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Section:	Prescription Drugs	**Effective Date:**	January 1, 2025
Subsection:	Antineoplastic Agents	**Original Policy Date:**	December 3, 2012
Subject:	Stivarga	**Page:**	1 of 5

Last Review Date: December 13, 2024

Stivarga

Description

Stivarga (regorafenib)

Background
Stivarga (regorafenib) is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment (1).

Regulatory Status
FDA-approved indications: Stivarga is a kinase inhibitor indicated for the treatment of patients with: (1)

1. Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan- based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy.
2. Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) in patients who have been previously treated with Gleevec (imatinib) and Sutent (sunitinib).
3. Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Off-Label Uses: (2)

1. Metastatic colorectal cancer (CRC) who have progressed through all available regimens with or without being previously treated with anti-VEGF therapy
2. Cholangiocarcinoma

Stivarga carries a boxed warning for severe and sometimes fatal hepatotoxicity. Liver function tests should be obtained before initiation of Stivarga, and it should be monitored at least every 2 weeks

during the first 2 months of treatment. Thereafter, monitor monthly or more frequently as clinically indicated. Monitor liver function tests weekly in patients experiencing elevated liver function tests until improvement to less than 3 times the upper limit normal (ULN) or baseline. Temporarily hold and then reduce or permanently discontinue Stivarga depending on the severity and persistence of hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis (1).

Other adverse events are hemorrhage, dermatological toxicity, hypertension, cardiac ischemia and infarction, wound healing complications, reversible posterior leukoencephalopathy syndrome (RPLS) and gastrointestinal perforation or fistula (1).

The safety and effectiveness of Stivarga have not been established in pediatric patients (1).

Related policies
Ayvakit, Fruzaqla, Nexavar, Qinlock, Sprycel, Sutent, Votrient

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Stivarga may be considered **medically necessary** if the conditions indicated below are met.

Stivarga may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 18 years of age and older

Diagnoses

Patient must have **ONE** of the following:

1. Metastatic colorectal cancer (CRC)
   a. Previously treated with fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy and if RAS wild type, an anti-EGFR therapy
2. Gastrointestinal stromal tumor (GIST)
   a. Unresectable **OR** metastatic **OR** locally advanced
   b. Previously treated with Gleevec (imatinib) and Sutent (sunitinib)
3. Hepatocellular carcinoma (HCC)
   a. Previously treated with sorafenib (Nexavar)

4. Cholangiocarcinoma

AND ALL of the following for **ALL** indications:
1. Assessment of ALT, AST, and bilirubin tests before initiation of therapy
    a. Agreement to monitor levels every 2 weeks during the first 2 months of treatment, then monitored at least monthly
2. **NO** signs or symptoms of severe hemorrhage

Prior – Approval *Renewal* Requirements

Age 18 years of age and older

Diagnoses

Patient must have **ONE** of the following:

1. Metastatic colorectal cancer (CRC)
2. Gastrointestinal stromal tumor (GIST)
    a. Unresectable **OR** metastatic **OR** locally advanced
3. Hepatocellular Carcinoma (HCC)
4. Cholangiocarcinoma

AND ALL of the following for **ALL** indications:
1. Liver function tests are < 3 times the upper limit of normal (ULN) or baseline
2. **NO** signs or symptoms of severe hemorrhage
3. **NO** signs or symptoms of gastrointestinal perforation or fistula
4. **NO** development of Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Quantity 252 tablets per 84 days

Duration 12 months

Prior – Approval *Renewal* Limits

Same as above

Rationale

Summary

Stivarga (regorafenib) is a multi-kinase inhibitor, designed to block enzymes that promote cancer growth. Stivarga is indicated for metastatic colorectal cancer; locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST); and hepatocellular carcinoma (HCC). Stivarga is also indicated off-label for use in cholangiocarcinoma (1-2).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Stivarga while maintaining optimal therapeutic outcomes.

References

1. Stivarga [package insert]. Wayne, NJ: Bayer Healthcare Pharmaceuticals Inc.; December 2020.
2. NCCN Drugs & Biologics Compendium® Regorafenib 2024. National Comprehensive Cancer Network, Inc. Accessed on October 3, 2024.

Policy History

Date	Action
October 2012	New addition
December 2012	Annual editorial review and update
March 2013	Addition of new FDA indication of advanced gastrointestinal tumor (GIST)
June 2013	Annual editorial review and update
March 2014	Annual review and reference update
September 2014	Annual review and reference update
March 2015	Annual editorial review and reference update.
March 2016	Annual editorial review and reference update. Policy number change from 5.04.26
June 2016	Annual review
May 2017	Addition of the treatment of hepatocellular carcinoma to criteria
September 2017	Annual review
June 2018	Annual editorial review
June 2019	Annual review and reference update

June 2020	Annual review and reference update
September 2020	Annual review and reference update
September 2021	Annual review and reference update
September 2022	Annual review and reference update
July 2023	Per reconsideration review, added diagnosis of cholangiocarcinoma and removed requirement to t/f anti-VEGF therapy for metastatic colorectal cancer (CRC)
September 2023	Annual review and reference update
December 2023	Annual review and reference update
March 2024	Annual review and reference update
December 2024	Annual review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 13, 2024 and is effective on January 1, 2025.