EMA/602832/2014

Summary of the risk management plan (RMP) for Cyramza (ramucirumab)

This is a summary of the risk management plan (RMP) for Cyramza, which details the measures to be taken in order to ensure that Cyramza 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 Cyramza, which can be found on Cyramza's EPAR page.

Overview of disease epidemiology

Cyramza is a medicine used to treat stomach (gastric) cancer. Stomach cancer is more commonly found in older patients, and because the disease shows no symptoms in its early stages, more than half of stomach cancers are diagnosed at an advanced stage, when surgical removal of the tumour is not possible. Symptoms include indigestion, feeling sick, abdominal pain, diarrhoea or constipation, vomiting, black stools, difficulty swallowing, rapidly feeling full when eating, pain after eating, weight loss, low numbers of red blood cells, and fatigue.

In the EU, stomach cancer is not common: the number of new cases of stomach cancer diagnosed in 2012 was 80,626. Men are approximately twice as likely as women to develop stomach cancer. Factors that are known to increase the risk of developing stomach cancer include dietary behaviours such as low consumption of fresh and citrus fruit, total meat intake, high dietary salt intake and drinking alcohol. Other factors known to increase the risk of developing stomach cancer include smoking, obesity, acid reflux, and infection with certain types of bacteria.

Summary of treatment benefits

Cyramza in combination with paclitaxel has been shown to increase survival of patients with advanced gastric or gastro-oesophageal junction cancer (cancer of the area where the oesophagus enters the stomach) which progressed while on/after a platinum and fluorpyrimidine-based therapy. In one study (RAINBOW) involving 665 patients, those treated with Cyramza and paclitaxel lived significantly longer on average than patients treated with paclitaxel and a placebo (a dummy treatment): 9.6 months versus 7.4 months respectively.

Similarly, in another study (REGARD) in 355 patients, those treated with Cyramza plus best supportive care lived significantly longer than patients treated with placebo plus best supportive care (an average of 5.2 months versus 3.8 months, respectively).

Unknowns relating to treatment benefits

There is no information about the use of Cyramza in children and women who are pregnant or breastfeeding, and there is limited information regarding Cyramza treatment in patients with severe kidney impairment and patients with impaired liver function.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Blocking of the arteries by a blood clot (arterial thromboembolic events)	Arterial blood clots can lead to serious conditions, including heart attack or stroke. In patients treated with Cyramza for advanced stomach cancer (in the REGARD study), 1.7% developed blood clots in the arteries and 0.8% of patients died from blood clots in the arteries. In patients treated with Cyramza plus paclitaxel (in the RAINBOW study) for advanced stomach cancer, 1.8% developed blood clots in the arteries. These events did not result in the death of any patient. It is not known how common arterial blood clots are in patients with advanced stomach cancer who do not receive drug treatment for their cancer.	Most blood clots in an artery do not have early warning signs. Patients should contact their doctor urgently if any of the following symptoms occur: • Chest pain or heaviness in the chest. These may be symptoms of a heart attack. • Sudden numbness or weakness of the arm, leg and face, feeling confused, difficulty speaking or understanding others, sudden difficulty in walking or loss of balance or coordination or sudden dizziness. These may be symptoms of a stroke. Cyramza treatment should be permanently stopped if a patient develops a severe blood clot in the arteries.
High blood pressure (hypertension)	In patients treated with Cyramza for advanced stomach cancer (REGARD study), 16.1% developed high blood pressure. This was considered more severe in 7.6% of patients but did not result in the death of any patient. These figures are similar to the rates of high blood pressure seen in patients with advanced stomach cancer who did not receive medicines to treat their cancer. In patients treated with Cyramza plus paclitaxel (RAINBOW study) for advanced stomach cancer, 25.1% experienced high blood pressure. These events did not result in the death of any patient.	Patients should talk to their doctor or nurse before they are given Cyramza if they have high blood pressure. The doctor will make sure that if a patient already has high blood pressure, it is brought under control before starting Cyramza. The doctor will monitor the patient's blood pressure and adjust blood pressure medication as needed during treatment with Cyramza. Treatment with Cyramza may need to be stopped temporarily until high blood pressure is controlled with medication, or stopped permanently if it cannot be controlled well enough.
Allergic reactions to Cyramza (infusion-related reactions)	Infusion-related reactions may happen with treatment with Cyramza. The doctor or nurse will check for side effects during the infusion. Symptoms may include increased muscle tension, back pain, chest pain and/or tightness, chills, flushing, difficulty in breathing,	Patients must not be given Cyramza if they are allergic to ramucirumab (the active substance in Cyramza) or any of the other ingredients it contains. If a patient experiences a mild or moderate allergic reaction, they will be

Risk	What is known	Preventability
	wheezing, and feeling of tingling or numbness in the hands or feet. In severe cases, symptoms may include breathing distress caused by narrowing of the airways, faster heartbeat, and fainting. In patients treated with Cyramza for advanced stomach cancer (REGARD study), 0.4% developed allergic-type reactions related to the infusion. These reactions were considered to be mild in all cases and did not result in any deaths. In patients treated with Cyramza plus paclitaxel (RAINBOW study) for advanced stomach cancer, 5.8% experienced allergic-type reactions. These events did not result in the death of any patient.	given medication to prevent another reaction before any remaining Cyramza infusions. If a patient experiences a more severe allergic type reaction, Cyramza will be immediately and permanently stopped.
Excess protein in the urine (proteinuria)	In patients treated with Cyramza for advanced stomach cancer (REGARD study), 3.0% had protein in their urine. This was considered more severe in 1 case. In patients treated with Cyramza plus paclitaxel (RAINBOW study) for advanced stomach cancer, 16.8% developed excess protein in the urine. This was considered more severe in 3 cases.	The amount of protein in a patient's urine will be checked regularly during treatment. If there is an increase, depending on the protein level measured, Cyramza may be temporarily discontinued. Once the urine protein level has decreased to a certain level, treatment may be restarted with a lower dose. Cyramza will be permanently stopped if the patient is passing more than a certain amount of protein in the urine or if they develop a severe kidney disease (nephrotic syndrome).
Developing holes in the wall of the gut (gastrointestinal perforations)	In patients treated with Cyramza for advanced stomach cancer (REGARD study), 0.8% developed holes in their gut wall which resulted in the death of 2 patients. In patients treated with Cyramza plus paclitaxel (RAINBOW study) for advanced stomach cancer, 1.2% developed holes in their gut wall resulting in the death of one patient.	Patient should talk to their doctor or nurse immediately if they experience severe pain in the belly, being sick (vomiting), fever, or chills during or after treatment with Cyramza, because these may be signs of developing holes in the gut wall. Cyramza will be permanently stopped if the patient develops a hole in the gut wall.
Bleeding (haemorrhagic events)	In patients treated with Cyramza for advanced stomach cancer (REGARD study), 12.7% developed bleeding, mainly mild to moderate nosebleeds.	Patients should tell their doctor or nurse if they are taking any medicines that may increase the risk of bleeding or that affect blood clotting ability. Patients

Risk	What is known	Preventability
	Bleeding from other sites was considered to be more severe in 3.4% and resulted in death in 0.8% of patients. In patients treated with Cyramza plus paclitaxel (RAINBOW) for advanced stomach cancer, 41.9% developed bleeding, with the majority of these events being mild to moderate nosebleeds. More severe bleeding events occurred in 4.3% of patients and resulted in death in 1 patient.	should also tell their doctor if they have any condition that increases the risk of bleeding. In such cases, the doctor will take regular blood samples to monitor the risk of bleeding. Patients should tell their doctor or nurse immediately if they experience symptoms of bleeding such as extreme tiredness, weakness, dizziness or changes in the colour of their stools. Cyramza treatment will be permanently stopped if a patient experiences severe bleeding.
Abnormal or slow/poor healing of wounds (impaired wound healing)	Although Cyramza has not been tested in patients with recent operations and with slow/poor healing of wounds, cancer treatments that work in the same way as Cyramza have been associated with delayed or poor healing of wounds. No cases of delayed or poor healing of wounds have been reported in patients treated with Cyramza for advanced stomach cancer (REGARD study) or in patients treated with Cyramza plus paclitaxel (RAINBOW) for advanced stomach cancer, but there is a risk based on the mechanism of action of Cyramza.	Patients should tell their doctor or nurse if they have had recent surgery or if they have a poorly healing wound after surgery. They should not receive Cyramza for at least 4 weeks before undergoing planned surgery and the doctor will decide when to re-start treatment. If a patient has a wound that heals poorly during treatment with Cyramza, Cyramza should be stopped until the wound is fully healed.
Low blood counts of neutrophils, a type of white blood cell (neutropenia)	In patients treated with Cyramza for advanced stomach cancer (REGARD study), 4.7% developed low white blood cell counts. In patients treated with Cyramza plus paclitaxel (RAINBOW) for advanced stomach cancer, 54.4% developed low white blood cell counts. This event did not result in the death of any patient.	Blood tests should be taken before each paclitaxel dose to check the numbers of white blood cells. Based on the numbers the doctor may then have to reduce the paclitaxel dose or not give it.
Abnormal tube-like connections or passageways between different organs in the body (fistula formation)	Treatment with drugs with a similar mechanism of action to Cyramza has been associated with development of fistulae. This is thought to be due to reduced oxygen supply and poor wound healing in the area where the fistula develops. One patient (0.4%) treated with Cyramza for advanced stomach cancer (REGARD study) experienced such a fistula.	Patients should tell their doctor or nurse immediately if they develop severe abdominal pain, chills or are sick (vomiting) during treatment with Cyramza or afterwards, because these may be symptoms of fistulae. Cyramza should be permanently stopped if the patient develops a fistula.

Risk	What is known	Preventability
	No events of *fistulae* were reported in patients treated with Cyramza plus paclitaxel (RAINBOW) for advanced stomach cancer.	
Liver damage or liver failure (liver failure and liver injury)	Liver damage or failure has been seen in a small number of patients treated with Cyramza, most of whom already had advanced liver cancer and liver cirrhosis. The majority of liver abnormalities or symptoms seen have been mild in nature. The mechanism by which this occurs is unknown at this time.	Patients should tell their doctor or nurse before being given Cyramza if they have severe liver disease ('cirrhosis') and associated conditions, such as excessive accumulation of fluid in the abdomen ('ascites'). Doctors should discuss with patients whether the potential benefits of treatment are judged to outweigh the potential risks. Patients who are receiving Cyramza in combination with paclitaxel will have blood tests to check that their blood counts are high enough and that their liver is functioning well before any paclitaxel infusion.
Worsening of heart function (congestive heart failure)	When used in combination with certain other cancer medicines (mitoxantrone, other anthracycline/anthracenedione agents) that are known to cause heart toxicity, Cyramza may possibly add to the worsening of heart function caused by these medicines. Worsening of heart function has not been observed more often in patients who received Cyramza in combination with paclitaxel than patients who received paclitaxel alone for the treatment of stomach cancer.	Patients should tell their doctor or nurse immediately if they experience symptoms of worsening of heart function such as chest pain, heaviness in the chest, shortness of breath or swelling of the feet and ankles. Your doctor will discuss with you if the potential benefits of treatment are judged to outweigh the potential risks for you.

Important potential risks

Risk	What is known
Effects on the brain with headache, confusion, seizure, and blindness (reversible posterior leukoencephalopathy syndrome)	This condition has been seen in patients who have received other types of cancer medicines. It is likely that there are several factors working together to cause this condition, including high blood pressure and damage to the lining of the blood vessels.
Lowered red blood cell count (anaemia)	Treatments with medicines with a similar mechanism of action to Cyramza have been associated with anaemia. In stomach cancer patients, anaemia is more likely to happen as a result of bleeding associated with the cancer or the administration of Cyramza. Cytotoxic (cell-killing) cancer medicines may also

Risk	What is known
	cause anaemia.
Pain in the stomach (abdominal pain)	Treatments with medicines with a similar mechanism of action to Cyramza have been associated with the development of stomach pain. Stomach pain can result from a wide variety of causes, including stomach cancer, infection, inflammation, trauma, obstruction, or other abnormal processes.
Problems getting pregnant; Risks when pregnant; Risks when breastfeeding (reproductive and developmental toxicity)	No animal studies have been specifically performed to evaluate whether Cyramza can affect fertility or cause harmful effects on reproduction. However, animal studies in the published literature show that blood vessel growth and the factors that control blood vessel growth are critical for female fertility, ovulation, development of the placenta and the development of the offspring before and after birth, so Cyramza is expected to have potentially harmful effects on these processes. There are no data on the use of Cyramza in pregnant women. Cyramza is not recommended during pregnancy and in women of child-bearing potential not using contraception. There are no data from the use of Cyramza in breastfeeding women; however, although the amount of Cyramza passing into breast milk is likely to be low, a risk to newborns/infants cannot be excluded. Breastfeeding should be stopped during treatment with Cyramza and for at least 3 months after the last dose.
Blood clot in veins (Venous Thromboembolic Events)	Treatment with cancer medicines, including medicines with a similar mechanism of action to Cyramza, has been associated with the development of blood clots in veins. Blood clots in veins were also experienced by patients who received Cyramza, particularly when administered in combination with cytotoxic (cell-killing) cancer treatment (i.e. paclitaxel). However, these events have not been seen more often in patients who received Cyramza alone or in combination with paclitaxel than patients who received paclitaxel alone for the treatment of gastric cancer.

Missing information

Risk	What is known
Risk of developing cancer (carcinogenicity) Risk of damaging DNA within cells (genotoxicity)	Animal studies have not been performed to test the potential for Cyramza to cause cancer. Laboratory tests have not been performed to test the potential for Cyramza to cause genetic (DNA) damage within cells.

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 Cyramza can be found on Cyramza's 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**
I4T-MC-JVDD: Safety and Effectiveness of Cyramza in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry	**Primary objective:** To evaluate the safety profile of Cyramza administered as monotherapy, or in combination therapy for second-line treatment, of adult patients with advanced gastric cancer under real-world disease conditions in the EU and North America **Secondary objective:** To evaluate the effectiveness of Cyramza administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions in the	Not applicable	Planned	Final Report: Estimated Q4 2021

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final results
	EU and North America			

Studies which are a condition of the marketing authorisation

None of the above studies are a condition of the marketing authorisation.

Summary of changes to the risk management plan over time

Major changes to the Risk Management Plan over time

Not applicable.

This summary was last updated in 01-2015.