Package leaflet: Information for the user

Cyramza® 10 mg/ml concentrate for solution for infusion
ramucirumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cyramza is and what it is used for

Cyramza is a cancer medicine that contains the active substance ramucirumab, which is a monoclonal antibody. This is a specialised protein that can recognise and attach to another protein found on blood vessels called 'VEGF receptor 2'. This receptor is needed in the development of new blood vessels. To grow, cancer needs new blood vessels to develop. By attaching to 'VEGF receptor 2' and blocking it the medicine cuts off the blood supply to the cancer cells.

Cyramza is given in combination with paclitaxel, another anti-cancer medicine, for the treatment of advanced stomach cancer (or cancer of the junction between the oesophagus and the stomach) in adults whose disease has worsened after treatment with medicines to treat cancer.

Cyramza is used for the treatment of advanced stomach cancer (or cancer of the junction between the oesophagus and the stomach) in adults whose disease has worsened after treatment with medicines to treat cancer and for whom treatment of Cyramza in combination with paclitaxel is not suitable.

Cyramza is used to treat advanced cancers of the colon or rectum (parts of the large intestine) in adults. It is given with other medicines called 'FOLFIRI chemotherapy', including '5-fluorouracil', 'folinic acid', and 'irinotecan'.

Cyramza is given in combination with docetaxel, another anti-cancer medicine, for the treatment of adult patients with advanced stage of lung cancer whose disease has worsened after treatment with medicines to treat cancer.

2. What you need to know before you are given Cyramza

You must not be given Cyramza
- if you are allergic to ramucirumab or any of the other ingredients of this medicine (listed in section 6).
- if there is X-ray evidence that the lung cancer has a cavity or hole in it or if the lung cancer is close to major blood vessels.

Warnings and precautions
Talk to your doctor or nurse **before** you are given Cyramza if you:

- have any condition which increases the risk of bleeding. Also tell your doctor if you are taking any medicines which may increase the risk of bleeding or which affect blood clotting ability. In such cases, your doctor will perform regular blood tests to monitor the risk of bleeding.

- have lung cancer and have had recent bleeding in the lung (coughing up bright red blood) or you are regularly taking non-steroidal anti-inflammatory medicines, or medicines which affect blood clotting ability.

- have high blood pressure. Cyramza can increase the incidence of high blood pressure. Your doctor will make sure that if you already have high blood pressure, it is brought under control before starting Cyramza. Your doctor will monitor your blood pressure and adjust your blood pressure medicine as needed during treatment with Cyramza. Treatment with Cyramza may need to be stopped temporarily until high blood pressure is controlled with medicines, or stopped permanently if it cannot be adequately controlled.

- are going to have planned surgery, if you had recent surgery or if you have poor wound healing after surgery. Cyramza may increase the risk of problems with wound healing. You should not receive Cyramza for at least 4 weeks before you undergo planned surgery and your doctor will decide when to re-start treatment. If you have a wound that heals poorly during treatment, dosing of Cyramza will be stopped until the wound is fully healed.

- have severe liver disease (‘cirrhosis’) and associated conditions, such as excessive accumulation of fluid in your abdomen (‘ascites’). Your doctor will discuss with you if the potential benefits of treatment are judged to outweigh the potential risks for you.

- have severe kidney problems. There are limited data available about the use of Cyramza in patients with severely impaired kidney function.

Talk to your doctor or nurse **immediately** if any of the following applies to you (or you are not sure) **during treatment** with Cyramza **or anytime thereafter:**

- **Blocking of the arteries by a blood clot** (‘arterial thromboembolic events’):
  Cyramza can cause blood clots in your arteries. Arterial blood clots can lead to serious conditions, including heart attack or stroke. Symptoms of a heart attack may include chest pain or heaviness in the chest. Symptoms of a stroke may include 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. Cyramza will be permanently stopped if you develop a blood clot in your arteries.

- **A hole in the wall of your gut** ('gastrointestinal perforation'): Cyramza may increase the risk of developing a hole in the wall of your gut. Symptoms include severe abdominal pain, being sick (vomiting), fever or chills. Cyramza will be permanently stopped if you develop a hole in the wall of your gut.

- **Severe bleeding:** Cyramza may increase the risk of severe bleeding. Symptoms may include: extreme tiredness, weakness, dizziness or changes in the colour of your stools. Cyramza will be permanently stopped if you experience severe bleeding.

- **Infusion-related reaction:** Infusion-related reactions may happen during treatment because Cyramza is given as an intravenous infusion via a drip (see section 3). Your doctor or nurse will check for side effects during your infusion. Symptoms may include: increased muscle tension, back pain, chest pain and/or tightness, chills, flushing, difficulty in breathing, wheezing, and feeling of tingling or numbness in hands or feet. In severe cases, symptoms may include breathing distress caused by narrowing of the airways, faster heartbeat, and feeling faint. Cyramza will be permanently stopped if you experience a severe infusion-related reaction.

- **Abnormal tube-like connections or passageways inside the body** ('fistula'): Cyramza may increase the risk of abnormal tube-like connections or passageways inside the body between internal organs and skin or other tissues. Cyramza will be permanently stopped if you develop a fistula.

- **Abnormal urine test** ('proteinuria'): Cyramza may increase the risk of developing or worsening of abnormal levels of protein in the urine. Treatment with Cyramza may need to be stopped temporarily until the levels of protein in the urine decrease and then treatment resumed at a lower dose, or stopped permanently if the urine protein level does not reduce sufficiently.

- **Inflammation of the mouth** ('stomatitis'): Cyramza, when given in combination with chemotherapy may increase the risk of developing inflammation of the mouth. Symptoms may include a burning sensation in the mouth, ulceration, blisters or swelling. Your doctor may prescribe treatment to help with the symptoms.

- **Fever or infection**: You may develop a temperature of 38 ºC or greater during treatment (since you might have fewer white blood cells than normal which is very common). Symptoms may include sweating or other signs of infection, such as headache, pain in the limbs or decreased appetite. Infection (sepsis) may be severe and could lead to death.

- **Elderly people with lung cancer**: Your doctor will carefully evaluate the most appropriate treatment for you.

Children and adolescents
Cyramza should not be given to patients under the age of 18 years because there is no information about how it works in this age group.

Other medicines and Cyramza
Tell your doctor if you are taking, have recently taken or might take any other medicines. This includes medicines obtained without a prescription and herbal medicines.

Pregnancy, breast-feeding and fertility
Before starting treatment you must tell your doctor if you are pregnant or breast-feeding, think you may be pregnant or you are planning to have a baby. You should avoid getting pregnant while

receiving this medicine and for at least 3 months after the last dose of Cyramza. Talk to your doctor about the best contraception for you.

As Cyramza inhibits the development of new blood vessels, it may decrease the likelihood of you becoming pregnant or maintaining a pregnancy. It may also cause damage to your unborn baby. You should not use this medicine during pregnancy. If you become pregnant during treatment with Cyramza, your doctor will discuss with you if the benefit of treatment for you is greater than any possible risk to you or your unborn baby.

It is not known if the medicine passes into breast milk and could affect a breastfed baby. Therefore, you should not breast-feed your baby during treatment with Cyramza and for at least 3 months after you receive the last dose.

Driving and using machines
It is not known whether Cyramza can affect your ability to drive or to use machines. If you experience any symptoms affecting your ability to concentrate and react, do not drive or use machines until the effect goes away.

Cyramza contains sodium

Each 10 ml vial contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium free'. Each 50 ml vial contains approximately 85 mg sodium (main component of cooking/table salt). This is equivalent to approximately 4% of the recommended maximum daily dietary intake of sodium for an adult.

3. How you are given Cyramza

This cancer treatment will be given to you by a doctor or nurse.

Dosage and frequency of administration
The correct amount of Cyramza needed to treat your disease will be calculated by your doctor or hospital pharmacist depending on your body weight.

The recommended dose of Cyramza for the treatment of gastric cancer and for the treatment of advanced cancer of the colon or rectum is 8 mg per kilogram of your body weight once every 2 weeks.

The recommended dose of Cyramza for the treatment of lung cancer is 10 mg per kilogram of your body weight once every 3 weeks.

The number of infusions you will receive depends on how you are responding to treatment. Your doctor will discuss this with you.

Route and method of administration
Cyramza is a concentrate for solution for infusion (also called "sterile concentrate"). A hospital pharmacist, nurse or doctor will have diluted the contents of the vial with sodium chloride 9 mg/ml (0.9%) solution before use. This medicine is given by infusion via a drip over a period of approximately 60 minutes.

Premedication
You may be given another medicine to reduce the risk of an infusion-related reaction before you receive Cyramza. If you experience an infusion-related reaction during Cyramza therapy, you will be given premedication for all future infusions.

Dose adjustments
During each infusion, your doctor or nurse will check for side effects.

If you experience an infusion-related reaction during treatment, the time taken to give your infusion will be increased for the rest of that infusion and for all future infusions.

The amount of protein in your urine will be checked regularly during treatment. 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 treatment will be temporarily stopped if you:
- develop high blood pressure, until it is controlled with anti-hypertensive medicine
- develop wound healing problems, until the wound is healed
- will undergo planned surgery, four weeks prior to surgery

Cyramza treatment will be permanently stopped if you:
- develop a blood clot in your arteries
- develop a hole in the wall of your gut
- experience severe bleeding
- experience a severe infusion-related reaction
- develop high blood pressure that cannot be controlled with medicine
- are passing more than a certain amount of protein with your urine or if you develop a severe kidney disease (nephrotic syndrome)
- develop abnormal tube-like connections or passageways inside the body between internal organs and skin or other tissues (fistula)

When receiving Cyramza in combination with paclitaxel or docetaxel
Paclitaxel and docetaxel are also given by a drip into a vein (intravenous infusion) over a period of approximately 60 minutes. If you are receiving Cyramza in combination with either paclitaxel or docetaxel on the same day, Cyramza will be given first.

The amount of paclitaxel or docetaxel needed depends on the surface area of your body. Your doctor or hospital pharmacist will calculate your body surface area by measuring your height and weight and will work out the right dose for you.
The recommended dose of paclitaxel is 80 mg for every square metre (m^2) of your body's surface area once every week for 3 weeks followed by 1 week without treatment.
The recommended dose of docetaxel is 75 mg for every square metre (m^2) of your body's surface area once every 3 weeks. If you are of East Asian origin, you may receive a reduced docetaxel starting dose of 60 mg per every m^2 of your body's surface area once every 3 weeks.

Prior to being given any paclitaxel infusion, you will have blood tests to check that your blood counts are high enough and that your liver is functioning well.

Read the paclitaxel or docetaxel package leaflet for further information.

When receiving Cyramza in combination with FOLFIRI
FOLFIRI chemotherapy is given by intravenous infusion, after the Cyramza infusion has finished. Please read the package leaflets for the other medicines that are part of your treatment, to see if they are suitable for you. If you are unsure, ask your doctor, pharmacist or nurse if there are any reasons why you can't use these medicines.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor **immediately** if you experience any of the following serious side effects that have been observed during Cyramza treatment (see also **What you need to know before you are given Cyramza**):

Common side effects (may affect up to 1 in 10 people):
- **hole in the wall of your gut:** this is a hole that develops in the stomach, gut or bowel. Symptoms include severe abdominal pain, being sick (vomiting), fever or chills.
- **severe bleeding in your gut:** symptoms may include extreme tiredness, weakness, dizziness or changes in the colour of your stools.
- **blood clots in the arteries:** arterial blood clots can lead to a heart attack or stroke. Symptoms of a heart attack may include chest pain or heaviness in the chest. Symptoms of a stroke may include 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.

Tell your doctor if you experience any of the following other side effects:

Very common side effects (may affect more than 1 in 10 people):
- low white blood cell counts (may increase the risk of infection)
- feeling tired or weak
- nose bleed
- diarrhoea
- inflammation of the lining of the mouth
- abdominal pain
- low platelet count (blood cells that help the blood to clot)
- high blood pressure
- swelling of hands, feet and legs due to fluid retention
- protein in the urine (abnormal urine test)
- inflammation of mucous membranes, such as digestive and respiratory tracts
- fever accompanied by low white blood cell counts
- redness, swelling, numbness/tingling, or pain and/or skin peeling in hands and/or feet (called hand-foot syndrome)
- low blood levels of a protein called albumin

Common side effects (may affect up to 1 in 10 people):
- headache
- low blood levels of potassium (hypokalaemia) which can cause muscle weakness, twitching or abnormal heart rhythm
- low blood levels of sodium (hyponatraemia) which can cause tiredness and confusion or muscle twitching
- rash
- serious infection (sepsis)
- intestinal blockage; symptoms may include constipation and abdominal pain
- abnormal growth of blood vessels

Rare side effects (may affect up to 1 in 1000 people):
- abnormal blood clotting in small blood vessels

Cyramza has been associated with infusion-related reactions.

Cyramza may cause changes in laboratory tests. From the side effects listed above, these are: low white blood cell counts; low platelet count in the blood; low blood levels of albumin, potassium or sodium; presence of protein in the urine.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cyramza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Do not freeze or shake the infusion solution. Do not administer the solution if you notice any particulate matter or discolouration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Cyramza contains
- The active substance is ramucirumab. One ml of concentrate for solution for infusion contains 10 mg of ramucirumab.
- Each 10 ml vial contains 100 mg of ramucirumab.
- Each 50 ml vial contains 500 mg of ramucirumab.
- The other ingredients are histidine, histidine monohydrochloride, sodium chloride, glycine (E640), polysorbate 80 (E433) and water for injections (see section 2 “Cyramza contains sodium”).

What Cyramza looks like and contents of the pack
The concentrate for solution for infusion (or sterile concentrate) is a clear to slightly opalescent and colourless to slightly yellow solution in a glass vial with a rubber stopper.

Cyramza is available in packs of:
- 1 vial of 10 ml
- 2 vials of 10 ml
- 1 vial of 50 ml

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Eli Lilly Nederland B.V.
Papendorpseweg 83
3528 BJ Utrecht
The Netherlands

Manufacturer

Lilly France Fegersheim
2 rue du Colonel Lilly
67640 Fegersheim
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

Ireland
Eli Lilly and Company (Ireland) Limited
Tel: + 353-(0) 1 661 4377

Malta
Charles de Giorgio Ltd.
Tel: + 356 25600 500

United Kingdom
Eli Lilly and Company Limited
Tel: + 44-(0) 1256 315000

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Do not shake the vial.

Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.

Each vial is intended for single use only. Inspect the content of the vials for particulate matter and discolouration (the concentrate for solution for infusion should be clear to slightly opalescent and colourless to slightly yellow without visible particles) prior to dilution. If particulate matter or discolouration is identified, discard the vial.

Calculate the dose and volume of ramucirumab needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/ml solution of ramucirumab. Only use sodium chloride 9 mg/ml (0.9%) solution for injection as a diluent.

In case of prefilled intravenous infusion container usage
Based on the calculated volume of ramucirumab, remove the corresponding volume of sodium chloride 9 mg/ml (0.9%) solution for injection from the prefilled 250 ml intravenous container. Aseptically transfer the calculated volume of ramucirumab to the intravenous container. The final total volume in the container should be 250 ml. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medicinal products.

In case of empty intravenous infusion container usage
Aseptically transfer the calculated volume of ramucirumab into an empty intravenous infusion container. Add a sufficient quantity of sodium chloride 9 mg/ml (0.9%) solution for injection to the container to make the total volume 250 ml. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medicinal products.

After dilution and preparation, the medicine must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 °C to 8 °C.

Parenteral medicinal products should be inspected visually for particulate matter prior to administration. If particulate matter is identified, discard the infusion solution.

Discard any unused portion of ramucirumab left in a vial, as the product contains no antimicrobial preservatives.

Administer via infusion pump. A separate infusion line with a protein sparing 0.22 micron filter must be used for the infusion and the line must be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection at the end of the infusion.

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