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Summary of the risk management plan (RMP) for Kyprolis (carfilzomib)

This is a summary of the risk management plan (RMP) for Kyprolis, which details the measures to be taken in order to ensure that Kyprolis is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Kyprolis, which can be found on Kyprolis' EPAR page.

Overview of disease epidemiology

Kyprolis is used to treat adults with multiple myeloma, a cancer of a type of blood cells called plasma cells.

Multiple myeloma occurs in approximately 3.3 people in 10,000 in the European Union. The exact causes of multiple myeloma are not known. However, it is more common in men than in women and in black people than among those of white or Asian descent. Most people diagnosed with multiple myeloma are over 65 years of age. The choice of treatment depends on several factors, including how advanced the disease is. With current treatments, about half of all patients with the disease survive for more than 45 to 60 months following diagnosis.

Summary of treatment benefits

Kyprolis has been investigated in one main study involving 792 patients with multiple myeloma whose disease had got worse after previous treatment. In the study, Kyprolis taken in combination with lenalidomide and dexamethasone was compared with lenalidomide and dexamethasone. The study showed that Kyprolis is effective at prolonging the average length of time before the patient's disease got worse again (progression-free survival): patients taking Kyprolis lived for an average of 26.3 months without their disease getting worse, compared with 17.6 months in the patients receiving only lenalidomide and dexamethasone.

Unknowns relating to treatment benefits

Kyprolis has not been studied in patients with liver problems, severe heart problems, or in pregnant or breastfeeding women.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Heart failure or heart attack	Patients with multiple myeloma are more likely to have heart problems.	Patients with signs and symptoms of heart failure, patients who recently had

Risk	What is known	Preventability
(cardiac toxicity)	Patients treated with Kyprolis may develop new or worsening of existing heart problems. This may include heart failure and heart attack.	a heart attack or other heart problems should have a comprehensive medical examination before starting treatment with Kyprolis. Subsequently they should be treated with caution and should be closely monitored by their doctor during treatment with Kyprolis. The doctor should also monitor blood pressure and fluid levels, as too much fluid in the body can make existing heart problems worse.
Lung problems (pulmonary toxicities)	Patients treated with Kyprolis may experience inflammation of the lungs, reduced lung capacity, or develop fibrosis ('scar tissue') in the lungs.	Patients should tell their doctor immediately if they experience difficulty breathing, rapid breathing, feeling like they can't breathe in enough air, wheezing, shortness of breath at rest or with activity (dyspnoea) or a cough. The doctor should evaluate the patient and treatment with Kyprolis should be interrupted until symptoms resolve.
High blood pressure in the lungs (pulmonary hypertension)	Some patients treated with Kyprolis in clinical studies developed a lung disorder in which the blood pressure in the arteries that carry blood from the heart to the lungs rises far above normal levels (pulmonary hypertension).	Patients should tell their doctor immediately if they experience shortness of breath, extreme tiredness, dizziness or feeling faint, chest pain, a racing heartbeat or swollen legs, ankles or feet. If pulmonary hypertension is diagnosed by the doctor, Kyprolis treatment should be interrupted until the symptoms resolve.
Breathlessness (dyspnoea)	More than 1 in 10 patients treated with Kyprolis may experience breathlessness, or difficulty breathing.	Patients should tell their doctor if they feel breathless, or have difficulty breathing. Doctors may need to stop treatment in severe cases, until the symptoms improve.
High blood pressure including crises of sudden high blood pressure (hypertensive crises)	Patients treated with Kyprolis may develop high blood pressure including sudden, dangerously high blood pressure (hypertensive crisis).	Patients should tell their doctor immediately if they experience severe chest pain, severe headache, confusion and blurred vision, nausea and vomiting, and severe anxiety. All patients should have their blood pressure routinely monitored and treated as appropriate. The dose of Kyprolis should be reduced in case of

Risk	What is known	Preventability
		uncontrolled high blood pressure and treatment should be stopped if a hypertensive crisis is diagnosed by the doctor until the symptoms resolve.
Kidney problems (kidney impairment)	Patients treated with Kyprolis may develop problems with their kidneys including kidney failure during treatment.	Doctors should take regular blood tests to monitor kidney function during treatment. Doctors may reduce the dose or stop treatment as appropriate.
Complications from the destruction of cancer cells (tumor lysis syndrome)	Patients treated with Kyprolis may get complications from the destruction of their cancer cells leading to increased blood levels of uric acid and electrolytes such as potassium and phosphorus, and decreased blood levels of calcium.	Patients should undergo tests for signs of tumour lysis syndrome, including regular measurements of blood electrolyte levels, especially at the start of treatment with Kyprolis, and should be given fluids to help prevent it. Any change should be managed promptly. Medicines to lower uric acid levels in the blood should be considered in patients at high risk for tumour lysis syndrome. In case of tumour lysis syndrome Kyprolis should be interrupted until resolution.
Infusion reactions	Reactions related to infusion of Kyprolis may include fever, chills, bone and/or muscle pains, flushing, face swelling, sickness, weakness, difficulty breathing, low blood pressure and chest pains.	A steroid medicine (dexamethasone) is given before Kyprolis infusion is started, to help reduce infusion reactions and severity of the reactions.
Decreased levels of platelets (blood cells that help the blood to clot)	In patients treated with Kyprolis levels of platelets may drop (thrombocytopenia). This can make the patient bruise or bleed more easily than normal.	Doctors should take regular blood tests to monitor blood counts during treatment. In case of decreased levels of platelets (thrombocytopenia), Kyprolis may have to be stopped or the dose reduced.
Liver problems (hepatic impairment)	Patients treated with Kyprolis may develop problems with their liver during treatment. Cases of liver failure have been reported.	Doctors should take regular blood tests to monitor liver function during treatment. They may reduce the dose or stop treatment as appropriate.
A blood disorder known as thrombotic microangiopathy	There have been reports of a blood disorder known as thrombotic microangiopathy where clots form in the small blood vessels of the body in patients treated with Kyprolis, which can cause bleeding, bruising, weakness, confusion, sickness and	Patients should tell their doctor immediately if they experience bleeding, if they bruise more easily than normal, if they feel weak, confused, or have sickness and diarrhoea. Kyprolis treatment should be discontinued if thrombotic microangiopathy is diagnosed by the

Risk	What is known	Preventability
	diarrhoea.	doctor.
A neurological condition known as posterior reversible encephalopathy syndrome (PRES)	There have been reports of a neurological condition known as PRES in patients treated with Kyprolis, which can cause headache, confusion, seizures (fits) and visual loss.	Patients should tell their doctor immediately if they experience headaches, confusion, seizures (fits) or visual loss. Kyprolis treatment should be discontinued if PRES is suspected by the doctor.
Low white blood cell count with fever (febrile neutropenia)	Patients treated with Kyprolis may experience low levels of white blood cells (neutropenia), which may be associated with fever (febrile neutropenia) and can decrease the patient's ability to fight against infection.	Doctors should take regular blood tests to monitor blood counts during treatment. In case of febrile neutropenia treatment with Kyprolis should be interrupted until resolution.

Important potential risks

Risk	What is known
Herpes zoster infections (shingles) resulting from reactivation of the varicella-zoster virus	Infection with varicella-zoster virus causes chickenpox. Once the illness resolves, the virus remains dormant and can reactivate later in a person's life and cause shingles. Another medicine that is similar to Kyprolis (called bortezomib) has been shown to affect the immune system in a way that can allow the varicella-zoster virus to reactivate. This only happens in people who have previously had chickenpox. It is not yet known whether Kyprolis can also increase the risk of shingles in the same way that bortezomib does.
Reproductive and developmental toxicity	The effects of carfilzomib (the active substance in Kyprolis) in pregnant women are unknown. In animal studies, carfilzomib had harmful effects on the embryos/fetuses of pregnant rabbits. Female patients should not take Kyprolis if they are pregnant, think they may be pregnant or are planning to have a baby. While taking Kyprolis, and for 30 days after stopping treatment, they should use a suitable method of contraception to ensure they do not become pregnant. Kyprolis may decrease the efficacy of oral contraceptives. While taking Kyprolis and for 90 days after stopping treatment, male patients should use a suitable method of contraception, such as a condom, to ensure their female partner does not become pregnant.

Missing information

Risk	What is known
Use in patients with	The benefits and risks of using Kyprolis in patients with liver disease have not been established. Kyprolis treatment can cause liver problems including liver

Risk	What is known
liver disease	failure, so a doctor will take regular blood tests to monitor liver function during treatment.
Use in patients with severe heart failure, including recent heart attacks	The benefits and risks of using Kyprolis in patients with severe heart failure have not been established. Kyprolis treatment can cause heart failure, so patients with risk factors for the development of heart problems, or existing heart problems will be closely monitored by their doctor during treatment with Kyprolis.
Use in pregnant or breastfeeding women	The effects of carfilzomib (the active substance in Kyprolis) in pregnant or breastfeeding women are unknown. In animal studies, carfilzomib had harmful effects on the embryos/fetuses of pregnant rabbits. Kyprolis should not be used during pregnancy. It is unknown whether carfilzomib or its metabolites pass into human milk. Kyprolis should therefore not be used while breastfeeding and for at least 2 days after stopping treatment with Kyprolis.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Kyprolis can be found on Kyprolis' EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
CFZ001 An open-label, single arm, phase 1 study of the pharmacokinetics and safety of carfilzomib in subjects with relapsed multiple myeloma and end	Primary: To assess the influence of end-stage renal disease (ESRD) on area under the curve (AUC), (both area under the curve, from time 0 to the last concentration measured [$AUC_{0\text{-last}}$] and area under the curve, from	Carfilzomib exposure (pharmacokinetic) in patients with renal (kidney) impairment, including those with renal failure, in patients receiving a higher dose (56 mg/m^2) of carfilzomib.	Ongoing	Final CSR Q2 2016 (planned)

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
stage renal disease	time 0 extrapolated to infinity [AUC_{0-inf}]) of carfilzomib 56 mg/m^2 at Cycle 2 Day 1 (C2D1) in subjects with relapsed multiple myeloma.			
CFZ002 An open-label, single-arm, phase 1 study of the pharmacokinetics and safety of carfilzomib in subjects with advanced malignancies and varying degrees of hepatic impairment.	Primary: To assess the influence of hepatic impairment on area under the curve (AUC), (both area under the curve, from time 0 to the last concentration measured [AUC_{0-last}] and area under the curve, from time 0 extrapolated to infinity [AUC0-inf]) of carfilzomib at Cycle 1 Day 16 (C1D16) in subjects with relapsed or progressive advanced malignancies.	Use in patients with hepatic (liver) impairment	Ongoing	Final CSR Q2 2016 (planned)

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 11-2015.