HOW DOES CYRAMZA® (ramucirumab) WORK?

CYRAMZA®
ramucirumab injection | 10 mg/mL solution
FOR PATIENTS WITH ADVANCED STOMACH OR GASTROESOPHAGEAL JUNCTION (GEJ) CANCER

CYRAMZA is used alone or in combination with paclitaxel (a type of chemotherapy) to treat specific kinds of advanced cancer of the stomach or where the stomach and esophagus meet. CYRAMZA is for patients whose cancer has progressed after being treated with certain types of chemotherapy. CYRAMZA is given through an intravenous infusion (IV).

WARNING: SEVERE BLEEDING, TEARS IN THE STOMACH OR BOWEL WALL, AND DIFFICULTY IN WOUND HEALING

Severe bleeding has occurred with CYRAMZA. These events are sometimes fatal. Tell your doctor right away if you have bleeding or symptoms of bleeding, including lightheadedness. Your treatment will have to be permanently stopped if severe bleeding occurs.

Tears in the stomach or bowel wall may occur with CYRAMZA. These events are sometimes fatal. Tell your doctor if you have severe diarrhea, vomiting, or severe abdominal pain. Your treatment will have to be permanently stopped if this occurs.

Wounds may have difficulty healing with drugs like CYRAMZA. Tell your doctor if you have a wound that doesn’t heal properly. If you develop a wound that won’t heal during treatment, your doctor will stop CYRAMZA until the wound is fully healed. Also tell your doctor if you have planned surgery, as CYRAMZA treatment should be interrupted prior to surgery. Your doctor may restart CYRAMZA after your surgical wound has healed.

Please see Important Safety Information, including Boxed Warning for severe bleeding, tears in the stomach or bowel wall, and difficulty in wound healing, on pages 3–4. See full Prescribing Information for additional information about CYRAMZA.
**HOW DOES CYRAMZA® (ramucirumab) WORK?**

CYRAMZA is not a traditional chemotherapy. It is a type of treatment called an anti-angiogenic. This means CYRAMZA is thought to block the development of new *blood vessels*. The development of new blood vessels is called angiogenesis.

**Why is angiogenesis important?**

There are many reasons why *angiogenesis* is a normal, healthy process for the body. For example, new blood vessels can help the body heal. However, in cancer, tumors use the blood supply from new blood vessels to help them grow. Without new blood vessels, a tumor may be starved of the nutrients it needs to keep growing. CYRAMZA is thought to stop or slow the growth of new blood vessels, including those that feed the tumor.

**DEFINITIONS**

- **Blood vessels**: Tubular structures, such as veins, arteries, or capillaries, that carry blood through tissues and organs
- **Receptors**: Structures located on a cell that when activated will cause a specific effect in the cell
- **Angiogenesis**: The process for making new blood vessels

**CYRAMZA was shown to interfere with angiogenesis to slow tumor growth** *

<table>
<thead>
<tr>
<th>WITHOUT TREATMENT</th>
<th>WITH CYRAMZA</th>
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<tbody>
<tr>
<td><strong>Tumor sends out signals asking receptors to build new blood vessels.</strong></td>
<td><strong>Tumor sends out signals asking a receptor to build new blood vessels.</strong></td>
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<tr>
<td><strong>Receptors receive the signals.</strong></td>
<td><strong>CYRAMZA attaches to a receptor and blocks the signals.</strong></td>
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<tr>
<td><strong>Development of new, tumor-feeding blood vessels begins.</strong></td>
<td><strong>Development of tumor-feeding blood vessels is limited.</strong></td>
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*The process of how CYRAMZA is thought to work was shown in laboratory studies.*

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What is the most important information I should know about CYRAMZA® (ramucirumab)?

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- Strokes, mini-strokes, blood clots, and heart attacks have occurred in clinical trials with CYRAMZA. These events are sometimes fatal. Your treatment will have to be permanently stopped if these events occur.
- Severe high blood pressure has occurred with CYRAMZA treatment. Your doctor will monitor your blood pressure every two weeks or more throughout treatment and may adjust, interrupt, or permanently stop treatment depending on the results. Tell your doctor if your blood pressure is high or if you have symptoms of high blood pressure, including severe headache or lightheadedness, or neurologic symptoms such as confusion, changes in your vision, or seizure.
- Infusion reactions related to injecting CYRAMZA have occurred. Most of these reactions happened during or after the first or second CYRAMZA infusion. Signs and symptoms of infusion reactions include shaking or stiffness of the body, back pain or spasms, chest pain or tightness, chills, flushing, difficulty breathing, wheezing, becoming blue due to lack of oxygen, and tingling or numbness of the skin. In severe cases, rapid heartbeat, low blood pressure, and severe trouble breathing may occur. Your healthcare team will monitor you for these side effects. In the case of a severe infusion reaction, your CYRAMZA treatment will have to be immediately and permanently stopped.
- CYRAMZA may worsen certain types of liver disease. Tell your doctor if you have or have had liver disease or other liver problems.
- RPLS (reversible posterior leukoencephalopathy syndrome), a very rare but serious brain disorder, has been reported in clinical trials with CYRAMZA. Signs and symptoms of RPLS may include headache, seizures, visual changes, and changes in mental function. These symptoms usually stop or improve within days, but some patients can experience continuing changes in mental function or death.
- Too much protein in the urine (proteinuria) has been reported in clinical trials with CYRAMZA. This may be a sign of kidney damage. Your doctor will monitor your urine protein levels during treatment. If you develop protein in your urine, your doctor may interrupt your treatment and decrease your dose of CYRAMZA. In severe cases your treatment will have to be permanently stopped.
- Thyroid gland problems have been reported in clinical trials with CYRAMZA. Your doctor will do blood tests to monitor your thyroid gland function during treatment.
- CYRAMZA can harm your unborn baby. You should avoid getting pregnant, and use adequate contraception while receiving CYRAMZA and for at least 3 months after stopping CYRAMZA.

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What are the most common side effects of CYRAMZA® (ramucirumab)?

- The most common side effects reported in patients treated with CYRAMZA when given alone were high blood pressure, diarrhea, headache, and low sodium. The most common serious adverse events were anemia (a decrease in red blood cells) and blockage of the intestine. Red blood cell transfusions were given to 11% of CYRAMZA-treated patients and 8.7% of patients who received placebo.

- The most common side effects reported in patients treated with CYRAMZA when given in combination with paclitaxel were tiredness; low white blood cell count; diarrhea; nosebleeds; high blood pressure; swelling in the arms, legs, hands, or feet; mouth sores; too much protein in the urine; low platelet count; low albumin (a protein in the blood); and bleeding in the gastrointestinal tract. The most common serious adverse events were low white blood cell count and low white blood cell count with fever; 19% of patients treated with CYRAMZA plus paclitaxel were given treatment to increase white blood cell count called granulocyte colony-stimulating factors.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/safety/medwatch or call 1-800-FDA-1088.

What should I tell my doctor before receiving treatment with CYRAMZA?

Before you receive CYRAMZA, tell your doctor if you:

- Have had or are at high risk for strokes or heart attack.

- Have high blood pressure or have blood pressure problems.

- Are planning to have surgery of any kind.

- Have or have had liver problems, including liver cirrhosis or other diseases of the liver.

- Are pregnant or may be pregnant: CYRAMZA can harm your unborn baby. You should avoid getting pregnant, and use adequate contraception while receiving CYRAMZA and for at least 3 months after stopping CYRAMZA.

- Are breastfeeding: your doctor will tell you to stop breastfeeding during treatment.

Tell your doctor about all the medications you are taking, including prescription and over-the-counter medications.

How is CYRAMZA given?

- CYRAMZA is slowly infused (injected) into your vein. The infusion will last about 60 minutes. You will usually receive CYRAMZA once every 2 weeks.

- Your doctor will also give additional medication(s) prior to your CYRAMZA infusion to address potential side effects.

CYRAMZA is available by prescription only.

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