Announcement regarding harshment (safety information) in the Physician Leaflet

הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך: 28.02.2016

Name of the product:

שם תכשיר באנגלית: Kyprolis

Registration No's:

מספר רישום: 151-21-33948-00

Name of the registration owner:

שם בעל הרישום Amgen Europe B.V.

----------DOSAGE AND ADMINISTRATION----------	----------DOSAGE AND ADMINISTRATION----------
• Administer intravenously over 2 to 10 minutes, 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). (2.1) • Recommended Cycle 1 dose is 20 mg/m^2/day and if tolerated increase Cycle 2 dose and subsequent cycles doses to 27 mg/m^2/day. (2.1) • Hydrate patients prior to and following administration. (2.2) • Pre-medicate with dexamethasone prior to all Cycle 1 doses, during the first cycle of dose escalation, and if infusion reaction symptoms develop or reappear. (2.3) • Modify dosing based on toxicity. (2.4)	• Hydrate prior to and following administration.as needed. (2.1) • Premedicate with dexamethasone prior to all Cycle 1 doses and if infusion reaction symptoms develop or reappear. (2.1, 2.2) • Administer intravenously as a 10 minute 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). (2.1, 2.2) • Kyprolis is administered at a starting dose of 20 mg/m^2/day in Cycle 1 on Days 1 and 2. If tolerated, the dose should be escalated to a target dose of 27 mg/m^2/day on Day 8 of Cycle 1. (2.2)
----------WARNINGS AND PRECAUTIONS----------	----------WARNINGS AND PRECAUTIONS----------
Cardiac Adverse Reactions including heart failure and ischemia: Monitor for cardiac complications. Treat promptly and withhold KYPROLIS. (2.4, 5.1) Pulmonary Hypertension: Withhold dosing if suspected. (2.4, 5.2) Pulmonary Complications: Monitor for and manage dyspnea immediately; interrupt KYPROLIS until symptoms have resolved or returned to baseline. (2.4, 5.3) Infusion Reactions: Pre-medicate with dexamethasone to prevent. (2.3) Advise patients to seek immediate medical attention if symptoms develop. (5.4) Tumor Lysis Syndrome (TLS): Hydrate patients to prevent. (2.2) Monitor for TLS and treat promptly. (5.5) Thrombocytopenia: Monitor platelet counts; reduce or interrupt	• Cardiac toxicities include cardiac failure and myocardial infarction with fatal outcome, and myocardial ischemia. Withhold Kyprolis and evaluate promptly. (5.1) • Acute Renal Failure: Monitor serum creatinine regularly (5.2) • Tumor Lysis Syndrome (TLS): Administer pre-treatment hydration. (2.1) Monitor for TLS, including uric acid levels and treat promptly. (5.3) • Pulmonary Toxicity: including Acute Respiratory Distress Syndrome, acute respiratory failure, and acute diffuse infiltrative pulmonary disease: Withhold Kyprolis and evaluate promptly. (5.4) • Pulmonary Hypertension: Withhold Kyprolis and evaluate. (5.5) • Dyspnea: For severe or life threatening dyspnea, withhold Kyprolis

dosing as clinically indicated. (2.4, 5.6) Hepatic Toxicity and Hepatic Failure: Monitor liver enzymes and withhold dosing if suspected. (2.4, 5.7) Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Monitor for signs and symptoms of TTP/HUS. Discontinue KYPROLIS if suspected. (5.8). Posterior reversible encephalopathy syndrome (PRES): Consider neuro-radiological imaging (MRI) for onset of visual or neurological symptoms; discontinue KYPROLIS if suspected. (5.9) Embryo-fetal Toxicity: KYPROLIS can cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated. (5.10,8.1)	and evaluate. (5.6) • Hypertension including hypertensive crisis: Monitor blood pressure regularly. If hypertension cannot be adequately controlled, a risk-benefit decision on continued Kyprolis therapy is needed. (5.7) • Venous Thrombosis: Thromboprophylaxis is recommended. (5.8)
----------ADVERSE REACTIONS---------- Most commonly reported adverse reactions (incidence ≥ 30%) are fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. (6)	**----------ADVERSE REACTIONS----------** The most common adverse events occurring in at least 20% of patients treated with Kyprolis in monotherapy trials: anemia, fatigue, thrombocytopenia, nausea, pyrexia, decreased platelets, dyspnea, diarrhea, decreased lymphocyte, headache, decreased hemoglobin, cough, edema peripheral. (6) The most common adverse events occurring in at least 20% of patients treated with Kyprolis in the combination therapy trial: decreased lymphocytes, decreased absolute neutrophil count, decreased phosphorus, anemia, neutropenia, decreased total white blood cell count, decreased platelets, diarrhea, fatigue, thrombocytopenia, pyrexia, muscle spasm, cough, upper respiratory tract infection, decreased hemoglobin, hypokalemia. (6)

----------USE IN SPECIFIC POPULATIONS----------	**----------USE IN SPECIFIC POPULATIONS----------**
Patients on dialysis: Administer KYPROLIS after the dialysis procedure. (8.6)	In the Kyprolis clinical trials, the incidence of adverse events was greater in patients ≥ 75 years of age. (8.5)
DOSAGE AND ADMINISTRATION	**2 DOSAGE AND ADMINISTRATION**
Dosing Guidelines	2.1 Administration Precautions
KYPROLIS is administered intravenously over 2 to 10 minutes, 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 1*).	• Hydration - Adequate hydration is required prior to dosing in Cycle 1, especially in patients at high risk of tumor lysis syndrome or renal toxicity. The recommended hydration includes both oral fluids (30 mL per kg at least 48 hours before Cycle 1, Day 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid prior to each dose in Cycle 1). If needed, give an additional 250 mL to 500 mL of intravenous fluids following Kyprolis administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor patients for evidence of volume overload and adjust hydration to individual patient needs, especially in patients with or at risk for cardiac failure [see Warnings and Precautions (5)].
In Cycle 1, KYPROLIS is administered at a dose of 20 mg/m^2. If tolerated in Cycle 1, the dose should be escalated to 27 mg/m^2 beginning in Cycle 2 and continued at 27 mg/m^2 in subsequent cycles. Treatment may be continued until disease progression or until unacceptable toxicity occurs [*see Dosage and Administration (2.4)*].	• Premedications - Premedicate with dexamethasone 4 mg for monotherapy (or the recommended dexamethasone dose if on combination therapy [see Dosage and Administration (2.2)]) 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 Warnings and Precautions (5.5)]. Reinstate dexamethasone premedication if these symptoms occur during subsequent cycles.
The dose is calculated using the patient's actual body surface area at baseline. Patients with a body surface area greater than 2.2 m^2 should receive a dose based upon a body surface area of 2.2 m^2.	• Administration - Infuse over 10 minutes. Do not administer as a bolus. Flush the intravenous administration line with normal saline or 5% dextrose injection, USP immediately before and after Kyprolis administration. Do not mix Kyprolis with or administer as an infusion with other medicinal products.

Dose adjustments do not need to be made for weight changes of less than or equal to 20%. ….. **Hydration and Fluid Monitoring** Hydrate patients to reduce the risk of renal toxicity and of tumor	• Dose Calculation - Calculate the Kyprolis dose [see Dosage and Administration (2.2)]The dose is calculated using the patient's actual body surface area at baseline. Patients with a body surface area greater than 2.2 m2 should receive a dose based upon a body surface area of 2.2 m2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%. • Thromboprophylaxis - Thromboprophylaxis is recommended for patients being treated with the combination of Kyprolis, lenalidomide, and dexamethasone. The thromboprophylaxis regimen should be based on an assessment of the patient's underlying risks [see Warnings and Precautions (5.8)]. • Infection Prophylaxis - Consider antiviral prophylaxis in patients being treated with Kyprolis to decrease the risk of herpes zoster reactivation. 2.2 Recommended Dosing Kyprolis in Combination with Lenalidomide and Dexamethasone For the combination regimen, administer Kyprolis intravenously as a 10 minute infusion on two consecutive days, each week for three weeks followed by a 12 day rest period as shown in Table 1. Each 28-day period is considered one treatment cycle. The recommended starting dose of Kyprolis is 20 mg/m2 in Cycle 1 on Days 1 and 2. If tolerated, escalate to a target dose of 27 mg/m2 on Day 8 of Cycle 1. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis. Discontinue Kyprolis after Cycle 18. Lenalidomide 25 mg is taken orally on Days 1–21 and dexamethasone 40 mg by mouth or intravenously on Days 1, 8, 15, and 22 of the 28 day cycles. …. Continue treatment until disease progression or unacceptable toxicity occurs. Refer to the lenalidomide and dexamethasone Prescribing

lysis syndrome (TLS) with KYPROLIS treatment [*see Warnings and Precautions (5.5)*]. Maintain adequate fluid volume status throughout treatment and monitor blood chemistries closely. Prior to each dose in Cycle 1, give 250 mL to 500 mL of intravenous normal saline or other appropriate intravenous fluid. Give an additional 250 mL to 500 mL of intravenous fluids as needed following KYPROLIS administration. Continue intravenous hydration, as needed, in subsequent cycles. Also monitor patients during this period for fluid overload [see *Warnings and Precautions (5.1)*]. **Dexamethasone Premedication** Pre-medicate with dexamethasone 4 mg orally or intravenously prior to all doses of KYPROLIS during Cycle 1 and prior to all KYPROLIS doses during the first cycle of dose escalation to 27 mg/m^2 to reduce the incidence and severity of infusion reactions [*see Warnings and Precautions (5.4)*]. Reinstate dexamethasone premedication (4 mg orally or intravenously) if these symptoms develop or reappear during subsequent cycles. …. **Administration Precautions**	Information for other concomitant medications, such as the use of anticoagulant and antacid prophylaxis, that may be required with those agents. *Kyprolis Monotherapy* For monotherapy, administer Kyprolis intravenously as a 10 minute infusion on two consecutive days, each week for three weeks followed by a 12 day rest period as shown in Table 2. Each 28-day period is considered one treatment cycle. The recommended starting dose of Kyprolis is 20 mg/m^2 in Cycle 1 on Days 1 and 2. If tolerated, escalate to a target dose of 27 mg/m^2 on Day 8 of Cycle 1. From Cycle 13, omit the Day 8 and 9 doses of Kyprolis. Continue treatment until disease progression or unacceptable toxicity occurs.

The quantity of KYPROLIS contained in one single-use vial (60 mg carfilzomib) may exceed the required dose. Caution should be used in calculating the quantity delivered to prevent overdosing. Do not mix KYPROLIS with or administer as an infusion with other medicinal products. The intravenous administration line should be flushed with normal saline or 5% Dextrose Injection, USP immediately before and after KYPROLIS administration. KYPROLIS should not be administered as a bolus. KYPROLIS should be administered over 2 to 10 minutes.	

Reconstitution/Preparation Steps:

Remove vial from refrigerator just prior to use.

- Aseptically reconstitute each vial by slowly injecting **29 mL** Sterile Water for Injection, USP, directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming.

Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution of any cake or powder occurs. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow solution to rest in vial for about 2 to 5 minutes, until foaming subsides.

After reconstitution, KYPROLIS is ready for intravenous administration. The reconstituted product should be a clear, colorless solution. If any discoloration or particulate matter is observed, do not use the reconstituted product.

Reconstitution/Preparation Steps:

Remove vial from refrigerator just prior to use.

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 less than or equal to 20%.

a. Aseptically reconstitute each vial by slowly injecting **29 mL** Sterile Water for Injection, USP, through the stopper and directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming.

- Gently swirl and/or invert the vial slowly for about 1 minute, or until

	complete dissolution. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow the solution to settle in the vial until foaming subsides (approximately 5 minutes) and the solution is clear. Visually inspect for particulate matter and discoloration prior to administration. The reconstituted product should be a clear, colorless solution and should not be administered if any discoloration or particulate matter is observed. Discard any unused portion left in the vial. Optionally, Kyprolis can be administered in an intravenous bag
WARNINGS AND PRECAUTIONS **Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia** Death due to cardiac arrest has occurred within a day of KYPROLIS administration. New onset or worsening of pre-existing congestive heart failure with decreased left ventricular function or myocardial ischemia have occurred following administration of KYPROLIS. Cardiac failure events (e.g., cardiac failure congestive, pulmonary edema, ejection fraction decreased) were reported in 7% of patients. Monitor for cardiac complications	**WARNINGS AND PRECAUTIONS** **Cardiac Toxicities** New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of Kyprolis. In clinical studies with Kyprolis, these events typically occurred early in the course of Kyprolis therapy (< 5 cycles). Death due to cardiac arrest has occurred within a day of Kyprolis administration.

and manage promptly. Withhold KYPROLIS for Grade 3 or 4 cardiac events until recovery and consider whether to restart KYPROLIS based on a benefit/risk assessment [*see Dosage and Administration (2.4)*]. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.	Withhold Kyprolis for Grade 3 or 4 cardiac adverse events until recovery, and consider whether to restart Kyprolis at 1 dose level reduction based on a benefit/risk assessment [*see Dosage and Administration (2)*]. While adequate hydration is required prior to each dose in Cycle 1, all patients should also be monitored for evidence of volume overload, especially patients at risk for cardiac failure. Adjust total fluid intake as clinically appropriate in patients with baseline cardiac failure or who are at risk for cardiac failure [*see Dosage and Administration (2)*]. In patients ≥ 75 years of age, the risk of cardiac failure is increased. Patients with New York Heart Association Class III and IV heart failure, recent myocardial infarction, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications [*see Use in Specific Populations (8)*]. **Acute Renal Failure** Cases of acute renal failure have occurred in patients receiving Kyprolis. Renal insufficiency adverse events (renal impairment, acute renal failure, renal failure) have occurred with an incidence of

	approximately 8% in a randomized controlled trial. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received Kyprolis monotherapy. This risk was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation). Monitor renal function with regular measurement of the serum creatinine and/or estimated creatinine clearance. Reduce or withhold dose as appropriate [*see Dosage and Administration (2)*]. **Tumor Lysis Syndrome** Cases of tumor lysis syndrome (TLS), including fatal outcomes, have been reported in patients who received Kyprolis. Patients with multiple myeloma and a high tumor 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 [*see Dosage and Administration (2)*]. Consider uric acid lowering drugs in patients at risk for TLS. Monitor for evidence of TLS during treatment and manage promptly including interruption of Kyprolis until TLS is resolved [*see Dosage and Administration (2)*]. **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 less than 1% of patients receiving Kyprolis. Some events have been fatal. In the event of drug-induced pulmonary toxicity, discontinue Kyprolis [*see Dosage and Administration (2)*].

Pulmonary Complications Dyspnea was reported in 35% of patients enrolled in clinical trials. Grade 3 dyspnea occurred in 5%; no Grade 4 events, and 1 death (Grade 5) was reported. Monitor and manage dyspnea immediately; interrupt KYPROLIS until symptoms have resolved or returned to baseline [*see Dosage and Administration (2.4) and Adverse Reactions (6.1)*].	**Dyspnea** Dyspnea was reported in 28% of patients treated with Kyprolis and was Grade 3 or greater in 4% of patients. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes. Stop Kyprolis for Grade 3 or 4 dyspnea until resolved or returned to baseline. Consider whether to restart Kyprolis based on a benefit/risk assessment [*see Dosage and Administration (2.3), Warnings and Precautions - Cardiac Toxicities (5.1), Pulmonary Toxicity (5.4), and Adverse Reactions (6)*]. **Hypertension** Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with Kyprolis. Some of these events have been fatal. Monitor blood pressure regularly in all patients. If hypertension cannot be adequately controlled, withhold Kyprolis and evaluate. Consider whether to restart Kyprolis based on a benefit/risk assessment [*see Dosage and Administration (2)*]. **1.8 Venous Thrombosis** Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with Kyprolis. In the

	combination study, the incidence of venous thromboembolic events in the first 12 cycles was 13% in the Kyprolis combination arm versus 6% in the control arm. With Kyprolis monotherapy, the incidence of venous thromboembolic events was 2%. Thromboprophylaxis is recommended and should be based on an assessment of the patient's underlying risks, treatment regimen, and clinical status.
Infusion Reactions Infusion reactions were characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina.	**5.9 Infusion Reactions** Infusion reactions, including life-threatening reactions, have occurred in patients receiving Kyprolis. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina.
6 ADVERSE REACTIONS The following adverse reactions are discussed in greater detail in other sections of the labeling: • Cardiac Arrest, Congestive Heart Failure, Myocardial Ischemia [see *Warnings and Precautions (5.1)*] • Pulmonary Hypertension [see *Warnings and Precautions (5.2)*] • Pulmonary Complications [see *Warnings and Precautions*	**6 ADVERSE REACTIONS** • Cardiac Toxicities [see *Warnings and Precautions (5.1)*] • Acute Renal Failure [*see Warnings and Precautions (5.2)*] • Tumor Lysis Syndrome [*see Warnings and Precautions (5.3)*] • Pulmonary Toxicity [*see Warnings and Precautions (5.4)*] • Pulmonary Hypertension [*see Warnings and Precautions (5.5)*]

(5.3)]

- Infusion Reactions [see *Warnings and Precautions (5.4)*]
- Tumor Lysis Syndrome [see *Warnings and Precautions (5.5)*]
- Thrombocytopenia [see *Warnings and Precautions (5.6)*]
- Hepatic Toxicity and Hepatic Failure [see *Warnings and Precautions (5.7)*]

The most common adverse reactions (incidence of 30% or greater) to KYPROLIS observed in clinical trials of patients with multiple myeloma were fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia.

A total of 526 patients with relapsed and/or refractory multiple myeloma received KYPROLIS as monotherapy or with pre-dose dexamethasone. Patients received a median of four treatment cycles with a median cumulative KYPROLIS dose of 993.4 mg.

Deaths due to all causes within 30 days of the last dose of KYPROLIS occurred in 37/526 (7%) of patients. Deaths not attributed to disease progression were cardiac in 5 patients (acute coronary syndrome, cardiac arrest, cardiac disorder), end-organ failure in 4 patients (multi-organ failure, hepatic failure, renal

- Dyspnea [*see Warnings and Precautions (5.6)*]
- Hypertension [*see Warnings and Precautions (5.7)]*
- Venous Thrombosis [*see Warnings and Precautions (5.8)*]
- Infusion Reactions [*see Warnings and Precautions (5.9)*]
- Thrombocytopenia [*see Warnings and Precautions (5.10)*]
- Hepatic Toxicity and Hepatic Failure [see *Warnings and Precautions (5.11)*]
- Thrombotic Thrombocytopenic Purpura /Hemolytic Uremic Syndrome [*see Warnings and Precautions (5.12)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) [*see Warnings and Precautions (5.13)*]

Safety Experience with Kyprolis in Combination with Lenalidomide and Dexamethasone in Patients with Multiple Myeloma

The safety of Kyprolis in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. Details of the study treatment are described in Section 14.1. The median number of cycles initiated was 22 cycles for the KRd arm and 14 cycles for the Rd arm.

Deaths due to adverse events within 30 days of the last dose of any therapy in the KRd arm occurred in 27/392 (7%) patients compared with 27/389 (7%) patients who died due to adverse events within 30 days of the

failure), infection in 4 patients (sepsis, pneumonia, respiratory tract bacterial infection), dyspnea and intracranial hemorrhage in 1 patient each, and 1 patient found dead of unknown causes. Serious adverse reactions were reported in 45% patients. The most common serious adverse reactions were pneumonia (10%), acute renal failure (4%), pyrexia (3%), and congestive heart failure (3%). Adverse reactions leading to discontinuation of KYPROLIS occurred in 15% of patients and included congestive heart failure (2%), cardiac arrest, dyspnea, increased blood creatinine, and acute renal failure (1% each). Adverse reactions occurring at a rate of 10% or greater are presented in *Table 4.* **Description of Selected Adverse Drug Reactions** *Renal Events* The most common renal adverse reactions were increase in blood creatinine (24%) and renal failure (9%), which were mostly Grade 1 or Grade 2 in severity. Grade 3 renal adverse reactions occurred in 6% of patients and Grade 4 events occurred in 1%. Discontinuations due to increased blood creatinine and acute renal	last dose of any Rd therapy. The most common cause of deaths occurring in patients (%) in the two arms (KRd versus Rd) included cardiac 10 (3%) versus 7 (2%), infection 9 (2%) versus 10 (3%), renal 0 (0%) versus 1 (< 1%), and other adverse events 9 (2%) versus 10 (3%). Serious adverse events were reported in 60% of the patients in the KRd arm and 54% of the patients in the Rd arm. The most common serious adverse events reported in the KRd arm as compared with the Rd arm were pneumonia (14% versus 11%), respiratory tract infection (4% versus 1.5%), pyrexia (4% versus 2%), and pulmonary embolism (3% versus 2%). Discontinuation due to any adverse event occurred in 26% in the KRd arm versus 25% in the Rd arm. Adverse events leading to discontinuation of Kyprolis occurred in 12% of patients and the most common events included pneumonia (1%), myocardial infarction (0.8%), and upper respiratory tract infection (0.8%). ***Common Adverse Events (≥ 10%)*** The adverse events in the first 12 cycles of therapy that occurred at a rate of 10% or greater in the KRd arm are presented in Table 5. There were 274 (70%) patients in the KRd arm who received treatment beyond Cycle 12. There were no new clinically relevant AEs that emerged in the later treatment cycles.

failure were 1% each. In one patient, death occurred with concurrent sepsis and worsening renal function [*see Dosage and Administration (2.4)*]. *Peripheral Neuropathy* Peripheral neuropathy (including all events of peripheral sensory neuropathy and peripheral motor neuropathy) occurred in 14% of patients enrolled in clinical trials. Grade 3 peripheral neuropathy occurred in 1% of patients. Serious peripheral neuropathy events occurred in < 1% of patients, which resulted in dose reduction in < 1% and treatment discontinuation in < 1%. Withhold or discontinue treatment as recommended [*see Dosage and Administration (2.4)*]. *Herpes Virus Infection* Herpes zoster reactivation was reported in 2% of patients. Consider antiviral prophylaxis for patients who have a history of herpes zoster infection.	***Adverse Reactions Occurring at a Frequency of < 10%*** **Blood and lymphatic system disorders**: febrile neutropenia, lymphopenia **Cardiac disorders**: cardiac arrest, cardiac failure, cardiac failure congestive, myocardial infarction, myocardial ischemia **Eye disorders:** cataract, vision blurred **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, toothache **General disorders and administration site conditions:** chills**,** infusion site reaction, multi-organ failure, pain **Infections and infestations:** influenza, sepsis, urinary tract infection, viral infection **Metabolism and nutrition disorders:** dehydration, hyperkalemia, hyperuricemia, hypoalbuminemia, hyponatremia, tumor lysis syndrome **Musculoskeletal and connective tissue disorders**: muscular weakness, myalgia **Nervous system disorders**: hypoesthesia, paresthesia, deafness **Psychiatric disorders**: anxiety, delirium **Renal and urinary disorders**: renal failure, renal failure acute, renal impairment **Respiratory, thoracic and mediastinal disorders**: dysphonia, epistaxis,

	oropharyngeal pain, pulmonary embolism, pulmonary edema **Skin and subcutaneous tissue disorders**: erythema, hyperhidrosis, pruritus **Vascular disorders**: deep vein thrombosis, hypotension Grade 3 and higher adverse reactions that occurred during Cycles 1-12 with a substantial difference (≥ 2%) between the two arms were neutropenia, thrombocytopenia, hypokalemia, and hypophosphatemia. ***Laboratory Abnormalities*** Table 6 describes Grade 3–4 laboratory abnormalities reported at a rate of ≥10% in the KRd arm for patients who received combination therapy. **Safety Experience with Kyprolis in Patients with Multiple Myeloma who Received Monotherapy** The safety of Kyprolis was evaluated in clinical trials in which 598 patients with relapsed and/or refractory myeloma received Kyprolis monotherapy starting with the 20 mg/m^2 dose in Cycle 1 Day 1 and escalating to 27 mg/m^2 on Cycle 1 Day 8 or Cycle 2 Day 1. The median age of these patients was 64 years (range 32–87). The patients received a median of 5 (range 1–20) prior regimens. Approximately 57% of the patients were male. The median number of cycles initiated was 4

	(range 1–35). Serious adverse events were reported, regardless of causality, in 50% of patients in the pooled Kyprolis monotherapy studies (n = 598). The most common serious adverse events were: pneumonia (8%), acute renal failure (5%), disease progression (4%), pyrexia (3%), hypercalcemia (3%), congestive heart failure (3%), multiple myeloma (3%), anemia (2%), and dyspnea (2%). In patients treated with Kyprolis, the incidence of serious adverse events was higher in those ≥ 65 years old and in those ≥ 75 years old [*see Geriatric Use (8.5)*]. Deaths due to adverse events within 30 days of the last dose of Kyprolis occurred in 30/598 (5%) patients receiving Kyprolis monotherapy. These adverse events were related to cardiac disorders in 10 (2%) patients, infections in 8 (1%) patients, renal disorders in 4 (< 1%) patients, and other adverse events in 8 (1%) patients. In a randomized trial comparing Kyprolis as a single agent versus corticosteroids with optional oral cyclophosphamide for patients with relapsed and refractory multiple myeloma, mortality was higher in the patients treated with Kyprolis in comparison to the control arm in the subgroup of 48 patients ≥ 75 years of age. The most common cause of discontinuation due to an adverse event was

	acute renal failure (2%). The common adverse events occurring at a rate of 10% or greater with Kyprolis monotherapy are presented in Table 7. ***Adverse Reactions Occurring at a Frequency of < 10%*** **Blood and lymphatic system disorders**: febrile neutropenia **Cardiac disorders**: cardiac arrest, cardiac failure congestive, myocardial infarction, myocardial ischemia **Eye disorders:** cataract, blurred vision **Gastrointestinal disorders:** abdominal pain, abdominal pain upper, dyspepsia, toothache **General disorders and administration site conditions**: infusion site reaction, multi-organ failure, pain **Hepatobiliary disorders**: hepatic failure **Infections and infestations:** bronchitis, influenza, nasopharyngitis, respiratory tract infection, sepsis, urinary tract infection **Metabolism and nutrition disorders:** hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, tumor lysis syndrome **Musculoskeletal and connective tissue disorders**: musculoskeletal chest pain, myalgia **Nervous system disorders**: hypoesthesia, paresthesia **Psychiatric disorders**: anxiety **Renal and urinary disorders**: renal impairment **Respiratory, thoracic and mediastinal disorders**: dysphonia,

	oropharyngeal pain, pulmonary edema **Skin and subcutaneous tissue disorders**: erythema, hyperhidrosis, pruritus, rash **Vascular disorders**: embolic and thrombotic events, venous (including deep vein thrombosis and pulmonary embolism), hypotension Grade 3 and higher adverse reactions occurring at an incidence of >1% include febrile neutropenia, cardiac arrest, cardiac failure congestive, pain, sepsis, urinary tract infection, hyperglycemia, hyperkalemia, hyperuricemia, hypoalbuminemia, hypocalcemia**,** hyponatremia, hypophosphatemia, renal failure, renal failure acute, renal impairment, pulmonary edema, and hypotension. ***Laboratory Abnormalities*** Table 8 describes Grade 3–4 laboratory abnormalities reported at a rate of > 10% for patients who received Kyprolis monotherapy.
	Risk Summary

Females of reproductive potential should be advised to avoid becoming pregnant while being treated with KYPROLIS. Based on its mechanism of action and findings in animals, KYPROLIS can cause fetal harm when administered to a pregnant woman. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. If KYPROLIS is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.	Kyprolis, a proteasome inhibitor, may cause fetal harm based on findings from animal studies [*see Data*] and the drug's mechanism of action [*see Clinical Pharmacology (12.1)*]. There are no adequate and well-controlled studies in pregnant women using Kyprolis. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. Consider the benefits and risks of Kyprolis and possible risks to the fetus when prescribing Kyprolis to a pregnant woman. **1.2 Lactation** **Risk Summary** There is no information regarding the presence of Kyprolis in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Kyprolis and any potential adverse effects on the breastfed infant from Kyprolis or from the underlying maternal condition. **Females and Males of Reproductive Potential**

Nursing Mothers It is not known whether KYPROLIS is excreted in human milk. Since many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from KYPROLIS, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Geriatric Use** In studies of KYPROLIS there were no clinically significant differences observed in safety and efficacy between patients less than 65 years of age and patients 65 years of age and older.	**Contraception** Kyprolis can cause fetal harm when administered to pregnant women [*see Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception measures to prevent pregnancy during treatment with Kyprolis and for at least 2 weeks following completion of therapy. **Geriatric Use** Of 598 patients treated with Kyprolis monotherapy, 293 patients (49%) were ≥ 65 years of age and 96 patients (16%) were ≥ 75 years of age. The median age was 64 years. The incidence of serious adverse events was 44% in patients ≤ 65 years of age, 55% in patients 65 to 74 years of age, and 56% in patients ≥ 75 years of age [*see Warnings and Precautions - Cardiac Toxicities (5.1)*]. In Study 2 (n = 266), no overall differences in effectiveness were observed between these and younger patients. Of 392 patients treated with Kyprolis in combination with lenalidomide and dexamethasone, 185 patients (47%) were ≥ 65 years of age and 43 patients (11%) were ≥ 75 years of age. The median age was 64 years. No overall differences in effectiveness were observed between these and

	younger patients. The incidence of serious adverse events was 50% in patients ≤ 65 years of age, 70% in patients 65 to 74 years of age, and 74% in patients ≥ 75 years of age [*see Warnings and Precautions - Cardiac Toxicities (5.1)*].
Renal Impairment The pharmacokinetics and safety of KYPROLIS were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic dialysis. On average, patients were treated for 5.5 cycles using KYPROLIS doses of 15 mg/m^2 on Cycle 1, 20 mg/m^2 on Cycle 2, and 27 mg/m^2 on Cycles 3 and beyond. The pharmacokinetics and safety of KYPROLIS were not influenced by the degree of baseline renal impairment, including the patients on dialysis.	**Renal Impairment** No starting dose adjustment is required in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. The pharmacokinetics and safety of Kyprolis were evaluated in a Phase 2 trial in patients with normal renal function and those with mild, moderate, and severe renal impairment and patients on chronic dialysis. In this study, the pharmacokinetics of Kyprolis was not influenced by the degree of baseline renal impairment, including the patients on dialysis.
Cardiac Impairment Patients with New York Heart Association Class III and IV heart failure were not eligible for the clinical trials. Safety in this population has not been evaluated.	**Cardiac Impairment** Patients with New York Heart Association Class III and IV heart failure or recent myocardial infarction (within 3 to 6 months in different protocols) were not eligible for the clinical trials. Safety in this population has not been evaluated.
OVERDOSAGE	**10 OVERDOSAGE** Acute onset of chills, hypotension, renal insufficiency, thrombocytopenia,

There is no known specific antidote for KYPROLIS overdosage. In the event of an overdosage, monitor the patient and provide appropriate supportive care.	and lymphopenia has been reported following a dose of 200 mg of Kyprolis administered in error. There is no known specific antidote for Kyprolis overdosage. In the event of overdose, the patient should be monitored, specifically for the side effects and/or adverse reactions listed in *Adverse Reactions (6)*.