regorafenib (Stivarga®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO150

Description

Regorafenib (Stivarga) is an orally administered kinase inhibitor acting on various membrane-bound and intracellular kinases.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
regorafenib (Stivarga)	40 mg tablets	Gastrointestinal stromal tumor, locally advanced, unresectable or metastatic disease after treatment with imatinib and sunitinib; Colorectal cancer, metastatic, previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy, an anti-VEGF therapy, and if RAS wild type an anti-EGFR therapy; Hepatocellular (liver) carcinoma, previously treated with sorafenib	84 tablets/28 days

Initial Evaluation

I. Regorafenib (Stivarga) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Not used in combination with any other oncolytic medication (i.e., used as monotherapy); **AND**
   D. A diagnosis of one of the following:
      1. **Colorectal Cancer**; **AND**
         i. The member has metastatic (stage IV) disease; **AND**
         ii. The member has previously progressed on or after a fluoropyrimidine [e.g., capecitabine, fluorouracil (5-FU)], oxaliplatin, AND irinotecan-containing chemotherapy; **AND**
         iii. The member has previously progressed on or after an anti-VEGF therapy [e.g., bevacizumab (Avastin)]; **AND**
         iv. The member is KRAS-mutated; **OR**

a. If KRAS wild-type, the member has been treated with an anti-EGFR therapy [e.g., cetuximab (Erbitux), panitumumab (Vectibix)]; **OR**

2. **Gastrointestinal Stromal Tumor**; **AND**
   i. The member has locally advanced (stage III), unresectable or metastatic (stage IV) disease; **AND**
   ii. The member has previously progressed on or after imatinib (Gleevec) AND sunitinib (Sutent); **OR**
3. **Hepatocellular Carcinoma; AND**
   i. The member has previously progressed on or after sorafenib (Nexavar)

II. Regorafenib (Stivarga) is considered investigational when used for all other conditions, including but not limited to:
   A. Biliary cancer, cholangiocarcinoma
   B. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
   C. Non-small cell lung cancer
   D. Renal cell carcinoma
   E. Soft tissue sarcoma
   F. Adenoid cystic carcinoma
   G. Urothelial carcinoma
   H. Ovarian cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
IV. Regorafenib (Stivarga) will not be used in combination with other oncolytic medications (i.e., will be used as monotherapy); **AND**
V. Documentation of clinical response to therapy, such as stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. Regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled study in adults with metastatic colorectal cancer after failure of standard therapy. The trial included 760 subjects that had been previously treated with fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy, as well as bevacizumab (Avastin). All but one subject with KRAS wild-type disease received ANTI-EGFR therapy [cetuximab (Erbitux), panitumumab (Vectibix)]. Regorafenib (Stivarga) showed a statistically significant improvement in overall survival (OS) compared to placebo [6.4 months vs. 5 months; HR 0.77 (CI 0.64-0.94), p – 0.0102].

II. The safety and efficacy of regorafenib (Stivarga) for gastrointestinal stromal tumors (GIST) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial in adults with unresectable, locally advanced or metastatic disease. Subjects had been previously treated with imatinib (Gleevec) and sunitinib (Sutent). The medication showed a statistically significant improvement in progression-free survival (PFS) [PFS was 4.8 vs. 0.9 months; HR 0.27 (0.19-0.39), p<0.0001]; however, there was no statistical difference in OS. This may have been influenced by cross-over to active therapy after disease progression on placebo.

III. The clinical safety and efficacy of regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial in adults with hepatocellular carcinoma. All subjects had documented disease progression on sorafenib (Nexavar), and those that had discontinued sorafenib (Nexavar) due to toxicity rather than disease progression were ineligible for the trial; thus, safety and efficacy with regorafenib (Stivarga) prior to progression on or after sorafenib (Nexavar) has not been established. Overall survival was the primary outcome and was statistically significant in favor of regorafenib (Stivarga) over placebo [10.6 vs. 7.8 months; HR 0.63 (0.5-0.79), p<0.0001].

IV. For all indications regorafenib (Stivarga) is dosed at 160 mg per day on days 1-21 of each 28-day cycle. Product availability is 40 mg tablets.

Investigational or Not Medically Necessary Uses

I. Regorafenib (Stivarga) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:
   A. Biliary cancer, cholangiocarcinoma
   B. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
   C. Non-small cell lung cancer
   D. Renal cell carcinoma
   E. Soft tissue sarcoma
   F. Adenoid cystic carcinoma
   G. Urothelial carcinoma
   H. Ovarian cancer

References

1. Stivarga [Package Insert]. Whippany NJ. Bayer Healthcare Pharmaceuticals Inc. 2017.
2. Wihelm SM., Dumas J., Adnane L., et al. Regorafenib: a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer. 2011;129(1): 245-255).
3. Van Cutsem E., Sobrero AF., Siena S., et al. Phase III CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC). J Clin Oncol. 2012: 2502.
4. Grothey A, Van Cutsem E, Sobrero A, et. al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan;381(9863):303-12.
5. Bruix, J, Qin, S, Merle, P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 07;389(10064):56-66.
6. Demetri GD, Reichardt P, Kang Y-K, et. al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan;381(9863):295-302.

7. Grothy A., Sobrero AF., Siena S., et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) or regorafenib plus best supportive care versus placebo in patients with metastatic colorectal cancer who have progressed after standard therapies.
8. Clinicaltrials.gov. November 2019. Available from: http://www.clinicaltrials.gov.

Policy Implementation/Update:

Date Created	January 2013
Date Effective	February 2013
Last Updated	November 2019
Last Reviewed	01/2013, 02/2013, 04/2014, 09/2014, 11/2019

Action and Summary of Changes	**Date**
Prior authorization transitioned to policy format. Addition of age edit, addition of monotherapy requirement. Renewal criteria transitioned to current formatting and language, and increase from three to 12 month approval.	11/2019