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Ramucirumab: Drug information

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(For additional information see "Ramucirumab: Patient drug information")

For abbreviations and symbols that may be used in Lexicomp (show table)

ALERT: US Boxed Warning

Hemorrhage:

Ramucirumab increased the risk of hemorrhage and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue ramucirumab in patients who experience severe bleeding.

Gastrointestinal perforation:

Ramucirumab can increase the risk of gastrointestinal perforation, a potentially fatal event. Permanently discontinue ramucirumab in patients who experience a gastrointestinal perforation.

Wound healing impairment:

Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue ramucirumab therapy in patients with impaired wound healing. Withhold ramucirumab prior to surgery and discontinue ramucirumab if a patient develops wound healing complications.

Brand Names: US

Cyramza

Brand Names: Canada

Cyramza

Pharmacologic Category

Antineoplastic Agent, Monoclonal Antibody; Antineoplastic Agent, Vascular Endothelial Growth Factor (VEGF) Inhibitor; Antineoplastic Agent, Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) Inhibitor

Dosing: Adult

Note: Premedicate prior to infusion with an IV H_1 antagonist (for patients who experienced a grade 1 or 2 infusion reaction with a prior infusion, also premedicate with dexamethasone or equivalent and acetaminophen).

Colorectal cancer, metastatic: IV: 8 mg/kg every 2 weeks in combination with FOLFIRI (irinotecan, leucovorin, and fluorouracil); continue until disease progression or unacceptable toxicity.

Gastric cancer, advanced or metastatic: IV: 8 mg/kg every 2 weeks as a single agent or in combination with paclitaxel; continue until disease progression or unacceptable toxicity.

Non-small cell lung cancer, metastatic: IV: 10 mg/kg on day 1 every 21 days in combination with docetaxel; continue until disease progression or unacceptable toxicity

Dosing: Geriatric

Refer to adult dosing.

Dosing: Renal Impairment

No dosage adjustment necessary.

Dosing: Hepatic Impairment

Mild impairment (normal bilirubin with AST > ULN **or** total bilirubin >1 to 1.5 times ULN and any AST): No dosage adjustment necessary.

Moderate impairment (total bilirubin >1.5 to 3 times ULN and any AST): No dosage adjustment necessary.

Severe impairment (total bilirubin >3 times ULN and any AST): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). Use in patients with Child-Pugh class B or C cirrhosis only if the potential benefits outweigh the potential risks.

Dosing: Adjustment for Toxicity

Infusion-related reaction:

Grade 1 or 2: Reduce infusion rate by 50%

Grade 3 or 4: Permanently discontinue

Hypertension:

Severe hypertension: Interrupt infusion until controlled with medical management

Severe hypertension, uncontrolled: Permanently discontinue

Proteinuria:

Urine protein ≥2 g/24 hours (first dose reduction): Withhold treatment; when urine protein returns to <2 g/24 hours, reinitiate at a reduced dose of 6 mg/kg (if initial dose was 8 mg/kg) or 8 mg/kg (if initial dose was 10 mg/kg)

Recurrent urine protein ≥2 g/24 hours (second dose reduction): Withhold treatment; when urine protein returns to <2 g/24 hours, reinitiate at a reduced dose of 5 mg/kg (if first dose reduction was to 6 mg/kg) or 6 mg/kg (if first dose reduction was to 8 mg/kg)

Urine protein >3 g/24 hours: Discontinue permanently

Nephrotic syndrome: Discontinue permanently

Arterial thrombotic events: Discontinue permanently

Bleeding, grade 3 or 4: Discontinue permanently

Gastrointestinal perforation: Discontinue permanently

Reversible posterior leukoencephalopathy syndrome (RPLS): Discontinue permanently for confirmed

diagnosis

Wound healing complications: Withhold treatment prior to surgery; do not reinitiate until the surgical wound is fully healed. If wound healing complications develop during treatment, withhold ramucirumab until the wound is fully healed.

Dosage Forms Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Solution, Intravenous [preservative free]:

Cyramza: 100 mg/10 mL (10 mL); 500 mg/50 mL (50 mL) [contains polysorbate 80]

Generic Equivalent Available (US) No

Administration Premedicate prior to infusion with an IV H_1 antagonist; for patients who experienced a grade 1 or 2 infusion reaction with a prior infusion, also premedicate with dexamethasone (or equivalent) and acetaminophen.

Infuse over 60 minutes through a separate infusion line using an infusion pump; the use of a 0.22 micron protein sparing filter is recommended. Do not administer as an IV push or bolus. Flush the line with NS after infusion is complete. Do not infuse in the same IV line with electrolytes or other medications. Administer ramucirumab prior to docetaxel, paclitaxel, or FOLFIRI if administering in combination. Monitor for infusion reaction; reduce infusion rate (by 50%) for grade 1 or 2 infusion reaction; discontinue permanently for grade 3 or 4 infusion reaction.

Use

Colorectal cancer, metastatic: Treatment (in combination with FOLFIRI [irinotecan, leucovorin, and fluorouracil]) of metastatic colorectal cancer (mCRC) in patients with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.

Gastric cancer, advanced or metastatic: Treatment (single-agent or in combination with paclitaxel) of advanced or metastatic gastric or gastroesophageal junction adenocarcinoma in patients with disease progression on or following fluoropyrimidine- or platinum-containing chemotherapy

Non-small cell lung cancer, metastatic: Treatment (in combination with docetaxel) of metastatic non-small cell lung cancer (NSCLC) in patients with disease progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab.

Medication Safety Issues

Sound-alike/look-alike issues:

Cyramza may be confused with Cimzia

Ramucirumab may be confused with ranibizumab, rituximab, regorafenib

Adverse Reactions As reported with monotherapy. Frequency not always defined.

Cardiovascular: Hypertension (16%; grades 3/4: 8%), arterial thrombosis (including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia; 2%)

Central nervous system: Headache (9%)

Dermatologic: Skin rash (4%)

Endocrine & metabolic: Hyponatremia (6%)

Gastrointestinal: Diarrhea (14%), intestinal obstruction (2%)

Genitourinary: Proteinuria (8% to 17%; grade ≥3: 1%)

Hematologic & oncologic: Decreased red blood cells (requiring transfusion; 11%), neutropenia (5%), anemia (4%), hemorrhage (2% to 4%)

Immunologic: Antibody development (3%; neutralizing: 1%)

Respiratory: Epistaxis (5%)

Miscellaneous: Infusion related reaction (≤16%; reactions minimized with premedications)

<1% and frequency not defined: Gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome

Contraindications

There are no contraindications listed in the manufacturer's US labeling.

Canadian labeling: Hypersensitivity to ramucirumab or any component of the formulation.

Warnings/Precautions

Concerns related to adverse effects:

• Arterial thrombotic events: Serious and fatal arterial thrombotic events, including MI, cardiac arrest, cerebrovascular accident, and cerebral ischemia, have occurred with ramucirumab. Discontinue permanently in patients who experience serious arterial thrombotic events.

• Bone marrow suppression: A higher incidence of neutropenia and thrombocytopenia were observed when ramucirumab was used in combination with paclitaxel (compared to paclitaxel with placebo); monitor CBC with differential when used in combination with paclitaxel.

• Gastrointestinal perforation: **[US Boxed Warning]: Ramucirumab may increase the risk of gastrointestinal perforation, a potentially fatal event. Discontinue permanently in patients who experience a gastrointestinal perforation.**

• Hemorrhage: **[US Boxed Warning]: Ramucirumab is associated with an increased risk of hemorrhage and gastrointestinal hemorrhage, which may be severe or sometimes fatal. Discontinue ramucirumab permanently in patients who experience serious bleeding.** Patients receiving NSAIDs were excluded from some clinical trials; the risk of gastric hemorrhage in patients

with gastric tumors receiving NSAIDs is not known. In addition, NSCLC patients receiving therapeutic anticoagulation or chronic NSAID or other antiplatelet therapy (other than aspirin), or with radiograph evidence of major airway or blood vessel involvement or intratumor cavitation were also excluded from the clinical study; the risk of pulmonary hemorrhage in such patients is not known.

• Hypertension: May cause and/or worsen hypertension; the incidence of severe hypertension is increased with ramucirumab. Blood pressure (BP) should be controlled prior to treatment initiation. Monitor BP every 2 weeks (more frequently if indicated) during treatment. If severe hypertension occurs, temporarily withhold until medically controlled. Discontinue permanently if medically significant hypertension cannot be controlled with antihypertensive therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

• Infusion reaction: Ramucirumab is associated with infusion-related reactions (may be severe), generally occurring with the first or second dose. Symptoms of infusion reactions have included chills, flushing, hypotension, bronchospasm, dyspnea, hypoxia, wheezing, chest pain/tightness, supraventricular tachycardia, back pain/spasms, rigors/tremors, and/or paresthesia. Monitor for infusion reaction symptoms during infusion; discontinue immediately and permanently for grade 3 or 4 infusion reactions. Administer in a facility equipped to manage infusion reactions.

• Proteinuria/nephrotic syndrome: Ramucirumab is associated with proteinuria (may be severe). Monitor proteinuria during treatment by urine dipstick and/or urinary protein creatinine ratio for the development of and/or worsening of proteinuria. Withhold treatment for urine protein levels ≥2 g/24 hours. Discontinue permanently for urine protein >3 g/24 hours or for nephrotic syndrome.

• Reversible posterior leukoencephalopathy syndrome: Cases of reversible posterior leukoencephalopathy syndrome (RPLS) have been reported (may be fatal). Symptoms of RPLS include headache, seizure, confusion, lethargy, blindness and/or other vision, or neurologic disturbances. Confirm diagnosis of RPLS with MRI; discontinue ramucirumab with confirmed RPLS diagnosis. Resolution of symptoms may occur within days after discontinuation, although neurologic sequelae may remain in some patients.

• Thyroid dysfunction: Hypothyroidism has been observed. Monitor thyroid function during treatment.

• Wound healing impairment: **[US Boxed Warning]: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue ramucirumab in patients with impaired wound healing. Withhold ramucirumab prior to surgery and discontinue in patients who develop wound healing complications.** Following surgery, use clinical judgment to resume based on adequate wound healing. If wound healing complications develop during treatment, withhold ramucirumab until wound is fully healed. Ramucirumab was not studied in patients with serious or nonhealing wounds.

Disease-related concerns:

• Cardiovascular disease: Antiangiogenic medications may increase the risk for heart failure (HF); events consistent with HF have been reported with ramucirumab. Use with caution in patients with known (or at risk of) coronary artery disease. Ramucirumab may enhance the cardiotoxicity of other chemotherapy with cardiotoxic potential (Cyramza Canadian labeling 2015).

• Hepatic impairment: Clinical deterioration, including new onset or worsening encephalopathy, ascites, or hepatorenal syndrome has been reported in patients with Child-Pugh class B or C

cirrhosis receiving ramucirumab. Use in patients with Child-Pugh class B or C cirrhosis only if the potential benefits outweigh the potential risks.

Metabolism/Transport Effects

None known.

Drug Interactions

(For additional information: Launch drug interactions program) Lexicomp®

Belimumab: Monoclonal Antibodies may enhance the adverse/toxic effect of Belimumab. *Risk X: Avoid combination*

Bisphosphonate Derivatives: Systemic Angiogenesis Inhibitors may enhance the adverse/toxic effect of Bisphosphonate Derivatives. Specifically, the risk for osteonecrosis of the jaw may be increased. *Risk C: Monitor therapy*

Pregnancy Implications

Ramucirumab inhibits angiogenesis, which is of critical importance to human fetal development. Based on the mechanism of action, ramucirumab may cause fetal harm if administered during pregnancy. Women of reproductive potential should use effective contraception during and for at least 3 months after the last ramucirumab dose. Ramucirumab may impair fertility in women.

Breast-Feeding Considerations

It is not known if ramucirumab is excreted in breast milk. Immunoglobulins are excreted in breast milk, and it is assumed that ramucirumab may appear in breast milk. Due to the potential for serious adverse reactions in the nursing infant, breast-feeding is not recommended by the manufacturer.

Monitoring Parameters

Liver function tests; urine protein (by urine dipstick and/or urinary protein creatinine ratio); thyroid function; CBC with differential (when used as a part of combination chemotherapy); blood pressure (every 2 weeks; more frequently if indicated); signs/symptoms of infusion-related reactions (during infusion); signs/symptoms of arterial thromboembolic events, bleeding/hemorrhage, gastrointestinal perforation, wound healing impairment, and reversible posterior leukoencephalopathy syndrome

Mechanism of Action

Ramucirumab is a recombinant monoclonal antibody which inhibits vascular endothelial growth factor receptor 2 (VEGFR2). Ramucirumab has a high affinity for VEGFR2 (Spratlin, 2010), binding to it and blocking binding of VEGFR ligands, VEGF-A, VEGF-C, and VEGF-D to inhibit activation of VEGFR2, thereby inhibiting ligand-induced proliferation and migration of endothelial cells. VEGFR2 inhibition results in reduced tumor vascularity and growth (Fuchs, 2014).

Pharmacodynamics/Kinetics

Half-life elimination: 14 days

Pricing: US

Solution (Cyramza Intravenous)

100 mg/10 mL (10 mL): $1298.96

500 mg/50 mL (50 mL): $6494.82

Disclaimer: The pricing data provide a representative AWP and/or AAWP price from a single manufacturer of the brand and/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing

functions. Pricing data is updated monthly.

International Brand Names Cyramza (AT, AU, CY, CZ, DE, DK, EE, ES, FR, GB, HK, HR, HU, IL, JP, KR, LT, LU, NO, PL, PT, RO, SE, SG, SI, SK)

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