

Regorafenib (Stivarga®)**Criteria for Use****July 2013**

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://vawww.pbm.va.gov> for further information.

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

- History of non-compliance or inability to swallow oral medications
- Known malabsorption condition
- History of non-compliance with laboratory monitoring
- Refuses to transfer oncology care to VA oncologist
- Cardiac conditions that include any of the following:
 - Congestive Heart Failure NYHA class 2 or worse
 - Unstable angina, new-onset angina begun with the last 3 months; Recent MI (within the past 6 months).
 - Arrhythmias requiring anti-arrhythmic therapy (beta blockers and digoxin permitted)
 - Uncontrolled hypertension
 - Recent (defined as within the past 6 months) arterial or venous thromboembolic events (i.e. CVA, TIA, DVT, PE)
- Pre-existing bleeding diathesis or coagulopathy
- Major surgical procedure within prior 28 days, non-healing wound, ulcer or bone fracture
- Hypersensitivity to regorafenib

Inclusion Criteria

- Goals of care and role of Palliative Care consult has been discussed and documented
- Life expectancy \geq 3 months
- ECOG Performance Status 0 or 1
- Adequate baseline bone marrow, liver and renal function defined as the following. ULN is defined as local laboratory range for parameter.
 - Total bilirubin \leq 1.5 x ULN
 - ALT and AST \leq 2x ULN (\leq 5x ULN if due to liver involvement of the cancer)
 - Alk phos \leq 2.5x ULN (\leq 5x ULN if due to liver involvement of the cancer)
 - Amylase and lipase \leq 1.5x ULN
 - GFR $>$ 30 ml/min/1.73 m²
 - Platelet count \geq 100,000/mm³, hemoglobin $>$ 9 g/dl, ANC $>$ 1500/mm³
- Patient with diagnosis of **metastatic colorectal cancer** AND (all of the following sub-criterion must be met)
 - Received prior treatment or is not a candidate to receive a fluoropyrimidine-based regimen
 - Received prior treatment or is not a candidate to receive an oxaliplatin-based regimen
 - Received prior treatment or is not a candidate to receive an irinotecan-based regimen
 - Received prior treatment or is not a candidate to receive an anti-VEGF agent (i.e. bevacizumab or ziv-aflibercept)
 - If KRAS wild type, received an anti-EGFR agent (i.e. cetuximab or panitumumab)
- Patient with diagnosis of locally advanced, unresectable or metastatic **gastrointestinal stromal tumor** AND (all of the following sub-criterion must be met)
 - Received prior treatment with imatinib mesylate for at least 6 months (see Issues for Consideration)
 - Received prior treatment with sunitinib malate
- For women of childbearing potential and their partners:
 - Pregnancy should be excluded prior to receiving regorafenib and the patient provided contraceptive counseling on potential risk vs.

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benefit of taking regorafenib if patient were to become pregnant

Effective contraception should be used by both men and women during regorafenib treatment and for up to 2 months after its completion

Dosage and Administration

- Dose: regorafenib 160 mg (4 x 40 mg tablets) orally once daily for 21 days followed by a 7-day rest period; each cycle is 28 days
- Take each regorafenib dose at the same time daily with a low-fat meal (contains < 30% fat)
- Regorafenib tablets should be stored at room temperature in their original bottle with desiccant and should NOT be transferred to a pill box
- Tablets not used within 28 days of opening the original bottle should be discarded
- Dose modify or interrupt per prescribing information for the following: Hand-Foot Skin Reaction/PPE, symptomatic HTN, AST/ALT elevation or any grade 3 or 4 adverse reaction

Monitoring

- Assess toxicity prior to dispense of each 28-day cycle
- Assess response via radiologic assessment in conjunction with RECIST*, version 1.1 every 8 weeks (2 cycles)
- Hepatic function (AST, ALT bilirubin) should be monitored at least every 2 weeks during the first 2 months of therapy, then continue on a monthly or more frequent basis, if needed; Patients with elevated LFT's should be monitored weekly until lab parameters have improved to less than 3x ULN or baseline level
- INR should be monitored more frequently in patients receiving warfarin
- Dermatologic symptoms may be noted during the first cycle of treatment and should be managed as directed in prescribing information
- BP should be monitored weekly for the first 6 weeks of treatment, then with every cycle unless needed more frequently; withhold doses in cases of severe/uncontrolled HTN as directed in prescribing information

Issues for Consideration

The PFS benefit was not recognized among patients who received imatinib treatment for less than 6 months.

Hepatotoxicity

- Risk of hepatotoxicity is a boxed warning; monitor liver function prior to and throughout treatment; doses should be interrupted, reduced or discontinued based upon monitoring

Drug-drug and drug-food interactions

- Avoid strong CYP3A4 inducers or inhibitors as they may affect the exposure of regorafenib and its active metabolites
- Avoid taking St. John's Wort
- Avoid grapefruit juice

Discontinuation Criteria (any of the following)

- Evidence of disease progression via radiologic assessment in conjunction with RECIST*, version 1.1 every 8 weeks (2 cycles)
- ECOG performance status worsens from ECOG PS 0 or 1 to ECOG PS 2, 3 or 4 (assessed prior to each cycle)
- Unacceptable toxicity (assessed prior to each cycle)

*RECIST = Response Evaluation Criteria in Solid Tumors

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