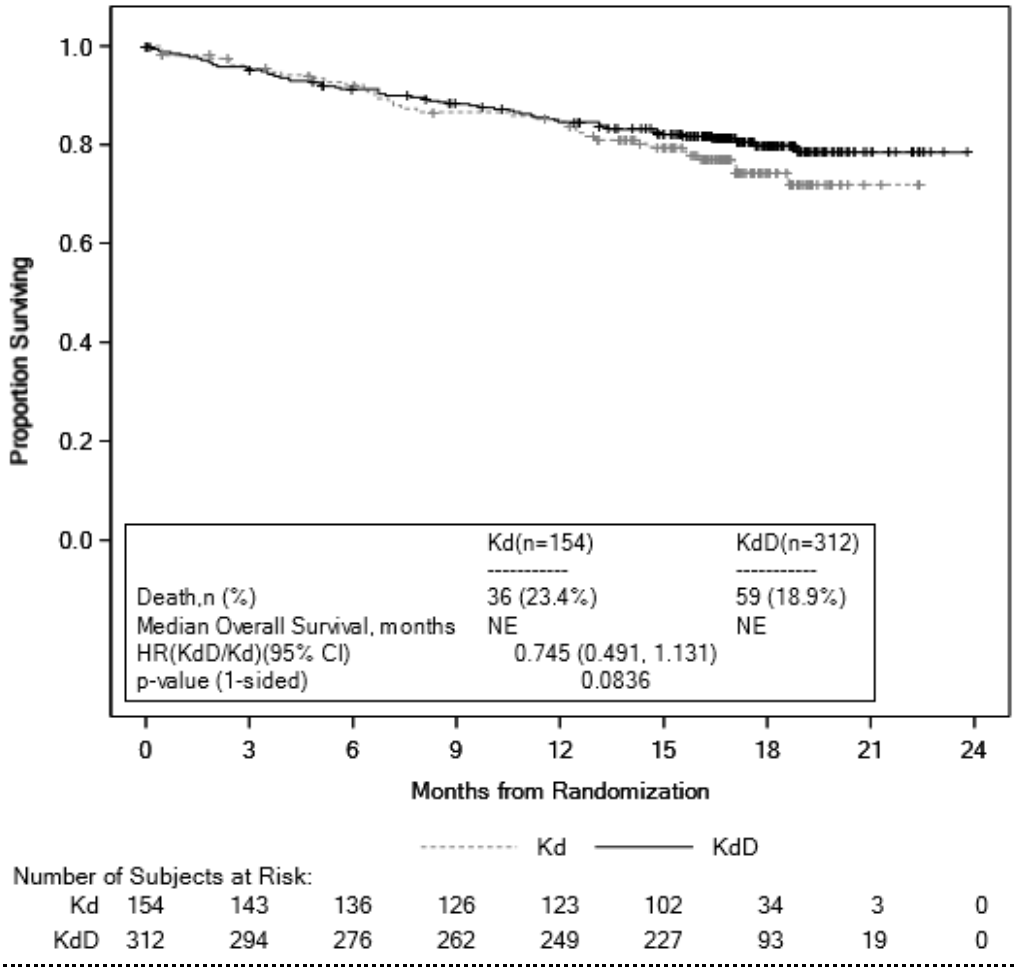


Figure 2: Kaplan-Meier Plot of Overall Survival



EQUULEUS was an open-label, multi-arm trial of intravenous daratumumab in combination with multiple myeloma therapy. The arm evaluating weekly KYPROLIS® with dexamethasone plus daratumumab (KdD) included 85 patients with relapsed or refractory multiple myeloma. 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. KYPROLIS was administered at a starting dose of 20 mg/m^2, which was increased to 70 mg/m^2 on Cycle 1, Day 8 and onward. KYPROLIS® was administered once weekly as a 30-minute infusion on Days 1, 8, and 15 of each 28 day cycle. Ten patients were administered a single first dose of daratumumab at 16 mg/kg on Cycle 1, Day 1. The remaining 75 patients were administered a split first dose of daratumumab at 8 mg/kg per day on Cycle 1, Day 1 and 2. Thereafter, a single 16 mg/kg dose was administered on Days 8, 15 and 22 of Cycle 1 and Days 1, 8, 15 and 22 of Cycle 2, every 2 weeks for 4 cycles

(cycles 3-6) and then every 4 weeks for the remaining cycles of each 28 day cycle. Dexamethasone is taken orally or intravenously at a dose of 20 mg in Cycle 1 and 2 on Days 1, 2, 8, 9, 15, 16, 22 and 23. In cycles 3-6, dexamethasone is taken at a dose of 20 mg on Days 1, 2, 15 and 16 and at a dose of 40 mg on Day 22. In cycles 7 and thereafter, dexamethasone is taken at a dose of 20 mg on Days 1 and 2 and at a dose of 40 mg on Days 8, 15, and 22. For patients >75 years of age, administer 20 mg of dexamethasone orally or intravenously weekly after the first week. Administer dexamethasone 30 minutes to 4 hours before KYPROLIS®. Dexamethasone 40 mg was administered on Days 1, 8, 15 and 22 of each 28 day cycle. Treatment continued until disease progression or unacceptable toxicity

The efficacy of KYPROLIS® was evaluated by PFS using IMWG response criteria. The median PFS was 26 months (95 % CI: 14.8, NE), after a median follow-up of 24 months. Other endpoints included ORR. ORR was 81 %. Median overall survival was not reached. The 12-month survival rate was 82 % and the 24 month survival rate was 71 %. The median time to response was 0.95 months (range: 0.9, 14.3). The median duration of response was 28 months (95 % CI: 20.5, not estimable). The median time to subsequent anti-myeloma therapy was 29 months (95 % CI: 19.5, NE).

Table 13: Summary of Efficacy Analysis

	Once weekly KdD 20/70 mg/m^2 Arm (N=85)
PFS	
Number of events, (n %)	40
Median, Months (95 % CI)	26 (14.8, NE)
Overall Response	
N with Response	69
ORR (%) (95 % CI)	81 (71, 89)
Response category, n(%)	
sCr	18 (21.2)
CR	12 (14.1)

VGPR	28 (32.9)
PR	11 (12.9)

K=KYPROLIS, d=dexamethasone, D=daratumumab

In PLEIADES, a multi-cohort, open-label trial, the efficacy of carfilzomib with dexamethasone plus subcutaneous daratumumab and hyaluronidase-fihj (KdD) was evaluated.
Patients received carfilzomib administered by IV infusion at a dose of 20 mg/m^2 on Cycle 1 Day 1 and if a dose of 20 mg/m^2 was tolerated carfilzomib was administered at a dose of 70 mg/m^2 as a 30-minute IV infusion on Cycle 1 Day 8 and Day 15, and then Day 1, 8 and 15 of each cycle: daratumumab 1,800 mg/30,000 units administered subcutaneously once weekly from Weeks 1 to 8, once every 2 weeks from Weeks 9 to 24 and once every 4 weeks starting with Week 25 until disease progression or unacceptable toxicity; and dexamethasone 40 mg per week (or a reduced dose of 20 mg per week for patients ≥75 years or BMI <18.5). The major efficacy outcome measure was ORR. The median duration of follow up for patients was 9.2 months.

A total of 66 patients received the KdD regimen. The median age was 61 years (range: 42 to 84); 52% were male; 73% were White and 3% Black or African American; and 68% had ISS Stage I, 18% had ISS Stage II, and 14% had ISS Stage III disease. A total of 79% of patients had a prior ASCT; 91% of patients received a prior PI. All patients received 1 prior line of therapy with exposure to lenalidomide and 62% of patients were refractory to lenalidomide

Efficacy results are summarized in Table 14.

Table 14: Summary of Efficacy Analysis

	KdD (N=66)
Overall response rate (sCR+CR+VGPR+PR), n (%)[a]	56 (84.8%)
95% CI (%)i	(73.9%, 92.5%)
Stringent complete response (sCR)	11 (16.7%)
Complete response (CR)	14 (21.2%)
Very good partial response (VGPR)	26 (39.4%)
Partial response (PR)	5 (7.6%)

MRD negativity ratea, b n(%)	16 (24.2%)
95% CI (%)	(14.5%, 36.4%)
MRD negativity rate in patients with CR or better	
Number of patients with CR or better[b]	N=25
MRD negativity rate n(%)	14 (56.0%)
95% CI (%)	(34.9%, 75.6%)

CI = confidence interval; MRD = minimal residual disease

[a] Based on treated patients

[b] Based on threshold of 10-5 using next generation sequencing assay (ClonoSEQ)

KYPROLIS® in combination with lenalidomide and dexamethasone multiple myeloma

The safety and efficacy of KYPROLIS® were evaluated in a randomised, open-label, multicentre study of 792 patients who had received 1 to 3 prior lines of therapy (median of 2), which evaluated the combination of KYPROLIS® with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone, randomised 1:1. Patients who had the following were excluded from the trial: creatinine clearance rates < 50 ml/min, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 4 months. 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.

Patients in the KYPROLIS®, lenalidomide, and dexamethasone (KRd) arm demonstrated improved 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 event as determined using standard objective International Myeloma Working Group (IMWG)/European Blood and Marrow Transplantation (EBMT) response criteria by an Independent Review Committee (IRC).

The median PFS was 26,3 months (95 % CI: 23,3 to 30,5 months) in the KRd arm versus 17,6 months (95 % CI: 15,0 to 20,6 months) in the Rd arm, a difference of 8,7 months at the median (see Figure 1). The PFS benefit of KRd was consistently observed in all subgroups (see Figure 2).

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 15 and Figure 3).

The overall response rate (ORR) was higher in the KRd arm versus the Rd arm (87,1 % versus 66,7 %; 1-sided p-value < 0,0001). Rate and depth of response were increased in the KRd versus Rd arm with 31,8 % CR and higher in the KRd arm (including 14,1 % stringent complete response [sCR]) versus 9,3 % CR and higher in the Rd arm (including 4,3 % sCR). Patients treated with KRd reported improved global health status, with higher Global Health Status/Quality of Life (QoL) scores compared with Rd over 18 cycles of treatment (1-sided p-value = 0,0001) measured with the EORTC QLQ-C30, an instrument validated in multiple myeloma (see Figure 4).

Table 15: Summary of Efficacy Analysis

	KRd Combination Therapy	
	Study PX-171-009	
	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[c]	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)
95 % CI of ORR	83,4; 90,3	61,8; 71,3
1-sided p-value[c]	< 0,0001	—
DOR Months, median (95 % CI)	28,6 (24,9; 31,3)	21,2 (16,7; 25,8)
TTR Months, median (min, max)[d]	1 (1; 14)	1 (1; 16)
CBR n (%)	360 (90,9)	302 (76,3)
95 % CI of CBR	87,6; 93,6	71,8; 80,4
DCB Months, median (95 % CI)	28,3 (24,3; 30,5)	20,3 (16,6; 24,0)
DCR n (%)	367 (92,7)	345 (87,1)
95 % CI of DCR[c]	89,7; 95,0	83,4; 90,3

CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DCB = duration of clinical benefit; DCR = disease control rate; DOR = duration of response; EBMT = European Blood and Marrow Transplantation; IMWG = International Myeloma Working Group; KRd = KYPROLIS®/lenalidomide/dexamethasone; NE = not estimable; OS = overall survival; ORR = overall response rate; PFS = progression-free survival; Rd = lenalidomide/dexamethasone; sCR = stringent complete response; TTR = time to response; VGPR = very good partial response

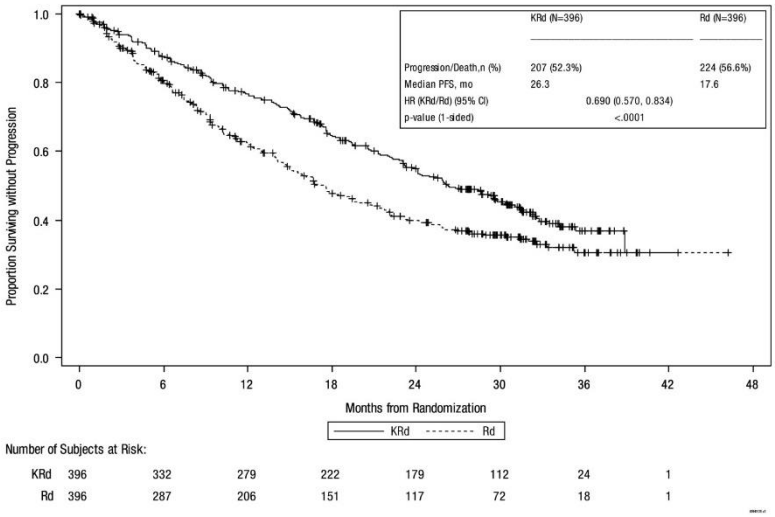
As determined by an Independent Review Committee using standard objective IMWG/EBMT response criteria.

Statistically significant.

The interim OS analysis did not meet the protocol-specified early stopping boundary for OS (p = 0,0051); hence, due to the hierarchical nature of the study design all subsequent p-values are provided for descriptive purposes only.

This is a sample median, not a Kaplan-Meier median.

Figure 3: Kaplan-Meier Curve of Progression-Free Survival



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

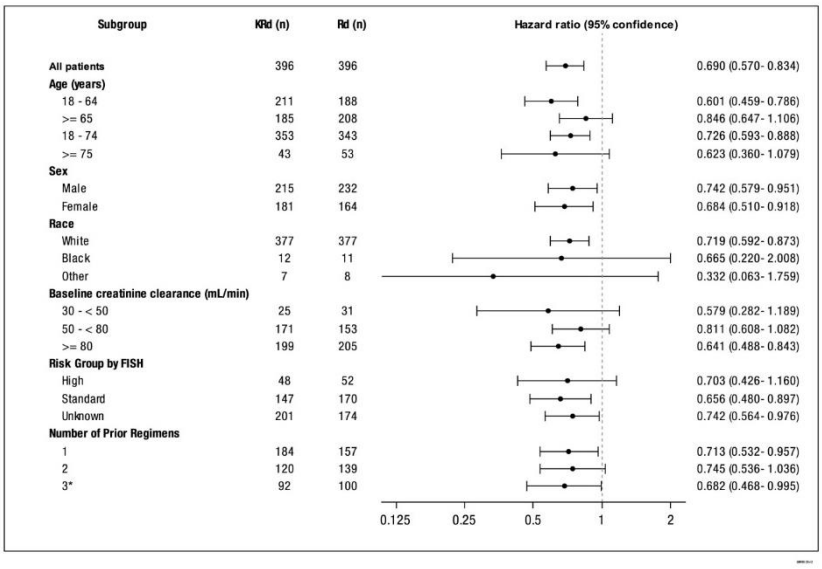
Note: The response and PD outcomes were determined using standard objective IMWG/EBMT response criteria.

[a] Study PX-171-009

Figure 4: Subgroup Analyses of Progression-Free Survival as Determined by

Independent Review Committee (Selected Subgroups)

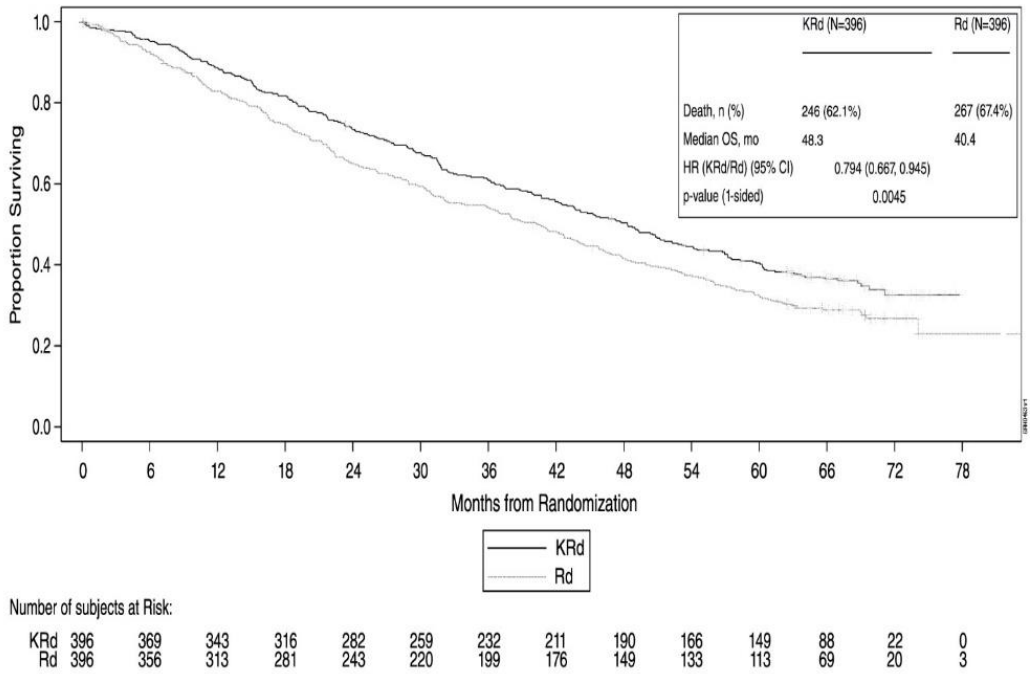
Intent-to-Treat Population



KRd = KYPROLIS®/lenalidomide/dexamethasone; FISH = fluorescent in situ hybridisation; Rd = lenalidomide/dexamethasone

* Including 2 subjects with 4 prior regimens.

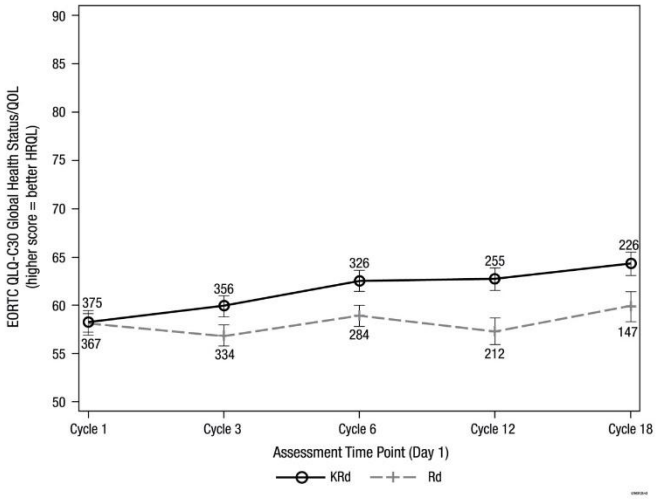
Figure 5: Kaplan-Meier Curve of Overall Survival



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

[a] Study PX-171-009

Figure 6: Study PX-171-009 Global QOL



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module; HRQL = health-related quality of life; KRd = KYPROLIS®/lenalidomide/dexamethasone; MMRM = mixed model for repeated measures; QoL = quality of life; Rd = lenalidomide/dexamethasone

Note: a 1-sided p-value of 0,0001 for overall treatment effect was obtained based on a type 3 test for fixed effects (MMRM).

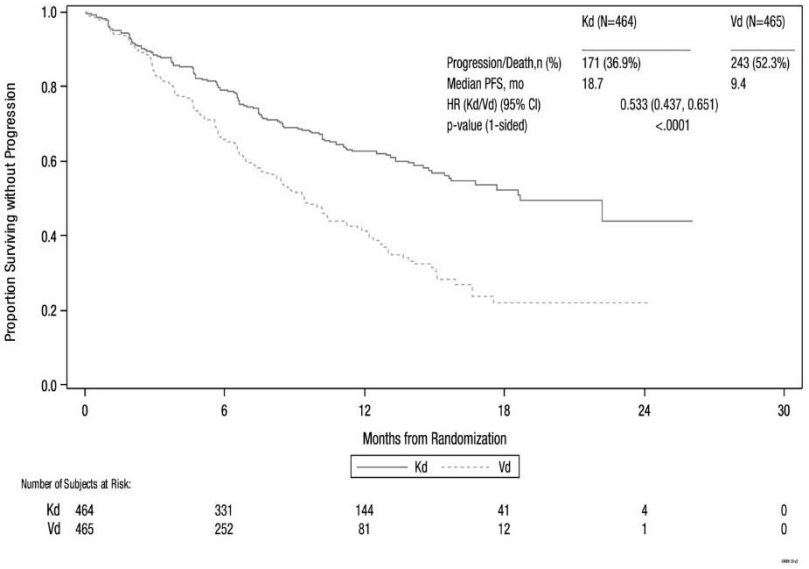
KYPROLIS® in combination with dexamethasone in multiple myeloma

Study 2011-003

The safety and efficacy of KYPROLIS® 56 mg/m^2 twice weekly were evaluated in a Phase 3, randomised, open-label, multicentre study of KYPROLIS® plus dexamethasone (Kd) versus bortezomib plus 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 randomised (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 endpoint of this study was PFS as determined by an Independent Review Committee (IRC) using standard objective IMWG/response criteria. The study showed 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 versus 9,4 months [95 % CI: 8,4; 10,4] in the Vd arm) (see Figure 7).

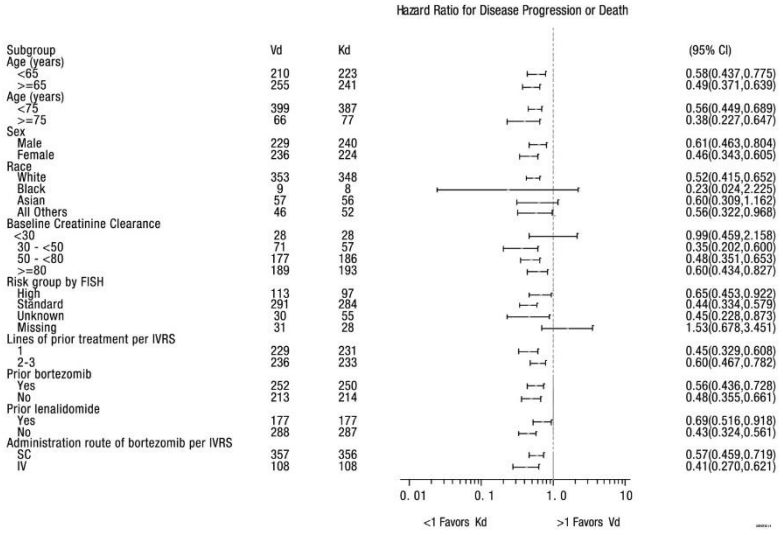
Figure 7: Kaplan-Meier Plot of Progression-Free Survival as Determined by the Independent Review Committee (Intent-to-Treat Population)[a]



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

[a]Study 2011-003

Figure 8: Subgroup Analyses of Progression-Free Survival as Determined by Independent Review Committee (Selected Subgroups) Intent-to-Treat Population



CI = confidence interval; FISH = fluorescent in situ hybridisation; IV = intravenous; IVRS = interactive voice response system; SC = subcutaneous

The key secondary endpoints were OS, ORR, and incidence of peripheral neuropathy

events (≥ Grade 2).

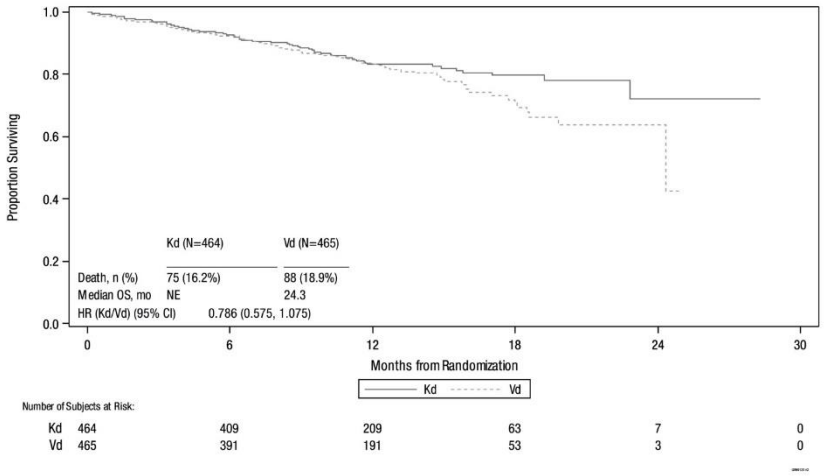
The pre-planned OS analysis was performed after 189 deaths in the Kd arm and 209 deaths in the Vd arm. The median follow-up was approximately 37 months. A statistically significant advantage in OS was observed in patients in the Kd arm compared to patients in the Vd arm (HR = 0.791; 95 % CI: 0.648, 0.964; p-value = 0.010) (see Figure 9).

ORR was 76,9 % (95 % CI: 72.8, 80.7) for patients in the Kd arm and 62,6 %

(95 % CI: 58,0; 67,0)for patients in the Vd arm (odds ratio = 2,032, 95 % CI: 1,519; 2,718;),

(p-value < 0,0001) (see Table ~~15~~16).

Figure 9: Kaplan-Meier Curve of Interim Overall Survival



CI = confidence interval; HR = hazard ratio; Kd = KYPROLIS® plus dexamethasone; mo = months; NE = not estimable; OS = overall survival; Vd = bortezomib plus dexamethasone

[a] Study 2011-003

At the time of the pre-planned OS analysis, the incidence of ≥ Grade 2 peripheral neuropathy

events in the Kd arm (event rate of 6,9 % 95 % CI: 4,6; 9,2) was approximately

5 times lower than in the Vd arm (event rate of 34.9 % 95 % CI: 30.5; 39.2)

(odds ratio = 0,139; 95 % CI: 0,092; 0,208; p-value < 0,0001).

Table 16: Summary of Key Results (Intent-to-Treat Population)

	Kd Combination Therapy	
	Study 2011-003 (Phase 3)	
	Kd Arm (N = 464)	**Vd Arm (N = 465)**

Progression-Free Survival (months)[a]		
Median (95 % CI)	18,7 (15,6; —)	9,4 (8,4; 10,4)
P-value (1sided)	< 0,0001	
Hazard Ratio (Kd/Vd) (95 % CI)	0,533 (0,44; 0,65)	
Overall Survival (months)		
Median (95 % CI)	47.6 (42.5, —)	40.0 (32.6, 42.3)
P-value (1-sided)	0.010	
Hazard Ratio (Kd/Vd) (95 % CI)	0.791 (0.648, 0.964)	
ORR[a]		
N with Response[b]	357	291
ORR (95 % CI)	76,9 (72,8; 80,7)	62,6 (58,0; 67,0)
P-value (1-sided)	< 0,0001	
Odds Ratio (Kd/Vd) (95 % CI)	2,032 (1,519; 2,718)	
≥ CR[c]		
N with ≥ CR	58	29
CR or Better (95 % CI)	12,5 (9,6; 15,9)	6,2 (4,2; 8,8)
P-value (1-sided)	0,0005	
Odds Ratio (Kd/Vd) (95 % CI)	2,140 (1,344; 3,408)	
≥ VGPR[c]		
N with ≥ VGPR	252	133
VGPR or Better (95 % CI)	54,3 (49,7; 58,9)	28,6 (24,5; 32,9)
P-value (1-sided)	< 0,0001	
Odds Ratio (Kd/Vd) (95 % CI)	3,063 (2,322; 4,040)	
DOR (months)[a]		
Median (95 % CI)	21,3 (21,3; —)	10,4 (9,3; 13,9)
Grade 2+ Peripheral Neuropathy Events[d]	463[e]	456[e]
N (%) with PN	32 (6.9)	159 (34.9)
95 % CI	4.6, 9.2	30.5, 39.2
P-value (1-sided)	< 0,0001	
Odds Ratio (Kd/Vd) (95 % CI)	0.139 (0.092, 0.208)	

CI = confidence interval; CR = complete response; DOR = duration of response; Kd = KYPROLIS®/dexamethasone; ORR = overall response rate; PN = peripheral neuropathy; Vd = bortezomib/dexamethasone; VGPR = very good partial response

[a] These endpoints were determined by an Independent Review Committee.

[b] Overall response is defined as achieving a response of PR or above. Analysis of duration of response includes patients achieving an overall response only.

[c] The p-values presented are provided for descriptive purposes only as they are not pre-specified secondary endpoints with statistical testing.

[d] The analysis of Grade 2 or higher PN events is based on the Safety Population, the sample size of which is listed for each arm.

[e] The safety population was used to determine peripheral neuropathy events.

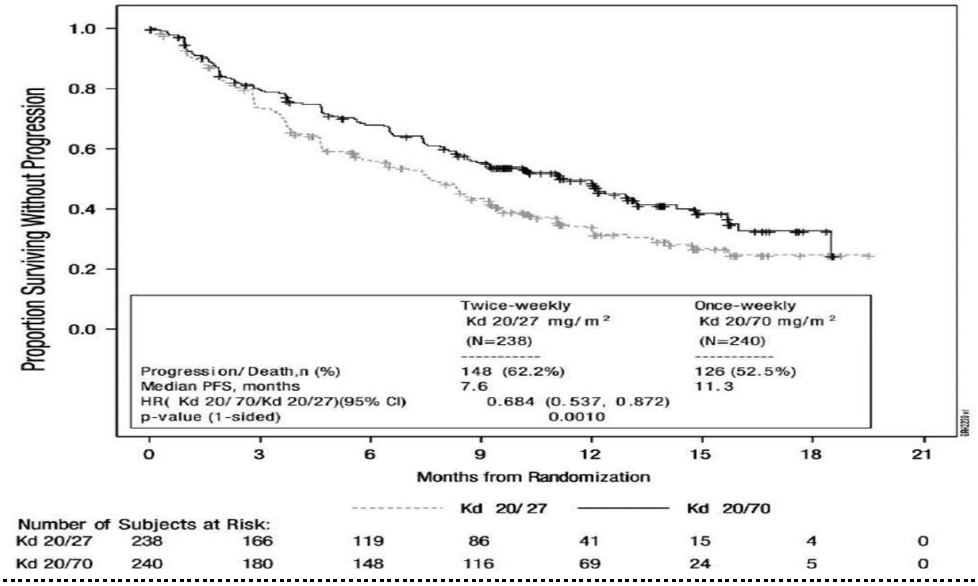
Study 20140355

The safety and efficacy of KYPROLIS® 70 mg/m^2 once weekly were evaluated in Phase 3, randomized, open-label, multicentre study of Kd 70 mg/m^2 once weekly versus 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 primary endpoint of this study was PFS. The study showed significantly longer duration of PFS for patients treated with Kd 70 mg/m^2 once weekly than those treated with Kd 27 mg/m^2 twice weekly (HR: 0.68, 95 % CI: 0.54, 0.87 [p-value = 0.0010]), with a difference in median PFS of 3.7 months (11.3 months in the Kd 70 mg/m^2 once weekly arm versus 7.6 months in the Kd 20/27 mg/m^2 twice weekly arm) (see Figure 10).

The efficacy of Kd once weekly is summarized in Table 17.

Figure 10: Kaplan-Meier Plot of Progression-Free Survival (Intent-to-Treat Population)



CI = confidence interval; HR = hazard ratio; Kd = KYPROLIS® plus dexamethasone; PFS = progression-free survival

[a] Study 20140355

[b] As determined by Independent Review Committee

The key secondary endpoints were ORR and OS.

ORR was 63.8 % (95 % CI: 57.3, 69.8) for patients in the Kd 70 mg/m^2 once weekly arm and 41.2 % (95 % CI: 34.9, 47.7) for patients in the Kd 27 mg/m^2 twice weekly arm (odds ratio = 2.53; 95 % CI: 1.75, 3.66; p-value < 0.0001) (see Table 17).

At the time of primary analysis of PFS, the HR for OS was 0.80 (95 % CI: 0.56, 1.14; 1-sided p =0.1070).

Table 17: Summary of Key Results (Intent-to-Treat Population)

	Kd Combination Therapy		
		Study 20140355 (Phase 3)	
	Study 20130403/2012-002 (Phase 1/2) **Kd 70 mg/m^2 Once Weekly (N=104)**	**Kd 70 mg/m^2 Once Weekly Arm[a] (N = 240)**	**Kd 27 mg/m^2 Twice Weekly Arm[a] (N = 238)**
Progression-free Survival (months)			
Median (95 % CI)	16.2 (10.2, 21.0)	11.3 (8.6, 13.2)	7.6 (5.7, 8.7)
P-value (1-sided)	–	0.0010	

Hazard Ratio (Kd 70 mg/m^2 Once weekly/Kd 27 mg/m^2 Twice weekly) (95 % CI)	–	0.68 (0.54 , 0.87)	
ORR			
N with Overall Response[b]	80	153	98
ORR (95 % CI)	76.9 (67.6, 84.6)	63.8 (57.3, 69.8)	41.2 (34.9, 47.7)
P-value (1-sided)	–	< 0.0001	
Odds Ratio (Kd 70 mg/m^2 Once weekly/Kd 27 mg/m^2 Twice weekly) (95 % CI)	–	2.53 (1.75, 3.66)	

CI = confidence interval; Kd = KYPROLIS®/dexamethasone; ORR = overall response rate

[a] As determined by Independent Review Committee.

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

Study 20130403/Study 2012-002

The safety and efficacy of KYPROLIS® 70 mg/m^2 once weekly were evaluated in a Phase 1/2 single-arm, multicentre open-label clinical trial. The maximum tolerated dose (MTD) of Kd 70 mg/m^2 once weekly was determined in Phase 1, and Phase 2 enrolled patients with relapsed or refractory multiple myeloma who had received 1 to 3 prior lines of therapy. There were a total of 104 patients in the Kd 70 mg/m^2 once weekly group in both phases combined. Patients who had the following were excluded from the trial: creatinine clearance rates < 30 ml/min, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 6 months.

The primary endpoint was the ORR defined as the proportion of subjects who achieved a confirmed partial response [PR] or better. The ORR (complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 76.9 % (95 % CI: 67.6, 84.6) (N = 104). The median duration of response (DOR) was 18.0 months (95 % CI: 14.5, 21.9). The efficacy of Kd once weekly is summarized in Table 17.

KYPROLIS® as monotherapy in multiple myeloma

KYPROLIS® monotherapy was evaluated in two relapsed and refractory multiple myeloma. The prior antimyeloma treatments are summarised in Table 18.

Study PX-171-003 A1

The safety and efficacy of KYPROLIS® were evaluated in a single-arm, multicentre clinical trial. A total of 266 patients with relapsed and refractory multiple myeloma who had received at least two prior therapies (including bortezomib and thalidomide and/or lenalidomide) were enrolled. Patients who had the following were excluded from the trial: creatinine clearance rates < 30 ml/min, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 6 months.
KYPROLIS® was administered intravenously over 2 to 10 minutes on two consecutive days each week for three weeks, followed by a 12 day rest period (28 day treatment cycle), until disease progression, unacceptable toxicity, or for a maximum of 12 cycles. Patients received 20 mg/m^2 at each dose in Cycle 1, and 27 mg/m^2 in subsequent cycles. To reduce the incidence and severity of fever, rigors, chills, dyspnoea, myalgia, and arthralgia, dexamethasone 4 mg by mouth or by intravenous infusion was administered prior to all KYPROLIS® doses during the first cycle and prior to all KYPROLIS® doses during the first dose-escalation (27 mg/m^2) cycle. Dexamethasone premedication (4 mg orally or intravenously) was reinstated if these symptoms reappeared during subsequent cycles.
The primary endpoint was the overall response rate (ORR) as determined by Independent Review Committee assessment using IMWG/EBMT criteria. The ORR (stringent complete response [sCR] + complete response [CR] + very good partial response [VGPR] + partial response [PR]) was 22,9 % (95 % CI: 18,0; 28,5) (N = 266). The median duration of response (DOR) was 7,8 months (95 % CI: 5,6; 9,2). The efficacy of KYPROLIS® as monotherapy in relapsed and refractory multiple myeloma studies is summarised in Table 18.

Study PX-171-011

Study PX-171-011 was a Phase 3 study of 315 patients with at least 3 prior lines of therapy, which evaluated KYPROLIS® monotherapy versus an active comparator arm (referred to in the protocol as Best Supportive Care [BSC]) of metronomic low-dose corticosteroids (84 mg/28 day cycle) and optional cyclophosphamide (1400 mg/28 day cycle, which was used by 91,8 % of patients randomised to the comparator arm).
Patients who had the following were excluded from the trial: creatinine clearance rates< 15 ml/min, New York Heart Association Class III to IV congestive heart failure, or myocardial infarction within the last 3 months.
Patients enrolled to Study PX-171-011 were more heavily pre-treated with lower organ and marrow function as compared to those enrolled in Study PX-171-003A1.

The study did not meet its primary efficacy endpoint of prolonging OS with KYPROLIS® monotherapy compared to control. The HR was 0,975 (95 % CI: 0,760 to 1,249); with a 1-sided p-value of 0,4172. The median OS was 10,2 months (95 % CI: 8,4 to 14,4 months) in the KYPROLIS® arm, versus 10,0 months (95 % CI: 7,7 to 12,0 months) in the comparator arm.

The median PFS was 3,7 months in the KYPROLIS® arm, versus 3,3 months in the comparator arm. The HR was 1,091 [95 % CI: 0,843 to 1,410]; with 1-sided p –value of 0,2479. The ORR in the KYPROLIS® arm was 19,1 % as compared to 11,4 % in the comparator arm (see Table 18).

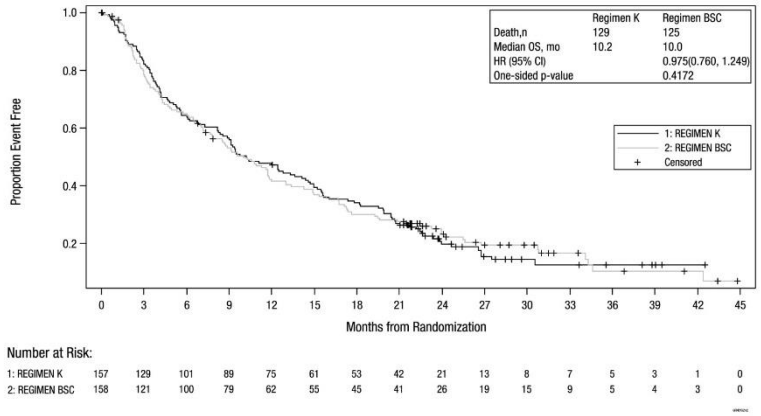
Table 18: Prior Antimyeloma Treatments

	Studies with Efficacy as a Primary Objective		
	PX-171-003 – Part 2 (A1) (Phase 2)	**PX-171-011 (Phase 3)**	
		KYPROLIS® Arm	**Comparator Arm**
	(N = 266)	**(N = 157)**	**(N = 158)**
Bortezomib, Alkylators, IMiD, and Corticosteroids, n (%)	241 (90,6)	157 (100)	158 (100)
Bortezomib, Alkylators, Anthracycline, IMiD, and Corticosteroids, n (%)	157 (59,0)	117 (74,5)	122 (77,2)
Refractory Status to Most Recent Therapy, n (%)	252 (94,7)	157 (100)	157 (99,4)

CBR = clinical benefit rate; CI = confidence interval; DCB = duration of clinical benefit; DCR = disease control rate; DOR = duration of response; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; NE = not estimable; NR = not reportable; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TTR = time to response

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

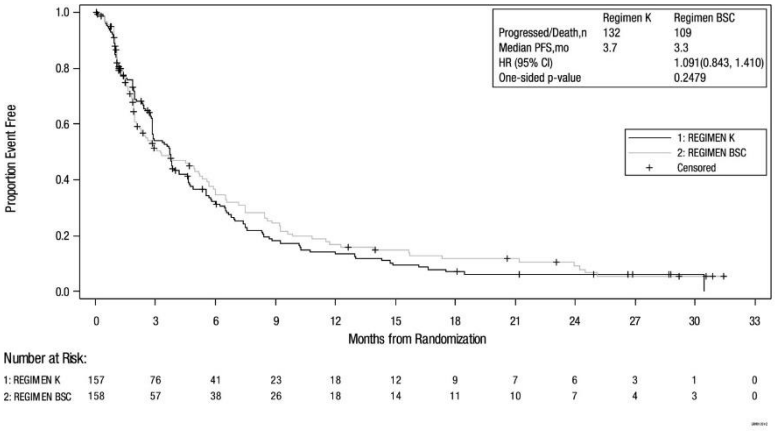
Figure 11: Kaplan-Meier Curve of Overall Survival (Intent-to-Treat Population)[a]



BSC = control (best supportive care, defined as corticosteroids with optional cyclophosphamide); CI = confidence interval; K = KYPROLIS®; HR = hazard ratio; mo = months; OS = overall survival

[a] Study PX-171-011

Figure 12: Kaplan-Meier Curve of Progression-Free Survival (Intent-to-Treat Population)[a]



BSC = control (best supportive care, defined as corticosteroids with optional cyclophosphamide); CI = confidence interval; EBMT = European Blood and Marrow Transplantation; HR = hazard ratio; IMWG = International Myeloma Working Group; K = KYPROLIS®; mo = months; PFS = progression-free survival

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

[a] Study PX-171-011

5.2. Pharmacokinetic Properties

Absorption

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 plasma concentration-time curve (AUC). 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.

Distribution

The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib 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 micromolar.

Biotransformation

Carfilzomib was rapidly and extensively metabolised. The predominant metabolites measured in human plasma and urine, and generated in vitro by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450 mediated mechanisms played a minor role in overall carfilzomib metabolism. 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, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. Carfilzomib is eliminated primarily via metabolism with subsequent excretion in urine.

Hepatic Impairment

Hepatic impairment: The pharmacokinetics of carfilzomib was studied in patients with relapsed or progressive advanced malignancies with mild or moderate chronic hepatic impairment relative to those with normal hepatic function.
No marked differences in exposures (AUC and C_{max}) were observed between patients with normal hepatic function and those with mild or moderate hepatic impairment.
The pharmacokinetics of carfilzomib has not been studied in patients with severe hepatic impairment (see section 4.2).

Renal Impairment

The pharmacokinetics of carfilzomib was studied in relapsed multiple myeloma patients

with normal renal function; mild, moderate or severe renal impairment; and patients with end-stage renal disease requiring haemodialysis. Exposures of carfilzomib (AUC and C_{max}) in patients with renal impairment were highly variable, with mean values similar to those with normal renal function. No starting dose adjustment is required in patients with baseline renal impairment (see section 4.2).

5.3. Preclinical safety data

Carcinogenesis, mutagenesis, and impairment of fertility

Carcinogenicity studies have not been conducted with carfilzomib.

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 and was not clastogenic in the in vivo mouse bone marrow micronucleus assay.

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.

Monkeys administered a single bolus intravenous dose of carfilzomib at 3 mg/kg (approximately 1,3 times the recommended dose in humans of 27 mg/m^2 based on body surface area) experienced hypotension, increased heart rate, and increased serum levels of troponin T. The repeated bolus intravenous administration of carfilzomib at ≥ 2 mg/kg/dose in rats and 2 mg/kg/dose in monkeys using dosing schedules similar to those used clinically resulted in mortalities that were due to toxicities occurring in the cardiovascular (cardiac failure, cardiac fibrosis, pericardial fluid accumulation, cardiac haemorrhage/degeneration), gastrointestinal (necrosis/haemorrhage), renal (glomerulonephropathy, tubular necrosis, dysfunction), and pulmonary (haemorrhage/inflammation) systems. The dose of 2 mg/kg/dose in rats is approximately half the recommended dose in humans of 27 mg/m^2 based on body surface area. The dose of 2 mg/kg/dose in monkeys is approximately equivalent to the recommended dose in humans based on body surface area.

Based on its mechanism of action and findings in animals, carfilzomib can cause foetal harm when administered to a pregnant woman. Carfilzomib caused embryo-foetal toxicity in pregnant rabbits at doses that were lower than in patients receiving

the recommended dose. Carfilzomib administered to pregnant rats and rabbits during the period of organogenesis was not teratogenic at doses up to 2 mg/kg/day in rats or up to 0.8 mg/kg/day in rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients*:*

Anhydrous citric acid

Sulfobutylether beta-cyclodextrin

Water for injection.

Sodium hydroxide (for pH adjustment)

6.2. Incompatibilities*:*

In the absence of compatibility studies, this medicine must not be mixed with other medicines**.** Normal saline should not be used for reconstitution of KYPROLIS®. Reconstituted KYPROLIS® for injection should not be diluted into a 0,9 % sodium chloride IV bag for IV administration.

6.3. Shelf life*:*

Powder vial (unopened): 36 months.

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 (between 2 °C and 8 °C) up to 24 hours or at room temperature (between 15 °C and 30 °C) for up to 4 hours.

6.4. Special Precautions for Storage

Store between 2 °C and 8 °C.

Unopened vials should be stored refrigerated (between 2 °C and 8 °C).

Retain in original package to protect from light.

Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5. Nature and contents of container

Single-use 50 ml Type 1 clear glass vial closed with a grey fluoropolymer laminated

elastomeric stopper (chlorobutyl rubber) and a grey aluminium, clear lacquer finish, polypropylene seal with a purple plastic flip off cap. Pack size of one vial (60 mg carfilzomib per vial) in a carton.

6.6. Special precautions for disposal and other handling

Reconstitution and preparation for intravenous administration

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

1. Remove vial from refrigerator just prior to use.
2. Calculate the dose (mg/m^2) and number of vials of KYPROLIS® required using the patient's body surface area (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 %.
3. Use only a 21-gauge or larger gauge needle (0,8 mm or smaller external diameter needle) to aseptically reconstitute each vial by slowly injecting 29 ml sterile water for injection through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimise 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 solution and should not be administered if any discolouration or particulate matter is observed.
6. 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 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). Do not dilute KYPROLIS® into normal saline.

Disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Amgen South Africa (Pty) Ltd.

Building D, Ballyoaks Office Park,

35 Ballyclare Drive, Bryanston Ext. 7

2021,

South Africa

8. REGISTRATION NUMBER(S)

51/26/0679

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14 July 2020

10. DATE OF REVISION OF THE TEXT

01 March 2024