**DRUG NAME:** Ramucirumab

**SYNONYM(S):** IMC-1121B¹

**COMMON TRADE NAME(S):** CYRAMZA®

**CLASSIFICATION:** molecular targeted therapy

*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.*

**MECHANISM OF ACTION:**

Ramucirumab is a human IgG1 monoclonal antibody that selectively binds to the extracellular vascular endothelial growth factor receptor (VEGFR)-2, resulting in inhibition of VEGF-induced endothelial cell proliferation, migration and angiogenesis.²³ Ramucirumab is a direct inhibitor of the VEGF-2 receptor, blocking VEGF ligands A, C, and D from binding to VEGFR-2. Ramucirumab's high specificity and broad target inhibition may lead to a more complete blockade of angiogenesis in comparison to bevacizumab.⁴⁵

**PHARMACOKINETICS:**

<table>
<thead>
<tr>
<th>Distribution</th>
<th>similar to total blood volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>cross blood brain barrier?</td>
<td>no information found</td>
</tr>
<tr>
<td>volume of distribution</td>
<td>5.5 L</td>
</tr>
<tr>
<td>plasma protein binding</td>
<td>no information found</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolism</th>
<th>primary elimination pathway is likely receptor-mediated clearance⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>active metabolite(s)</td>
<td>no information found</td>
</tr>
<tr>
<td>inactive metabolite(s)</td>
<td>no information found</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Excretion</th>
<th>dose dependent elimination and nonlinear exposure consistent with saturable clearance⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>urine</td>
<td>no information found</td>
</tr>
<tr>
<td>feces</td>
<td>no information found</td>
</tr>
<tr>
<td>terminal half life</td>
<td>15 days</td>
</tr>
<tr>
<td>clearance</td>
<td>0.014 L/h</td>
</tr>
</tbody>
</table>

Adapted from standard reference⁵ unless specified otherwise.

**USES:**

*Primary uses:*

- *Gastric cancer²*
- *Colorectal cancer⁶*
- *Lung cancer, non-small cell⁶*

*Other uses:*

- *Health Canada approved indication*

**SPECIAL PRECAUTIONS:**

*Caution:*

- preexisting **hypertension** should be controlled prior to starting treatment²
- increased risk of **post-operative bleeding** and **wound healing complications**; consider holding ramucirumab before surgery and until surgical wounds are fully healed²
- increased risk of **congestive heart failure**: use caution in patients with coronary artery disease and/or prior cardiotoxic chemotherapy drug exposure.\(^2\)
  - premedicate with intravenous diphenhydramine prior to each infusion to prevent **infusion-related reactions**.\(^2\)
  - patients with preexisting **Child-Pugh B or C cirrhosis** may experience clinical deterioration (e.g., new or worsening encephalopathy, ascites, or hepatorenal syndrome).\(^2\)
  - increased risk of **GI perforation** in patients with intra-abdominal malignancy and metastases, inflammatory bowel disease, diverticulitis, peptic ulcer, obstruction, and injury from surgery/procedures.\(^6\)

**Special Populations:** Safety in children is not known. In animal studies, adverse effects on the epiphyseal growth plate were reported at doses lower than the recommended human dose.\(^5\)

**Carcinogenicity:** no information found

**Mutagenicity:** no information found

**Fertility:** In animal studies, inhibition of VEGFR-2 in females affected the development of tissues critical for reproduction. Inhibition resulted in hormone level changes, increased duration of the follicular cycle, and increased follicular mineralization of the ovary.\(^2\)

**Pregnancy:** Disruption of VEGF signaling in animals has been associated with developmental abnormalities such as poor development of the cranial region, forelimbs, forebrain, heart, and blood vessels. Effective contraception is recommended during treatment and for three months following the last dose of ramucirumab.\(^2,5\)

**Breastfeeding** is not recommended during treatment and for three months following the last dose due to the potential secretion into breast milk.\(^2\)

**SIDE EFFECTS:**

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.\(^7,8\) When placebo-controlled trials are available, adverse events will generally be included if the incidence is >5% higher in the treatment group.\(^3\)

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>blood and lymphatic system/ febrile</td>
<td>anemia (4%)(^5)</td>
</tr>
<tr>
<td>system/ neutropenia</td>
<td>neutropenia (4-5%, severe 1%)(^2,9)</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia (4%, severe &lt;1%)</td>
</tr>
<tr>
<td>cardiac</td>
<td><strong>arterial thromboembolic events</strong> including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia (2%)(^2,9); can be fatal</td>
</tr>
<tr>
<td>endocrine</td>
<td>hypothyroidism (1%)</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td><strong>emetogenic potential: low</strong>(^10)</td>
</tr>
<tr>
<td></td>
<td>diarrhea (14%, severe 1%)</td>
</tr>
<tr>
<td></td>
<td>fistula (&lt;1%)(^6); requires treatment discontinuation</td>
</tr>
<tr>
<td></td>
<td><strong>gastrointestinal perforation</strong> (&lt;1%); see paragraph following Side Effects table</td>
</tr>
<tr>
<td></td>
<td><strong>intestinal obstruction</strong> (2%)(^2,9)</td>
</tr>
<tr>
<td></td>
<td>vomiting (20%)</td>
</tr>
</tbody>
</table>
**Gastrointestinal perforation** is rarely reported and may be fatal. Symptoms of GI perforation include; severe abdominal pain, vomiting, diarrhea, and fever or chills. Permanently discontinue ramucirumab following GI perforation.1

**Hemorrhage**, including gastrointestinal hemorrhage, is a reported complication of antiangiogenic therapy and may be fatal. Permanently discontinue ramucirumab in patients who experience grade 3 or 4 bleeding.2

**Hypertension** is a known effect of VEGF inhibition which, in most cases, can be managed with standard antihypertensive medication. Blood pressure should be controlled prior to starting treatment and monitored throughout therapy. Permanently discontinue ramucirumab for severe hypertension that cannot be managed with antihypertensive medication or if hypertensive crisis or hypertensive encephalopathy occurs.2,5

**Infusion reactions** are generally associated with the first or second ramucirumab infusion, and can occur during or after the infusion.12 Symptoms include: rigors, back pain, chest pain/tightness, chills, flushing, dyspnea, wheezing, and paresthesias. Severe cases can include bronchospasm, supraventricular tachycardia, and hypotension. Premedication with an intravenous histamine H1 antagonist such as diphenhydramine is recommended prior to infusion. Following grade 1-2 infusion reactions, the infusion rate should be reduced by 50% for the duration of the infusion, as well as for all subsequent infusions. In addition, premedication for subsequent infusions should include dexamethasone (or equivalent) and acetaminophen along with the histamine H1 antagonist. Permanently discontinue ramucirumab for any grade 3-4 infusion related reactions. Refer to BCCA Protocol SCDRUGRX Management of Hypersensitivity Reactions to Chemotherapeutic Agents.2,5

**Proteinuria** is reported with ramucirumab treatment. Baseline and routine dipstick urinalysis is recommended to monitor for the development or worsening of proteinuria during treatment. Based on urine protein levels, suspension of treatment or dose adjustment may be necessary. Permanently discontinue ramucirumab in patients developing nephrotic syndrome.2

**Reversible Posterior Leukoencephalopathy Syndrome (RPLS)** is rarely reported. Symptoms may include: headache, seizure, confusion, lethargy, and blindness, as well as other vision or neurologic disturbances. Symptoms may resolve or improve within days; however, some patients may experience ongoing neurologic sequelae or death. Permanently discontinue ramucirumab if diagnosis is confirmed.2,9

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**ORGAN SITE** | **SIDE EFFECT**
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General disorders and administration site conditions | Extravasation hazard: none17
Immune system | Infusion related reactions (1-16%)2,9; see paragraph following Side Effects table
Metabolism and nutrition | Hyponatremia (6%, severe 3%)
Nervous system | Headache (9%)
Reversible posterior leukoencephalopathy syndrome (<1%); see paragraph following Side Effects table
Renal and urinary | Proteinuria (3-17%, severe 1%); see paragraph following Side Effects table
Respiratory, thoracic and mediastinal | Epistaxis (5%)
Skin and subcutaneous tissue | Rash (4%)
Vascular | Hemorrhage (2-4%); see paragraph following Side Effects table
Hypertension (16%, severe 8%); see paragraph following Side Effects table

Adapted from standard reference2 unless specified otherwise.
INTERACTIONS: none known\[^{2,5}\]

SUPPLY AND STORAGE:

*Injection*: Eli Lilly Canada Inc. supplies ramucirumab as 100 mg and 500 mg single-use, preservative-free vials at a concentration of 10 mg/mL. Refrigerate. Protect from light. Do not freeze or shake.\[^{2}\]

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
- administer with a 0.22 micron filter\[^{2}\]
- use 0.9% sodium chloride solution for further dilution and flushing lines; do NOT use dextrose containing solutions (e.g., D5W)\[^{2}\]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

<table>
<thead>
<tr>
<th>Method</th>
<th>BCCA administration guideline noted in <strong>bold, italics</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous</td>
<td>no information found</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>no information found</td>
</tr>
<tr>
<td>Direct intravenous[^{2}]</td>
<td>do NOT use</td>
</tr>
<tr>
<td>Intermittent infusion[^{2}]</td>
<td>over 60 minutes; maximum infusion rate 25 mg/min</td>
</tr>
<tr>
<td>Continuous infusion</td>
<td>no information found</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>no information found</td>
</tr>
<tr>
<td>Intrapleural</td>
<td>no information found</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>no information found</td>
</tr>
<tr>
<td>Intra-arterial</td>
<td>no information found</td>
</tr>
<tr>
<td>Intravesical</td>
<td>no information found</td>
</tr>
</tbody>
</table>

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Dosage may be reduced, delayed or discontinued.

**Adults:**

**Cycle Length:**

**Intravenous:** \[^{2,5,13}\] 4 weeks \[^{2,5,13}\]: 8 mg/kg (range 5-8 mg/kg) IV for one dose on days 1 and 15 (total dose per cycle 16 mg/kg [range 10-16 mg/kg])
Ramucirumab

**BCCA usual dose noted in bold, italics**

**Cycle Length:**
- **2 weeks**: 8 mg/kg (range 5-8 mg/kg) IV for one dose on day 1 (total dose per cycle 8 mg/kg [range 5-8 mg/kg])
- **3 weeks**: 10 mg/kg (range 6-10 mg/kg) IV for one dose on day 1 (total dose per cycle 10 mg/m² [range 6-10 mg/kg])

**Concurrent radiation:** no information found

**Dosage in myelosuppression:** modify according to protocol by which patient is being treated; if no guidelines available, refer to Cancer Drug Manual Appendix "Dosage Modification for Myelosuppression"

**Dosage in renal failure:** no dose adjustment necessary

**Dosage in hepatic failure:**
- Mild or moderate impairment: no dose adjustment necessary
- Severe impairment: no information found regarding starting dose adjustment; however, clinical deterioration was observed in patients with Child-Pugh B or C cirrhosis

**Dosage in dialysis:** no information found

**Children:** no information found

**REFERENCES:**