Regimen Monograph

A - Regimen Name

RAMU Regimen

Ramucirumab

Disease Site

Gastrointestinal
- Esophagus
- Gastric / Stomach

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior platinum and fluoropyrimidine chemotherapy.

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B - Drug Regimen

ramucirumab	8 mg /kg	IV	Day 1

(This drug is not currently publicly funded for this regimen and intent)

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C - Cycle Frequency

REPEAT EVERY 14 DAYS

Until disease progression or unacceptable toxicity occurs

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

- Also refer to CCO Antiemetic Recommendations.

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

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

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

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).

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.

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 grade 3 proteinuria and nephrotic syndrome were reported in Asian patients living in East Asia compared to Caucasian patients.

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F - Adverse Effects

Refer to ramucirumab drug monograph(s) for additional details of adverse effects

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Abdominal pain	• Hypertension (may be severe) • Diarrhea	• Arterial thromboembolism • Venous thromboembolism • Cardiotoxicity • Arterial aneurysm • Arterial dissection • Thrombotic microangiopathy • GI perforation • Fistula • Infusion-related reactions • Myelosuppression ± infection, bleeding • Increased LFTs • Increased creatinine • Proteinuria, nephrotic syndrome

		• Hypothyroidism (not usually severe) • PRES • Delayed wound healing

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G - Interactions

Refer to ramucirumab drug monograph(s) for additional details

- Use with caution and monitor with other anti-angiogenic drugs and bisphosphonates; risk of ONJ may be increased.

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H - Drug Administration and Special Precautions

Refer to ramucirumab drug monograph(s) for additional details

Administration:

- 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.
- 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.

Contraindications:

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

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.

Pregnancy/Lactation:

- 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.
- 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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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

- 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
- Thyroid function tests; Baseline and every 2 to 3 cycles. Continue after treatment as indicated (thyroid dysfunction may persist).

- 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)
- 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 - Administrative Information

Approximate Patient Visit	1.5 hours
Pharmacy Workload (average time per visit)	19.600 minutes
Nursing Workload (average time per visit)	42.417 minutes

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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.

Ramucirumab drug monograph, Ontario Health (Cancer Care Ontario).

PEBC Advice Documents or Guidelines

- Systemic Therapy for Advanced Gastric and Gastro-Esophageal Carcinoma

March 2023 Modified Dosage with toxicity and Adverse effects sections

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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