KyrpolisÔ (carfilzomib)Brief Prescribing Information Please refer to the Summary of Product Characteristics before prescribing KyprolisÔ.Pharmaceutical Form: Powder for solution for injection. White to off-white lyophilized powder, available as a single-use vial. Each vial contains 60 mg of carfilzomib.The reconstituted solution contains 2 mg/mL carfilzomib. Each mL of reconstituted Kyprolis contains 0.3 mmol sodium, which is 7 mg of sodium. Therapeutic indications: Kyprolis is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified. Posology and method of administration: Posology: 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. Please refer to SmPC section 4.2 for information related to Hydration and fluid monitoring, Dexamethasone premedication and the Dose modifications based on toxicities. Special populations: Paediatric use:The safety and effectiveness of Kyprolis in paediatric patients have not been established. Geriatric use: No dose adjustment is necessary in patients over 65 years of age. Method of administration: Kyprolis should be administered over 2 to 10 minutes. 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. 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. Contraindications: Hypersensitivity to the active substance or to any of the excipients. Special warnings and precautions for use: 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 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. 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. Pulmonary hypertension: Pulmonary arterial hypertension (PAH) was reported in 2% of patients treated with Kyprolis and was Grade 3 or greater in less than 1% of patients. Evaluate with cardiac imaging and/or other tests as indicated. Withhold Kyprolis for pulmonary hypertension until resolved or returned to baseline and consider whether to restart Kyprolis based on a benefit/risk assessment. 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. 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. These reactions can occur immediately following or up to 24 hours after administration of Kyprolis. Administer dexamethasone prior to Kyprolis to reduce the incidence and severity of reactions. Inform patients of the risk and symptoms and to contact physician if symptoms of an infusion reaction occur. Tumor lysis syndrome Tumor lysis syndrome (TLS) occurred following Kyprolis administration in < 1% of patients. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS. Prior to receiving Kyprolis, ensure that patients are well hydrated (see section 4.2). Monitor for evidence of TLS during treatment, and manage promptly. Interrupt Kyprolis until TLS is resolved. Thrombocytopenia Kyprolis causes thrombocytopenia with platelet nadirs occurring around Day 8 of each 28-day cycle and recovery to baseline by the start of the next 28-day cycle. In patients with multiple myeloma, 36% of patients experienced thrombocytopenia, including Grade 4 in 10%. Thrombocytopenia following Kyprolis administration resulted in a dose reduction in 1% of patients and discontinuation of treatment with Kyprolis in < 1% of patients. Monitor platelet counts frequently during treatment with Kyprolis. Reduce or interrupt dose as clinically indicated. Hepatic toxicity and hepatic failure: Cases of hepatic failure, including fatal cases, have been reported (< 1%). Kyprolis can cause elevations of serum transaminases and bilirubin. Withhold Kyprolis in patients experiencing Grade 3 or greater elevations of transaminases, bilirubin, or other liver abnormalities until resolved or returned to baseline. After resolution, consider if restarting Kyprolis is appropriate. Monitor liver enzymes frequently. Thrombocytopenic thrombotic purpura /hemolytic uremic syndrome Cases of thrombocytopenic thrombotic purpura/hemolytic uremic syndrome (TTP/HUS) including fatal outcome have been reported in patients who received Kyprolis. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop Kyprolis and manage per standard of care including plasma exchange as clinically appropriate. 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 (PRES) PRES, formerly termed reversible posterior leukoencephalopathy syndrome (RPLS), is a rare, 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 (MRI). If diagnosed early and treated, the symptoms of PRES may be reversible. 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. Embryo-fetal toxicity Kyprolis can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. There are no adequate and well-controlled studies in pregnant women using Kyprolis. Carfilzomib caused embryo-fetal toxicity in pregnant rabbits at doses that were lower than in patients receiving the recommended dose. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis. If this drug 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.Interaction with other medicinal products and other forms of interaction: Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs. Fertility, pregnancy and lactation: Pregnancy: 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. There are no or limited amount of data from use of carfilzomib in pregnant women. Studies in animals have shown reproductive toxicity. Carfilzomib is not recommended during pregnancy and in women of childbearing potential not using contraception. Lactation It is not known whether carfilzomib is excreted in human breast milk. The excretion of carfilzomib in milk has not been studied in animals. Patients should be advised to not take Kyprolis while breastfeeding. 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 .Fertility: Fertility studies with carfilzomib have not been conducted. Effects on ability to drive and use machines: No studies on the effects on the ability to drive or use machines have been performed. Kyprolis may cause fatigue, dizziness, fainting, and/or drop in blood pressure. Patients should be advised not to drive or operate machinery if they experience any of these symptoms. Undesirable effects: 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. Clinical trials safety experience: 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).Overdose: There is no known specific antidote for Kyprolis overdosage. In the event of an overdosage, monitor the patient and provide appropriate supportive care. Special precautions for storage: Store in a refrigerator (2 °C to 8 °C). Retain in original package to protect from light.Special precautions for disposal and other handling: Kyprolis vials contain no antimicrobial preservatives and are intended only for single use.Any unused product or waste material should be disposed of in accordance with local requirements.Legal Category: POM. Administrative information: Date of PI: January 2015. Marketing Authorisation Holder: ONYX Pharmaceuticals Inc. 249 E. Grand Avenue, South San Francisco, CA 94080, USA. Marketing Authorisation Number: 1-5063-17 Local representative Salehiya Trading Est. Address: P.O.Box 991, Riyadh 11421, Kingdom of Saudi Arabia. Tel: 00966 1 464 6955 Ext. 127.

Any suspected adverse reactions should be reported immediately to Amgen in accordance with local spontaneous reporting requirements. Amgen Global Fax: +44 2071361046 or send to AGS mailbox: svc-ags-in-uk@amgen.com and Safety-MEA@amgen.com and/or National Pharmacovigilance Centre (NPC), Email: npc.drug@sfda.gov.sa, Fax: +966-11-2057662

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Kyprolis Nurse Checklist

Important for the Safe use of Carfilzomib

Kyprolis® (carfilzomib) Powder for solution for infusion

AMGEN®

Kyprolis® (carfilzomib) Powder for solution for infusion

Patient Name: ..... Date: .....

This checklist is intended for nurses to use prior to dosing each patient and at any follow-up visits or calls with the patient to identify some of the signs and symptoms associated with adverse reactions related to treatment with Kyprolis. Early identification of adverse reactions and interventions are an important part of the safe use of Kyprolis.

Please note: this checklist is not meant to be all-inclusive.

If the patient responds "Yes" to any of these questions, consult the patient's Hematologist before administering Kyprolis

QUESTIONS	RESPONSE		NOTES
Do you have swelling of the feet or legs?	Yes	No	
Have you felt drowsy or extremely tired?	Yes	No	
Have you felt dizzy or fainted?	Yes	No	
Have you felt Shortness of breath?	Yes	No	
Do you bleed or bruise more easily than normal?	Yes	No	
Do you have Fever?	Yes	No	
Have you had severe weakness?	Yes	No	
Have you had confusion or seizures?	Yes	No	
Have you had a loss of sight?	Yes	No	
Have you started taking any new medications (prescription, nonprescription, or herbal)? If yes, which and how often?	Yes	No	
Do you have chills or shivering?	Yes	No	
Are you having chest pain?	Yes	No	
Did you have recent myocardial infarction (within the prior 4 months)?	Yes	No	
Do you have a High Heart Rate?	Yes	No	
Do you have Pre-existing Hypertension?	Yes	No	
Do you have Pre-existing Cardiac Failure (NYHA III or IV)	Yes	No	
Are you experiencing Sudden weight change?	Yes	No	
Are you having cough?	Yes	No	
Are you severely nauseous and/or vomiting?	Yes	No	
Have you seen blood or mucus in your stools?	Yes	No	
Are your currently Pregnant or breastfeeding)?	Yes	No	

Please see additional Important Safety Information on reverse side.

Kyprolis® (carfilzomib) Powder for solution for infusion

What are the possible side effects of Kyprolis® (carfilzomib) for Injection?

Serious side effects

Heart problems: KYPROLIS can cause heart problems or worsen pre-existing heart conditions. Death due to cardiac arrest has occurred within a day of KYPROLIS administration. You will be closely monitored during treatment

Kidney problems: There have been reports of sudden kidney failure in patients receiving KYPROLIS. Your kidney function will be closely monitored during treatment

Tumor lysis syndrome (TLS): Cases of TLS have been reported in patients receiving KYPROLIS, including fatalities. You will be closely monitored during treatment for any signs of TLS. Interrupt KYPROLIS until TLS is managed

Lung damage: Cases of lung damage have been reported in patients receiving KYPROLIS, including fatal cases

Pulmonary hypertension (high blood pressure in the lungs): There have been reports of pulmonary hypertension in patients receiving KYPROLIS

Lung complications: Shortness of breath was reported in patients receiving KYPROLIS. Your lung function will be closely monitored during treatment

High blood pressure: Cases of high blood pressure, including fatal cases, have been reported in patients receiving KYPROLIS. Your blood pressure will be closely monitored during treatment

Blood clots: There have been reports of blood clots in patients receiving KYPROLIS. If you are at high risk for blood clots, your doctor can recommend ways to lower the risk

Infusion reactions: Symptoms of infusion reactions included fever, chills, joint pain, muscle pain, facial flushing and/or swelling, vomiting, weakness, shortness of breath, low blood pressure, fainting, chest tightness, and chest pain. These symptoms can occur immediately following infusion or up to 24 hours after administration of KYPROLIS

Very low platelet count: Low platelet levels can cause unusual bruising and bleeding. You will have regular blood tests to check your platelet count during treatment

Liver problems: Cases of liver failure, including fatal cases, have been reported in patients receiving KYPROLIS. Your liver function will be closely monitored during treatment

Blood problems: Cases of a blood disease called thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), including fatal cases,have been reported in patients who received KYPROLIS. Your doctor can monitor your signs and symptoms

Brain problems: A nerve disease called Posterior Reversible Encephalopathy Syndrome (PRES), formerly called Reversible Posterior Leukoencephalopathy Syndrome (RPLS), has been reported in patients receiving KYPROLIS. It can cause seizure, headache, lack of energy, confusion, blindness, altered consciousness, and other visual and nerve disturbances, along with high blood pressure. Your doctor can monitor your signs and symptoms

Fetal harm: KYPROLIS can cause harm to a fetus (unborn baby) when administered to a pregnant woman. Women should avoid becoming pregnant during treatment with KYPROLIS

Reference

KYPROLIS® Summary of Product Characteristics Jan 2015.