Ramucirumab (Cyramza®)

Criteria for Use

June 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive ramucirumab.*

☐ Unwilling to transfer hematology/oncology care to VA provider
☐ Patient with history of non-adherence with follow-up appointments or laboratory visits
☐ Non-healing wound or fracture
☐ Major surgery within prior 28 days
☐ Chronic anti-platelet therapy, NSAIDs (including aspirin ≥ 325mg/day); these drugs can affect platelet function and put patient at increased risk of bleeding, especially if concomitant marrow-suppressive chemotherapy causes thrombocytopenia; some may also cause GI irritation leading to ulcers/inflammation and potentially increase risk of GI perforation
☐ Therapeutic anticoagulation, unless on stabilized outpatient doses (see Issues for Consideration)
☐ CNS metastases
☐ Pre-existing bleeding diathesis or coagulopathy
☐ History of GI perforation and/or fistulae within prior 6 months
☐ History of gross hemoptysis (defined as bright red blood or ≥1/2 teaspoon) within 2 months of therapy initiation
☐ Patients with tumor involving major blood vessels or intratumor cavitation.
☐ Unstable cardiac condition, which may/may not include the following:
- Major cardiovascular event within previous 12 months (examples: uncontrolled HTN, MI, unstable angina, serious cardiac arrhythmia requiring medication, peripheral and arterial ischemic events)
- Uncontrolled NYHA grade II or greater CHF if patient has a history of prior anthracycline exposure or prior radiotherapy to the chest wall

☐ Chronic or unresolved infection
☐ Pregnancy
☐ Renal impairment defined as CrCl < 40 ml/min (drug has not been studied in this setting)
☐ Pre-existing proteinuria (≥ 2 g urine protein/24 hrs)
☐ AST (SGOT) or ALT (SGPT) ≥ 3.0x ULN [or 5.0x ULN in setting of liver metastases] or bilirubin > 1.5x ULN (see Issues for Consideration)
☐ Absolute Neutrophil Count (ANC) < 1000 cells/µL, hemoglobin < 9 g/dL and/or platelet count < 100,000 cells/µL

Inclusion Criteria ***One*** *of the following must be fulfilled in order to meet criteria.*

☐ Diagnosis of advanced or metastatic Gastric or Gastro-esophageal Junction (GEJ) adenocarcinoma
WITH disease progression on prior fluoropyrimidine- or platinum-containing chemotherapy
AND is not amenable to potentially curative resection
[fluoropyrimidines include fluorouracil, capecitabine; platinum agents include cisplatin, carboplatin, oxaliplatin]

☐ Diagnosis of metastatic Non-Small Cell Lung Cancer (NSCLC) in combination with docetaxel in patients less than 65 years of age
WITH disease progression on prior platinum-based chemotherapy (for patients over 65 years old, see Issues for Consideration)
[EGFR+ or ALK+ disease should have also progressed on FDA-approved therapies prior to receiving ramucirumab]

☐ Diagnosis of metastatic colorectal cancer in combination with FOLFIRI (fluorouracil, leucovorin, irinotecan)
WITH disease progression on prior first-line therapy with bevacizumab, oxaliplatin and a fluoropyrimidine

AND

☐ Goals of care and role of Palliative Care consult have been discussed and documented.

☐ ECOG Performance Status 0 – 1^

For women of childbearing potential

□ Pregnancy should be excluded prior to receiving ramucirumab and the patient provided contraceptive counseling on potential risk vs. benefit of taking ramucirumab if patient were to become pregnant; effective contraception should be used during treatment and for at least 3 months after the last dose of ramucirumab

Dosage and Administration *Refer to PI for Dose Modifications, Preparation for Administration and Administration*

Premedication to be given prior to each ramucirumab dose:

- Patients should receive an intravenous H_1 antagonist (e.g. diphenhydramine HCl)
- For patients who experienced a Gr 1 or 2 infusion-related reaction, also give dexamethasone (or equivalent) and acetaminophen prior to subsequent infusions

Gastric or GEJ Adenocarcinoma

- Ramucirumab can be given as a single-agent or in combination with weekly paclitaxel
- Ramucirumab 8 mg/kg IV over 60 minutes given every 2 weeks until disease progression or unacceptable toxicity
- Administer ramucirumab PRIOR to paclitaxel, if given in combination
- Refer to Prescribing Information for recommended Dose Modifications for toxicities.

NSCLC

- Ramucirumab 10 mg/kg IV over 60 minutes given on day 1 of a 21-day cycle until disease progression or toxicity
- Administer ramucirumab PRIOR to docetaxel

Metastatic Colorectal Cancer

- Ramucirumab 8 mg/kg IV over 60 minutes given every 2 weeks until disease progression or toxicity.
- Administer ramucirumab PRIOR to FOLFIRI administration

Monitoring

- Monitor for infusion-related reactions; permanently discontinue ramucirumab for Grade 3 or 4 events.
- Blood pressure should be monitored at baseline and then every 2 weeks or more frequently, as clinically indicated. Those who develop hypertension or worsening of existing HTN may require more frequent monitoring. Antihypertensives may be needed. Ramucirumab should be discontinued in patients with hypertensive crises.
- Check urinalysis or urine dipstick for protein at least on a monthly basis. If urine protein $\geq$ 2 g/24 hrs, interrupt therapy until proteinuria < 2 g/24 hrs. If protein level $\geq$ 2 g/24 hrs again, interrupt ramucirumab and reduce the dose once the level < 2 g/24 hrs (see Dose Modifications). Ramucirumab should be discontinued in patients with urine protein > 3 g/24 hrs or in setting of nephrotic syndrome
- Withhold ramucirumab prior to surgery; resume therapy based on clinical judgment of adequate wound healing.
- Monitor for bleeding and/or bruising. Ramucirumab should be discontinued in patients with grades 3 / 4 bleeding (defined as requiring transfusion and/or other interventional procedure for hemostasis and catastrophic bleeding).
- Monitor for venous and/or arterial thromboembolic events
- Monitor CBC, differential at baseline and prior to each cycle.
- Monitor LFTs at baseline and periodically throughout treatment
- Fever and signs/symptoms of infection
- New onset or worsening encephalopathy, ascites or hepatorenal syndrome (see Issues for Consideration)
- Thyroid function during treatment. Incidence of hypothyroidism in mCRC was 2.6% among those receiving ramucirumab.

Issues for Consideration

- An exploratory subgroup analysis of the REVEL trial noted that the hazard ratio for overall survival in patients ≤ 65 years old was 0.75 (95% CI: 0.62, 0.87) while in patients ≥ 65 years, the hazard ratio was 1.10 (95% CI: 0.89, 1.36). Of note, the data was obtained in an exploratory fashion that was not a prespecified finding. Safety findings of REVEL note that there were 18 (8%) deaths in the age ≥ 65-years population on treatment or within 30 days of discontinuation of ramucirumab + docetaxel compared to 9 (4%) deaths in the placebo + docetaxel arm. For those under age 65 years, there were 13 (3%) deaths on treatment within 30 days of discontinuation of ramucirumab + docetaxel vs. 26 (6%) in the placebo + docetaxel arm. Use of ramucirumab in patients ≥ 65 years of age can be considered in those patients with good functional status and adjudicated locally, on a case-by-case basis.
- Clinical deterioration, noted by new onset or worsening encephalopathy, ascites or hepatorenal syndrome, was reported in patients with moderate-severe hepatic impairment (Child-Pugh B or C) who received single-agent ramucirumab. Use with caution and only if the potential benefits of treatment are felt to outweigh the risks.
- Anticoagulation. Patients on full-dose anticoagulation must be on a stable dose (minimum duration 14 days) of oral anticoagulant or low molecular weight heparin and no active bleeding or pathologic condition that carries a high bleed risk (e.g. tumor involving major vessels or known varices).

Discontinuation Recommendations

- Non-adherence with therapy, laboratory or follow-up requests
- Decline in ECOG performance status to level unacceptable for patient to maintain quality of life
- Evidence of disease response or progression (via radiographic scan or symptomatology)
- Unmanageable or severe toxicity, as specified under Monitoring

^ http://www.ecog.org/general/perf_stat.html

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