Clinical Policy: Regorafenib (Stivarga)
Reference Number: CP.PHAR.107
Effective Date: 12.01.12
Last Review Date: 05.18
Line of Business: Commercial, HIM, Medicaid

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
Regorafenib (Stivarga®) is a kinase/VEGFR inhibitor.

FDA Approved Indication(s)
Stivarga is indicated for treatment of patients with:

- Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine, oxaliplatin and irinotecan-based chemotherapy, an anti-vascular endothelial growth factor (VEGF) therapy, and, if RAS wild-type, an anti-endothelial growth factor (EGFR) therapy.
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.
- Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Stivarga is medically necessary when the following criteria are met:

I. Initial Approval Criteria
   A. Colorectal Cancer (must meet all):
      1. Diagnosis of CRC;
      2. Previously treated with systemic chemotherapy;
      3. Prescribed by or in consultation with an oncologist;
      4. Age ≥ 18 years;
      5. Dose does not exceed 160 mg/day.
      Approval duration:
      Medicaid/HIM - 6 months
      Commercial - Length of Benefit

   B. Gastrointestinal Stromal Tumor (must meet all):
      1. Diagnosis of GIST;
      2. Previously treated with imatinib (Gleevec®)* or sunitinib (Sutent®)* unless contraindicated or clinically significant adverse effects are experienced;
      *Prior authorization is (or may be) required
      3. Prescribed by or in consultation with an oncologist;
      4. Age ≥ 18 years;
5. Dose does not exceed 160 mg/day.

**Approval duration:**
- Medicaid/HIM - 6 months
- Commercial - Length of Benefit

**C. Hepatocellular Carcinoma** (must meet all):
1. Diagnosis of HCC;
2. Previously treated with sorafenib (Nexavar®)* unless contraindicated or clinically significant adverse effects are experienced;
   - *Prior authorization is (or may be) required
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 years;
5. Dose does not exceed 160 mg/day.

**Approval duration:**
- Medicaid/HIM - 6 months
- Commercial - Length of Benefit

**D. Other diagnoses/indications**
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. All Indications in Section I** (must meet all):
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Stivarga for CRC, GIST, or HCC and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 160 mg/day.

**Approval duration:**
- Medicaid/HIM - 12 months
- Commercial - Length of Benefit

**B. Other diagnoses/indications** (must meet 1 or 2):
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less); or**

2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**III. Diagnoses/Indications for which coverage is NOT authorized:**

**A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies –**
IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

<table>
<thead>
<tr>
<th>Abbreviation/Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>colorectal cancer</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GIST</td>
<td>gastrointestinal stromal tumor</td>
</tr>
<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>VEGFR</td>
<td>vascular endothelial growth factor receptor</td>
</tr>
</tbody>
</table>

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Regimen</th>
<th>Dose Limit/Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colorectal Cancer (CRC): Examples of Systemic Chemotherapy</strong></td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>5-FU (fluorouracil)†</td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>Avastin® (bevacizumab)</td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>Camptosar® (irinotecan)</td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>Cyramza® (ramucirumab)</td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>Eloxatin® (oxaliplatin)</td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>Erbitux® (cetuximab)</td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>Lonsurf® (trifluridine and tipiracil)</td>
<td>35 mg/m²/dose by mouth (PO) twice daily (BID) on Days 1 through 5 and Days 8 through 12 of each 28-day cycle.</td>
<td>70 mg/m²/day</td>
</tr>
<tr>
<td>Vectibix® (panitumumab)</td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>Xeloda® (capecitabine)†</td>
<td>1250 mg/m² PO BID for 2 weeks followed by a 1-week rest period given as 3-week cycles.</td>
<td>2500/m²/day</td>
</tr>
<tr>
<td>Zaltrap® (ziv-aflibercept)</td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Gastrointestinal Stromal Tumor (GIST)</strong></td>
<td>Varies upon protocol and patient tolerance</td>
<td>Varies</td>
</tr>
<tr>
<td>imatinib (Gleevec®)</td>
<td>400 mg PO daily up to 400 mg PO BID</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Sutent® (sunitinib)</td>
<td>50 mg PO daily for 4 weeks followed by 2 weeks off</td>
<td>87.5 mg/day</td>
</tr>
</tbody>
</table>
CLINICAL POLICY  
Regorafenib

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular Carcinoma (HCC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nexavar® (sorafenib)</td>
<td>400 mg PO BID</td>
<td>800 mg/day</td>
</tr>
</tbody>
</table>

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

*FOLFOX: oxaliplatin, leucovorin, fluorouracil (5-FU); CAPEOX: oxaliplatin, capecitabine (Xeloda); FOLFIRI: irinotecan, leucovorin, 5-FU; FOLFOXIRI: irinotecan, oxaliplatin, leucovorin, 5-FU; IROX: oxaliplatin, irinotecan
†Examples of fluoropyrimidines include fluorouracil (5-FU) and capecitabine (Xeloda).

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
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<tbody>
<tr>
<td>CRC, GIST, HCC</td>
<td>160 mg PO daily for the first 21 days of each 28-day cycle</td>
<td>160 mg/day</td>
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</tbody>
</table>

VI. Product Availability

Oral tablet: 40 mg

VII. References


Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.14</td>
<td>01.15</td>
</tr>
<tr>
<td>12.15</td>
<td>01.16</td>
</tr>
</tbody>
</table>

Updated disease state information
Added safety and monitoring parameters
Added Table 2: Dose modifications

Converted policy to new template.
Criteria: added age restriction; added max dose criteria; changed initial approval period to 3 months.
Appendices limited to abbreviation key and safety appendix for use in criteria.

Converted policy to new template.
Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,
contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

For Health Insurance Marketplace members, when applicable, this policy applies only when the prescribed agent is on your health plan approved formulary. Request for non-formulary drugs must be reviewed using the formulary exception policy.

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