Drug Monograph

A - Drug Name

ramucirumab

COMMON TRADE NAME(S): Cyramza®

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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.

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:

- Gastric cancer
- Gastro-esophageal junction adenocarcinoma

Refer to the product monograph for a full list and details of approved indications.

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D - Adverse Effects

Emetogenic Potential: Minimal

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 (2%)	E
	Artery aneurysm (rare)	E
	Artery dissection (rare)	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
	Fistula (rare)	E
	Wound dehiscence (rare)	E
Hematological	Myelosuppression ± infection, bleeding (4%) (severe; 41% with paclitaxel)	E
	Thrombotic microangiopathy (rare)	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
	Posterior reversible encephalopathy syndrome (PRES) (rare)	E
Renal	Creatinine increased (<1%) (4% with paclitaxel)	E
	Proteinuria (3%) (17% with paclitaxel; may be severe)	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.

** 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. Symptoms may resolve or improve within days; however some patients experienced ongoing neurologic effects or fatal outcomes.

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 been reported and may be fatal; the risk may be increased with prior GI procedures (such as endoscopy) and diseases (such as diverticulitis). Ramucirumab may also increase the risk of **fistulas**.

There is increased risk of myelosuppression, including **severe neutropenia and thrombocytopenia** 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.

An increased incidence of **proteinuria**, including **nephrotic syndrome** has been reported and is more frequent in Asian 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 ramucirumab discontinued in case of severe reactions.

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

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Hold ramucirumab for at least 4 weeks prior to elective surgery until the wound is fully healed.

Pre-existing hypertension should be controlled before starting treatment.

Premedications (prophylaxis for infusion reactions):

- H1-receptor antagonist IV (e.g. diphenhydramine)

For patients who experienced a grade 1 or 2 infusion reaction:

- H1-receptor antagonist IV (e.g. diphenhydramine)
- Dexamethasone IV (or equivalent)
- Acetaminophen

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

Adults:

Single agent:

Intravenous: 8 mg/kg every 2 weeks

Combination therapy:

Refer to the related regimen monographs for details.

Dosage with Toxicity:

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

Toxicity	Severity	Ramucirumab dose
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	
	3rd occurrence OR urine protein > 3 g/24 hours OR nephrotic syndrome	Discontinue
Delayed wound healing	n/a	Hold for at least 4 weeks prior to scheduled surgery until the wound is fully healed. Discontinue if wound healing complications arise.
Cardiac failure	Any	Consider hold. Discontinue if severe or as clinically indicated.
Arterial thromboembolism Life-threatening VTE Bleeding	Grade 3 or 4	Discontinue
GI perforation Fistula PRES	Any	Discontinue
Other non-hematologic toxicity	Grade 4	Discontinue

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

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • Slow the rate to 50% of the original rate at which the IR occurred for the remainder of the infusion.	• Consider re-challenge pre-medications (H1-receptor antagonist, dexamethasone and acetaminophen) and reduce administration rate by 50% at which the IR occurred.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

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 proteinuria and nephrotic syndrome were reported in Asian patients living in East Asia compared to Caucasian patients.

Children:

Safety and effectiveness have 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 to a total volume of 250 mL. 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 0.22 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). Protect from light and DO NOT freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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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 concomitant antiplatelets and/or anticoagulants.
- Ramucirumab has not been evaluated in patients with serious or non-healing wounds and may impair healing. Withhold prior to surgery until the wound has fully healed.
- Use with caution in patients with risk factors for GI perforation, including intra-abdominal metastases, inflammatory bowel disease, diverticulitis, ischemic bowel, peptic ulcers, obstruction and injury from endoscopy and surgery.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Genotoxicity: Unknown
- Embryotoxicity: Probable
  Ramucirumab is not recommended for use 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 during treatment and for at least **3 months** after the last dose.
- 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

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

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. Continue after treatment as indicated (thyroid dysfunction may persist)
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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J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Ramucirumab - Advanced or Metastatic Gastric Cancer or Gastroesophageal Junction Adenocarcinoma

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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., June 2022.

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.

March 2023 Modified Adverse Effects and Dosage with Toxicity sections

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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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