Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is to be supplied by a physician's prescription only

Cyramza 10 mg/ml

Concentrate for solution for infusion

Each ml of the concentrate contains 10 mg of ramucirumab.

Inactive ingredients and allergens in the preparation: See section 6 "Additional information" and "important information about some of the ingredients of this medicine" in section 2.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, contact your doctor or pharmacist.

This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

Cyramza is intended to treat adults (over the age of 18) only.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Cyramza is a medicine for the treatment of cancer:

- **Cyramza** is given in combination with paclitaxel, for the treatment of adults with advanced gastric cancer (or cancer of the junction between the oesophagus and the stomach) with disease progression after prior treatment with chemotherapy (platinum and fluoropyrimidine).
- **Cyramza** is given as a monotherapy for the treatment of adults with advanced gastric cancer (or cancer of the junction between the oesophagus and the stomach) with disease progression after prior treatment with chemotherapy (platinum or fluoropyrimidine), for whom treatment of **Cyramza** in combination with paclitaxel is not appropriate.
- **Cyramza** is given for the treatment of adults with metastatic colorectal cancer with disease progression, on or after prior therapy with oxaliplatin, bevacizumab, and a fluoropyrimidine. This treatment is administered in combination with other medicines called "FOLFIRI chemotherapy", which include 5-fluorouracil, folinic acid, and irinotecan.
- **Cyramza** is given in combination with erlotinib, for the first-line treatment of adults with metastatic non-small cell lung adenocarcinoma with activating epidermal growth factor receptor (EGFR) mutations.
- **Cyramza** is given in combination with docetaxel, for the treatment of adults with locally advanced or metastatic non-small cell lung cancer with disease progression after platinum-based chemotherapy.
- **Cyramza** is given as a monotherapy for the treatment of adults with advanced or unresectable hepatocellular carcinoma who have a serum alpha fetoprotein (AFP) of ≥400 ng/ml and who have been previously treated with sorafenib.

Therapeutic group:

Antineoplastic agents, monoclonal antibodies.

What **Cyramza** is

Cyramza contains the active substance ramucirumab, which is a monoclonal antibody. This is a specialised protein that can recognize 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.

2. BEFORE USING THIS MEDICINE

Do not use this medicine if:

- you are hypersensitive (allergic) to ramucirumab or any of the other ingredients of this medicine (listed in section 6).
- In patients with non-small cell lung cancer, when 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.

- For indication in elderly patients with metastatic non-small cell adenocarcinoma lung cancer with a mutation in the epidermal growth factor (EGFR) receptor gene, the drug must not be used if the cancer has spread to the brain as these patients were not included in the study.

Special warnings regarding the use of this medicine

Before using **Cyramza**, tell your doctor 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 instruct you to perform regular blood tests to monitor the risk of bleeding.
- have liver cancer and have had previous bleeding from enlarged veins in your food pipe (oesophagus) or have high blood pressure in the portal vein, which carries the blood from the bowel and spleen to the liver.
- have lung cancer and have had recent bleeding in the lung (coughing up bright red blood) or if you are regularly taking non-steroidal anti-inflammatory medicines (NSAIDs), 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.
- have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- 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. If you have liver cancer your doctor will monitor you for signs and symptoms of confusion and/or disorientation associated with chronic liver problems and will stop treatment with **Cyramza** if you develop these signs and symptoms.
- 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 color 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.

- **A rare but serious brain condition** called 'posterior reversible encephalopathy syndrome' or 'PRES': **Cyramza** may increase the risk of developing this brain condition. Symptoms may include fits (seizures), headache, feeling sick (nausea), being sick (vomiting), blindness or reduced level of consciousness, with or without high blood pressure. **Cyramza** will be stopped if you experience this brain condition.
- **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** ('proteinura'): **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°C 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.

There is no information on the safety and efficacy of this medicine in children and adolescents under 18 years of age.

Tests and follow-up

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.

Drug interactions

If you are taking or have recently taken any other medicines, including nonprescription medications and nutritional supplements, inform your doctor or pharmacist.

Pregnancy, breastfeeding and fertility

Pregnancy

Before starting treatment, you must tell your doctor if you are pregnant or breastfeeding, think you may be pregnant, or you are planning to become pregnant. 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**, you must refer to the doctor immediately. 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.

Breastfeeding

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

Fertlity
There are no data on the effect of **Cyramza** on human fertility. Female fertility is likely to be compromised during treatment with **Cyramza** based on studies in animals.

Driving and using machines
Cyramza has no or negligible influence on your ability to drive or 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.

Important information about some of the ingredients of this medicine
Cyramza contains sodium chloride.

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 SHOULD YOU USE THIS MEDICINE?

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

Dosage and frequency of administration

The dosage and manner of treatment will be determined only by the doctor.

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

Do not exceed the recommended dose.

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.

Route and method of administration
Cyramza is a concentrate for solution for infusion (also called "sterile concentrate"). A hospital pharmacist, nurse or doctor will dilute 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.

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)
- develop confusion and/or disorientation associated with chronic liver problems
- decline in kidney function (in the setting of liver failure)

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.

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 patient leaflet for further detailed information.

When receiving Cyramza in combination with FOLFIRI:

FOLFIRI chemotherapy is given by intravenous infusion, after the **Cyramza** infusion has finished. Please read the patient leaflet 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.

When receiving Cyramza in combination with erlotinib

Please read the erlotinib package leaflet for information on erlotinib and whether it is suitable for you. If you are unsure, ask your doctor, pharmacist or nurse if there are any reasons why you can’t use erlotinib.

If you have accidentally taken a higher dose

There is no information on overdose, in case of overdose supportive care will be given.

Treatment should be continued as recommended by the doctor.

Even if there is an improvement in your health, do not stop treatment with this medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take a medicine. Wear glasses if you need them.

If you have any further questions regarding the use of this medicine, consult the doctor or pharmacist.

4. <u>SIDE EFFECTS</u>

As with any medicine, **Cyramza** can cause side effects in some users. Do not be alarmed by reading the list of side effects. You may not experience any of them.

Tell your doctor **immediately** if you experience any of the following serious side effects that have been observed during **Cyramza** treatment (see also section 2**: Before using this medicine**):

<u>Common side effects</u> <u>(may affect up to 1 in 10 people):</u>

- **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 color 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.

Rare side effects (may affect up to 1 in 1,000 people):

- **a brain condition** called posterior reversible encephalopathy syndrome: symptoms may include fits (seizures), headache, feeling sick (nausea), being sick (vomiting), blindness or reduced level of consciousness, with or without high blood pressure.

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):

- feeling tired or weak
- low white blood cell counts (may increase the risk of infection)
- infections
- diarrhea
- hair loss
- nose bleed
- inflammation of the lining of the mouth
- high blood pressure
- reduction in red blood cells which can make the skin pale
- swelling of hands, feet and legs due to fluid retention
- low platelet count (blood cells that help the blood to clot)
- abdominal pain
- protein in the urine (abnormal urine test)
- headache
- inflammation of mucous membranes, such as digestive and respiratory tracts

Common side effects (may affect up to 1 in 10 people):

- fever accompanied by low white blood cell counts
- low blood levels of a protein called albumin
- infusion-related reactions
- rash
- redness, swelling, numbness/tingling, or pain and/or skin peeling in hands and/or feet (called hand-foot syndrome)
- hoarseness
- bleeding in your lungs
- low blood levels of sodium (hyponatremia) which can cause tiredness and confusion or muscle twitching
- bleeding gums
- confusion and/or disorientation in patients with chronic liver problems
- intestinal blockage; symptoms may include constipation and abdominal pain
- underactive thyroid gland which can cause tiredness or weight gain (hypothyroidism)
- abnormal growth of blood vessels
- serious infection (sepsis)
- low blood levels of potassium (hypokalemia) which can cause muscle weakness, twitching or abnormal heart rhythm

Rare side effects (may affect up to 1 in 1,000 people):

- abnormal blood clotting in small blood vessels

Not known (frequency cannot be estimated from the available data):
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections).

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.

If you experience any side effect, if a side effect gets worse, or if you suffer from a side effect not mentioned in this leaflet, you should consult the doctor.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Reporting side effects due to drug treatment" that can be found on the Home Page of the Ministry of Health's website (www.health.gov.il), which refers to the online form for reporting side effects, or by entering the following link:

https://sideeffects.health.gov.il

5. HOW TO STORE THIS MEDICINE?

Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach of children and/or infants in order to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.

Do not use this medicine after the expiry date (exp. date) which is stated on the outer carton and vial label. 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 discoloration.

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. ADDITIONAL INFORMATION

In addition to the active ingredient, the medicine also contains:

Glycine, sodium chloride, L-histidine monohydrochloride, L-histidine, polysorbate 80 and water for injections.
(see section 2 "**Important information about some of the ingredients of this medicine**").

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 colorless to slightly yellow solution in a glass vial with a rubber stopper.

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

Not all pack sizes may be marketed.

Registration holder: Eli Lilly Israel Ltd., 4 HaSheizaf St., Ra'anana 4366411

Manufacturer: Eli Lilly and Company Ltd., Indianapolis, Indiana, USA

I CYRAVL A 06

Revised in April 2021 according to MOH Guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
156-19-34510-00

I CYRAVL A 06

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 discoloration (the concentrate for solution for infusion should be clear to slightly opalescent and colorless to slightly yellow without visible particles) prior to dilution. If particulate matter or discoloration 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, the solution could be stored up to 24 hours at a temperature of 2°C to 8°C or up to 4 hours at room temperature (below 30°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.