DRUG NAME: Ramucirumab

SYNONYM(S): IMC-1121B[1]

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.[2,3] 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.[4,5]

PHARMACOKINETICS:

Distribution	similar to total blood volume	
	cross blood brain barrier?	no information found
	volume of distribution	5.5 L
	plasma protein binding	no information found
Metabolism	primary elimination pathway is likely receptor-mediated clearance[4]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	dose dependent elimination and nonlinear exposure consistent with saturable clearance[4]	
	urine	no information found
	feces	no information found
	terminal half life	15 days
	clearance	0.014 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Gastric cancer[2]

Other uses:
Colorectal cancer[5]
Lung cancer, non-small cell[5]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- preexisting ***hypertension*** should be controlled prior to starting treatment[2]
- increased risk of ***post-operative bleeding*** and ***wound healing complications***; consider holding ramucirumab before surgery and until surgical wounds are fully healed[2]

- 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]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (4%)[9]
	neutropenia (4-5%, severe 1%)[2,9]
	thrombocytopenia (4%, severe <1%)
cardiac	***arterial thromboembolic events*** including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia (2%)[2,9]; can be fatal
endocrine	hypothyroidism (1%)
gastrointestinal	*emetogenic potential: low*[10]
	diarrhea (14%, severe 1%)
	fistula (<1%)[6]; requires treatment discontinuation
	gastrointestinal perforation (<1%); see paragraph following **Side Effects** table
	intestinal obstruction (2%)[2,9]
	vomiting (20%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
general disorders and administration site conditions	*extravasation hazard: none*[11]
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%)[2,9]; see paragraph following **Side Effects** table
respiratory, thoracic and mediastinal	***epistaxis*** (5%)
skin and subcutaneous tissue	rash (4%)
vascular	***hemorrhage*** (2-4%)[9]; see paragraph following **Side Effects** table
	hypertension (16%, severe 8%)[2,9]; see paragraph following **Side Effects** table

Adapted from standard reference[2] unless specified otherwise.

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.[2]

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 H_1 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 H_1 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]

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:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous[2]	do NOT use
Intermittent infusion[2]	***over 60 minutes***; maximum infusion rate 25 mg/min
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	no information found

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*:**

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

	Cycle Length:	
Intravenous:	***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])

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

Cycle Length:
2 weeks[2,5]: 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[5]: 10 mg/kg (range 6-10 mg/kg) IV for one dose on day 1 (total dose per cycle 10 mg/m^2 [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[5]

Dosage in hepatic failure: mild or moderate impairment: no dose adjustment necessary[5]
severe impairment: no information found regarding starting dose adjustment; however, clinical deterioration was observed in patients with Child-Pugh B or C cirrhosis[5]

Dosage in dialysis: no information found

Children: no information found

REFERENCES:

1. Spratlin J. Ramucirumab (IMC-1121B): Monoclonal antibody inhibition of vascular endothelial growth factor receptor-2. Curr.Oncol.Rep. 2011;13(2):97-102.
2. Eli Lilly Canada Inc. CYRAMZA® product monograph. Toronto, Ontario; 16 July 2015.
3. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. The Lancet 2014;383(9911):31-39.
4. Spratlin J, Cohen RB, Eadens M, et al. Phase I pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010;28(5):780-787.
5. Eli Lilly and Company. CYRAMZA® product monograph. Indianapolis, Indiana, USA; October 2016.
6. Eli Lilly Canada Inc. CYRAMZA® product monograph. Toronto, Ontario; 26 January 2017.
7. Janine Davies MD. Personal communication. BC Cancer Agency Gastrointestinal Cancer Tumour Group; 25 January 2017.
8. Jackie Buston BScPharm. Personal communication. BC Cancer Agency Genitourinary Tumour Group; 17 Jan 2017.
9. Lexi-Drugs® (database on the Internet). Ramucirumab. Lexi-Comp Inc., 27 October 2016. Available at: http://online.lexi.com. Accessed 15 November 2016.
10. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 Mar 2012.
11. BC Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; January 2016.
12. AHFS Drug Information® (database on the Internet). Ramucirumab. Lexi-Comp Inc., 6 April 2016. Available at: http://online.lexi.com. Accessed 15 November 2016.
13. BC Cancer Agency Gastrointestinal Tumour Group. (UGIGAVRAMT) BCCA Protocol Summary for Second-Line Therapy for Metastatic or Locally Advanced Gastri or Gastroesophageal Junction Cancer Using Weekly PACLitaxel and Ramucirumab. Vancouver, British Columbia: BC Cancer Agency; 1 May 2017.