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	Indication	Dosage Form	Quantity Limit
regorafenib (Stivarga)	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	40 mg tablets	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. Medication is **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 chemotherapy regimen history of all of the following:
            a. fluoropyrimidine [e.g., capecitabine, fluorouracil (5-FU)]

b. oxaliplatin
c. 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 has KRAS-mutated colorectal cancer; **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** The member has previously progressed on or after sunitinib (Sutent); **OR**

3. Hepatocellular Carcinoma; AND

i. Provider attests the patient has Child-Pugh class A; **AND**

ii. 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
I. Osteosarcoma

Renewal Evaluation

I. Member has received a previous prior authorization 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. Regorafenib (Stivarga) will **not** be used in combination with other oncolytic medications (i.e., will be used as monotherapy); **AND**
IV. Documentation of clinical response to therapy, such as stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. Regorafenib (Stivarga) has not been evaluated in patients under the age of 18; therefore, its safety and efficacy in the pediatric population is unknown.

II. Due to the complex nature of treating any of the diagnoses regorafenib (Stivarga) is approved for, treatment should be prescribed by, or in consultation with, an oncologist.

III. Regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled study, the CORRECT trial, in adults with metastatic colorectal cancer after failure of standard therapy. The trial included 760 subjects, 505 in the regorafenib arm and 255 in the placebo arm, 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].

IV. The safety and efficacy of regorafenib (Stivarga) for gastrointestinal stromal tumors (GIST) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial (GRID) in adults with unresectable, locally advanced or metastatic disease. A total of 199 patients, 133 in the regorafenib arm and 66 in the placebo arm, 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 as patients were allowed to change to regorafenib after progression and 56 of the 66 patients moved to the treatment arm.

V. The clinical safety and efficacy of regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in adults with hepatocellular carcinoma, Child-Pugh class A. All subjects (379 in the regorafenib arm and 194 in the placebo, 573 total) 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].

VI. In the clinical trials, severe drug-induced liver injury with fatal outcomes did occur. In the CORRECT study, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In the GRID study, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm. In the RESORCE study, there was no increase in the incidence of fatal hepatic failure as compared to placebo. These drug-induced injuries were typically high-

grade elevation of bilirubin, AST, ALT, and ALP with risk of developing injury roughly two-fold in the regorafenib arms compared to placebo.

VII. As regorafenib was only studied in Child-Pugh class A (patients in the lower risk/best survival chances), safety of regorafenib in patients with Child-Pugh class B7 or beyond is unknown with the possibility of drug toxicity with worsening overall outcomes. Additionally, a clinical outreach to a key opinion leader (KOL) specializing in the treatment of liver cancer, agreed that use of regorafenib should be considered after failure of sorafenib, and only in patients with Child-Pugh class A liver status, as they have the best outcomes for a favorable prognosis while balancing the risk of treatment-induced hepatotoxicity. Additionally, the KOL expert noted that the best approach to the management of HCC patients with Child-Pugh class B7 or beyond may be via clinical trial enrollment or a liver transplant.

VIII. 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 and for patients experiencing dose-dependent intolerance (adverse reactions), the dose of regorafenib (Stivarga) should be reduced in 40mg increments, with the lowest recommended dose of 80mg/day.

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. Osteosarcoma
      i. First-line therapy for osteosarcoma is surgically removing the tissue/bone involved (either limb-sparing or limb-amputation) with radiation therapy followed by chemotherapy - based on the type and affected site of osteosarcoma (chondrosarcoma, Ewing sarcoma, Giant Cell Tumor of bone, etc.). Recommended systemic therapy options in this setting are: pembrolizumab (Keytruda), dasatinib (Sprycel), pazopanib (Votrient) or cisplatin/doxorubicin or MAP (high-dose methotrexate, cisplatin, and doxorubicin).
      ii. The NCCN panel updated guidelines to give regorafenib a category 1 recommendation for second-line therapy for osteosarcoma (relapsed, refractory, or metastatic disease), based on the following data of two phase 2 clinical trials (REGOBONE and SARC024) noting that regorafenib displayed antitumor activity in progressive metastatic osteosarcoma, delaying disease progression. However, at this time, regorafenib has not received FDA approval for the treatment of osteosarcoma.
      iii. In the REGOBONE study, the primary endpoint was the number of patients without disease progression at 8 weeks. Patients were randomly assigned 2:1 to regorafenib or placebo with 38 patient total in the end efficacy analysis. 17 of 26

patients in the regorafenib arm (65%) were non-progressive at 8 weeks compared with 0 patients in the placebo arm. Although a preliminary indicator of efficacy, these results were not statistically significant, neither the study powered to evaluate the difference between the treatment and placebo arms.

iv. In the SARC024 (randomized, double-blind, phase 2 study), progression free survival (PFS) was the primary endpoint. SARC024 had 42 patients randomized 1:1 to regorafenib or placebo with allowance of crossover at time of disease progression. Median PFS was significantly improved with regorafenib versus placebo: 3.6 months (95% CI, 2.0 to 7.6 months) versus 1.7 months (95% CI, 1.2 to 1.8 months), respectively (hazard ratio, 0.42; 95% CI, 0.21 to 0.85; *p* 0.017). In the context of the crossover design, there was no statistically significant difference in overall survival. Additionally, based on consensus recommendations from the clinical experts, a progression-free survival (PFS) of ≥ 4months has been regarded as a clinically meaningful metric of positive outcomes in the setting of osteosarcoma, which this trial did not attain.

B. Biliary cancer, cholangiocarcinoma
C. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
D. Non-small cell lung cancer
E. Renal cell carcinoma
F. Soft tissue sarcoma
G. Adenoid cystic carcinoma
H. Urothelial carcinoma
I. Ovarian cancer

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Related Policies

Policy Name	Disease state
Avapritinib (Ayvakit)	Unresectable or metastatic gastrointestinal stromal tumor with PDGFRA exon 18 mutation
Cabozantinib (Cabometyx, Cometriq)	Progressive or metastatic hepatocellular carcinoma, in patients previously treated with sorafenib
Dasatinib (Sprycel)	Gastrointestinal Stromal Tumors (GIST)
Encorafenib (Braftovi), binimetinib (Mektovi)	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
Ripretinib (Qinlock)	Gastrointestinal Stromal Tumor, advanced disease after treatment with three or more tyrosine kinase inhibitors
Sunitinib (Sutent)	Gastrointestinal stromal tumor
Trifluridine/tipiracil (Lonsurf)	Colorectal cancer-metastatic, previously untreated
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable hepatocellular carcinoma

Policy Implementation/Update:

Action and Summary of Changes	Date
Added in Child-Pugh class A to hepatocellular cancer requirement based on KOL, NCCN, and clinical trial recommendations. Updated supporting evidence for the three FDA indications.	08/2022
Removed split fill	01/2022
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
Previous Reviews	01/2013; 02/2013; 04/2014;

	09/2014;