Drug Monograph

A - Drug Name

ramucirumab

SYNONYM(S): IMC-1121B

COMMON TRADE NAME(S): Cyramza® (Eli Lilly)

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B - Mechanism of Action and Pharmacokinetics

Ramucirumab is a VEGF2 receptor antagonist that blocks the binding of VEGF-A, VEGF-C and VGEF-D, thereby having an inhibitory effect on tumour angiogenesis.

Distribution		
Metabolism	No information found. Antibodies are generally cleared by catabolism.	
Elimination	Half-life	15 days

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C - Indications and Status

Health Canada Approvals:

For the treatment of advanced gastric cancer or gastro-esophageal junction adenocarcinoma, as a single agent or in combination with paclitaxel, with disease progression on or after prior platinum and fluoropyrimidine chemotherapy.

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D - Adverse Effects

Emetogenic Potential: Low

Extravasation Potential: None

The following adverse effects include those considered related to ramucirumab; incidence in combination with paclitaxel is presented where there appeared to be a clinically relevant increased incidence when compared to single-agent ramucirumab. Adverse effects likely related to paclitaxel are not reported.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (1.7%)	E
	Cardiotoxicity (rare)	E D
	Hypertension (16%) (8% severe; 15% severe with paclitaxel)	E
	Venous thromboembolism (2%)	E
Dermatological	Rash (4%) (11% with paclitaxel)	E
Gastrointestinal	Abdominal pain (29%)	E
	Diarrhea (14%) (32% with paclitaxel)	E
	GI perforation (2%)	
	Nausea, vomiting (<1%) (35% with paclitaxel)	E
General	Edema - limbs (<1%) (25% with paclitaxel)	E
	Fatigue (<1%) (57% with paclitaxel)	E
	Wound dehiscence (rare)	E
Hematological	Myelosuppression ± infection, bleeding (4%) (severe; 41% with paclitaxel)	E
Hepatobiliary	↑ LFTs (1%) (8% with paclitaxel; may be severe)	E
Hypersensitivity	Infusion related reaction (rare)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (6%) (decreased Na)	E
	Hypothyroidism (1%)	E
	Other (<1%) (Hypoalbuminemia; 11% with paclitaxel)	E
Nervous System	Headache (9%)	E
	PRES (rare)	E

Renal	Creatinine increased (<1%) (4% with paclitaxel)	E
	Proteinuria (3%) (17% with paclitaxel)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.
Dose-limiting side effects are underlined.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for ramucirumab include abdominal pain, hypertension, diarrhea, headache, abnormal electrolyte(s), myelosuppression ± infection, bleeding, rash, and proteinuria.

Severe **arterial thromboembolic** events as well as **congestive heart failure** have been reported with antiangiogenic drugs, including ramucirumab. Patients with an increased risk of coronary artery disease should be treated with caution.

Hypertension is common and may be severe. In most cases it is manageable with antihypertensive therapy. **Posterior reversible encephalopathy syndrome** (PRES) has been reported rarely. Ramucirumab should be discontinued if PRES is confirmed.

Severe **gastrointestinal hemorrhage** and fatal events were reported in patients with gastric cancer treated with combination therapy, and other cancers treated with monotherapy. **Gastrointestinal perforation** has also been reported.

There is increased risk of myelosuppression, including **severe neutropenia** in patients treated with combination therapy compared to paclitaxel alone. Patients should be closely monitored and treated, as indicated.

Ramucirumab can cause new or worsening encephalopathy, ascites or hepatorenal syndrome in patients with **Child-Pugh B or C cirrhosis**. Treat only if potential benefit outweighs the risk in these patients.

Infusion-related reactions generally occur during or following the first or second infusion. Patients should be monitored for signs and symptoms of hypersensitivity and ramucirimab discontinued in case of severe reactions.

Three percent of patients develop anti-ramucirumab antibodies, some of which are neutralising; the clinical significance is unclear.

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E - Dosing

Refer to protocol by which patient is being treated. Hold ramucirumab prior to elective surgery.

Pre-existing hypertension should be controlled before starting treatment.

Prior to dosing, the following should be met:

	Ramucirumab		Paclitaxel	
	Day 1	Day 15	Day 1	Day 8 or 15
Neutrophils			≥ 1.5 x 10^9/L	
Platelets			≥ 100 x 10^9/L	
Bilirubin & Creatinine			≤ 1.5 x ULN	≤ 1.5 x ULN
AST/ALT*			≤ 3 x ULN	≤ 3 x ULN
Drug related toxicity	≤ grade 1 or baseline (except hypertension, VTE and other toxicity in this table and below)			
Proteinuria	< 2 + or < 2g/24 hours			
* ≤ 5 x ULN with known liver metastases				

Adults:

Premedications for ramucirumab:

- diphenhydramine IV (or other IV histamine 1 antagonist)

For patients with previous grade 1 or 2 reaction, give the following premedications before each ramucirumab dose:

- diphenhydramine IV (or other IV histamine 1 antagonist)
- dexamethasone (or equivalent)
- acetaminophen

Consult the paclitaxel drug monograph and PACL(W)+RAMU regimen monograph for premedications for the combination.

Ramucirumab in combination with paclitaxel:

Intravenous: 8 mg/kg over 60 minutes on days 1 and 15 of 28 day cycle

with paclitaxel 80 mg/m^2 days 1, 8 and 15. Give ramucirumab BEFORE paclitaxel on days 1 and 15.

Ramucirumab single agent:

Intravenous: 8 mg/kg over 60 minutes Every 2 weeks

Dosage with Toxicity:

Dose level	Ramucirumab dose (mg/kg)
0	8
-1	6
-2	5

Toxicity	Severity	Ramucirumab dose
Infusion-related reactions	Grade 1 or 2	Reduce infusion rate by 50% and for all subsequent infusions.
	Grade 3 or 4	Discontinue
Hypertension	Grade 3 or 4	Hold until controlled with antihypertensive therapy. Discontinue if cannot be controlled.
Proteinuria	1st occurrence urine protein ≥ 2 g/24 hours	Hold* and restart at ↓ 1 dose level once urine protein < 2 g/24 hours.
	2nd occurrence urine protein ≥ 2 g/24 hours	Hold* and restart at ↓ 2 dose levels once urine protein < 2 g/24 hours.
	3rd occurrence OR urine protein > 3 g/24 hours OR nephrotic syndrome	Discontinue
Delayed wound healing	n/a	Hold prior to scheduled surgery until the wound is fully healed. Discontinue if wound healing complications arise.
Arterial thromboembolism Life-threatening VTE Bleeding	Grade 3 or 4	Discontinue

GI perforation PRES	Any	Discontinue

*In the clinical trial, doses were held up to 2 weeks. If urine protein does not return to < 2 g/24 hours, discontinue.

Dosage with Hepatic Impairment:

New onset or worsening ascites, encephalopathy or hepatorenal syndrome can occur in patients with Child-Pugh B or C cirrhosis. Treat only if potential benefit outweighs risk in these patients. No studies have been conducted for patients with hepatic impairment.

Dosage with Renal Impairment:

Population pharmacokinetic analysis suggests no dosage adjustment needed for mild to moderate renal impairment. No data available for patients with CrCl < 30 ml/min.

Dosage in the elderly:

No dose adjustment required. No overall differences in safety or effectiveness were observed between patients ≥65 years compared with younger patients.

Dosage based on ethnicity:

Higher incidences of neutropenia and proteinuria were reported in combination with paclitaxel in Asian patients compared to Caucasian patients.

Children:

Safety and effectiveness has not been established in pediatric patients.

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F - Administration Guidelines

- Administer as IV infusion only. DO NOT administer as IV push or bolus.
- Withdraw required volume and transfer into an empty IV container
- Dilute with normal saline, as required to desired volume. DO NOT use dextrose as a diluent.
- Gently invert container to mix. DO NOT shake.
- Give ramucirumab before administering paclitaxel when used in combination.
- Infuse IV over approximately 60 minutes (maximum rate 25 mg/min) using a separate infusion line, with a protein sparing 0.2 or 0.22 micron filter.
- Flush the line with normal saline at the end of the infusion.

• DO NOT dilute or co-administer with other electrolytes or medications.

• Refrigerate unopened vials in original carton (2-8°C). DO NOT freeze.

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G - Special Precautions

Contraindications:

- Hypersensitivity to ramucirumab or any of the components in the formulation

Other Warnings/Precautions:

- Treat only if potential benefit outweighs risk in patients with Child-Pugh Class B or C cirrhosis as clinical deterioration has been reported.
- Use with caution in patients with known or increased risk of coronary artery disease and/or those receiving cardiotoxic chemotherapy.
- Use with caution in patients at risk of bleeding, including those receiving concomittant antiplatelets and/or anticoagulants.
- Ramucirumab has not been evaluated in patients with serious or non-healing wounds and may impair healing. Withhold prior to surgey until the wound has fully healed.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unknown
- Embryotoxicity: Probable

Ramucirumab should not be used in pregnancy. Adequate contraception should be used by both sexes during treatment and at least for 3 months after the last dose.

- Excretion into breast milk: Unknown
  IgGs are secreted into breast milk. Breastfeeding is not recommended.
- Fertility effects: Probable
  Female fertility may be compromised based on animal studies.

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H - Interactions

No pharmacokinetics interactions were observed between ramucirumab and paclitaxel. No other drug-drug interaction studies have been performed.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Bisphosphonates, anti-angiogenic drugs	↑ risk of osteonecrosis of the jaw	Additive	Caution and monitor

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Blood pressure	Baseline and every 2 weeks, or more frequently as clinically indicated
CBC	Baseline and before each dose
Liver function tests	Baseline and before each dose
Urinalysis (for protein)	Baseline and before each cycle; if urine protein level is 2+ or higher, perform 24-hour urine collection (see dose modifications table under proteinuria)
Thyroid function tests	Baseline and every 2 to 3 cycles
Clinical toxicity assessment for infusion-related reactions, bleeding, infection, thromboembolism, cardiotoxicity, GI and neurologic effects, and impaired wound healing	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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K - References

Fuchs CS, Tomasek J, Yong CJ, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014 Jan 4;383(9911):31-9.

Product monograph Cyramza (ramucirumab). Eli Lilly Canada Inc. July 2015.

Ramucirumab: Drug information. Lexicomp Inc. 2015.

Wilke H, Muro K, Van Cutsem E, et al; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1224-35.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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