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 indication: Stivarga is a kinase inhibitor indicated for the treatment of patients with:

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.

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 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. Stivarga also carries a pregnancy category D (1).

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

Related policies
Nexavar, 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 medially necessary in patients that are 18 years of age or older with a diagnosis of metastatic colorectal cancer, gastrointestinal stromal tumors (GIST), or hepatocellular carcinoma, when the conditions indicated below are met.

Stivarga is considered investigational in patients who are less than 18 years of age and for all other indications.

Prior-Approval Requirements

Age 18 years of age and older

Diagnoses

Must have ONE of the following:

1. Metastatic colorectal cancer (CRC)
   a. Previously treated with fluoropyrimidine-, oxaliplatin-and irinotecan-based chemotherapy, an anti-VEGF therapy, 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)

AND ALL of the following:
  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**

Must have **ONE** of the following:
  1. Metastatic colorectal cancer (CRC)
  2. Locally advanced, unresectable OR metastatic gastrointestinal stromal tumor (GIST)
  3. Hepatocellular Carcinoma (HCC)

AND ALL of the following:
  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**

**Duration** 12 months

**Quantity** 252 tablets per 84 days
Prior – Approval *Renewal* Limits

**Duration** 12 months  
**Quantity** 252 tablets per 84 days

**Rationale**

**Summary**
Stivarga (regorafenib) is a multi-kinase inhibitor, designed to block enzymes that promote cancer growth. Stivarga has been approved to treat colorectal cancer that has spread despite prior treatment and for locally advanced gastrointestinal cancer. Stivarga is indicated for metastatic colorectal cancer in patients who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy and an anti-VEGF therapy. If the patient has the KRAS wild type, they must have previously been treated with an anti-EGFR therapy. Stivarga is also indicated for locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with Gleevec (imatinib) and Sutent (sunitinib). Additionally, Stivarga is indicated for the treatment of hepatocellular carcinoma (HCC) who have been previously treated with sorafenib (1).

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

**References**

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>October 2012</td>
<td>New addition</td>
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<tr>
<td>December 2012</td>
<td>Annual editorial review and update</td>
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<tr>
<td>March 2013</td>
<td>Addition of new FDA indication of advanced gastrointestinal tumor (GIST)</td>
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<tr>
<td>June 2013</td>
<td>Annual editorial review and update</td>
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<tr>
<td>March 2014</td>
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<tr>
<td>September 2014</td>
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<tr>
<td>March 2015</td>
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Policy number change from 5.04.26
Section: Prescription Drugs  Effective Date: July 1, 2019
Subsection: Antineoplastic Agents  Original Policy Date: December 3, 2012
Subject: Stivarga  Page: 5 of 5

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

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 20, 2019 and is effective on July 1, 2019.