

## Clinical Policy: Regorafenib (Stivarga)

Reference Number: CP.PHAR.107

Effective Date: 12.01.12

Last Review Date: 05.20

Line of Business: Commercial, HIM, Medicaid

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### Description

Regorafenib (Stivarga<sup>®</sup>) is a kinase/vascular endothelial growth factor receptor (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-epidermal growth factor receptor (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<sup>®</sup> 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  $\geq$  18 years;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 160 mg per day;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

##### 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®\*, unless clinically significant adverse effects are experienced or both are contraindicated;  
*\*Prior authorization may be required*
3. Prescribed by or in consultation with an oncologist;
4. Age  $\geq$  18 years;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 160 mg per day;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

**C. Hepatocellular Carcinoma (must meet all):**

1. Diagnosis of HCC;
2. Previously treated with Nexavar®\* or Lenvima®\*, unless clinically significant adverse effects are experienced or both are contraindicated;  
*\*Prior authorization may be required*
3. Prescribed by or in consultation with an oncologist;
4. Age  $\geq$  18 years;
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 160 mg per day;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

**D. Soft Tissue Sarcoma (off-label) (must meet all):**

1. Diagnosis of non-adipocytic sarcoma or pleomorphic rhabdomyosarcoma;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  18 years;
4. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 160 mg per day;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

**E. Bone Cancer (off-label) (must meet all):**

1. Diagnosis of osteosarcoma;

2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  18 years;
4. Request is for second-line therapy for relapsed/refractory or metastatic disease (*see Appendix D*);
5. Request meets one of the following (a or b):\*
  - a. Dose does not exceed 160 mg per day;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration:**

**Medicaid/HIM** – 6 months

**Commercial** – Length of Benefit

## 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 a covered indication 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, request meets one of the following (a or b):\*
  - a. New dose does not exceed 160 mg per day;
  - b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*\*Prescribed regimen must be FDA-approved or recommended by NCCN*

**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 – CP.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

## IV. Appendices/General Information

### Appendix A: Abbreviation/Acronym Key

CRC: colorectal cancer

EGFR: epidermal growth factor receptor

FDA: Food and Drug Administration

GIST: gastrointestinal stromal tumor

HCC: hepatocellular carcinoma  
VEGF: vascular endothelial growth factor

VEGFR: vascular endothelial growth factor receptor

*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.*

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
<b>Colorectal Cancer (CRC): Examples of Systemic Chemotherapy</b>		
5-FU (fluorouracil)†	Varies upon protocol and patient tolerance	Varies
Avastin <sup>®</sup> (bevacizumab)	Varies upon protocol and patient tolerance	
Camptosar <sup>®</sup> (irinotecan)	Varies upon protocol and patient tolerance	
Cyramza <sup>®</sup> (ramucirumab)	Varies upon protocol and patient tolerance	
Eloxatin <sup>®</sup> (oxaliplatin)	Varies upon protocol and patient tolerance	
Erbix <sup>®</sup> (cetuximab)	Varies upon protocol and patient tolerance	
Lonsurf <sup>®</sup> (trifluridine and tipiracil)	35 mg/m <sup>2</sup> /dose by mouth (PO) twice daily (BID) on Days 1 through 5 and Days 8 through 12 of each 28-day cycle.	70 mg/m <sup>2</sup> /day
Vectibix <sup>®</sup> (panitumumab)	Varies upon protocol and patient tolerance	Varies
Xeloda <sup>®</sup> (capecitabine)†	1250 mg/m <sup>2</sup> PO BID for 2 weeks followed by a 1-week rest period given as 3-week cycles.	2500/m <sup>2</sup> /day
Zaltrap <sup>®</sup> (ziv-aflibercept)	Varies upon protocol and patient tolerance	Varies
FOLFOX*	Varies upon protocol and patient tolerance	
CAPEOX*	Varies upon protocol and patient tolerance	
FOLFIRI*	Varies upon protocol and patient tolerance	
FOLFOXIRI*	Varies upon protocol and patient tolerance	
IROX*	Varies upon protocol and patient tolerance	
<b>Gastrointestinal Stromal Tumor (GIST)</b>		
imatinib (Gleevec <sup>®</sup> )	400 mg PO daily up to 400 mg PO BID	800 mg/day
Sutent <sup>®</sup> (sunitinib)	50 mg PO daily for 4 weeks followed by 2 weeks off	87.5 mg/day
<b>Hepatocellular Carcinoma (HCC)</b>		
Nexavar <sup>®</sup> (sorafenib)	400 mg PO BID	800 mg/day
Lenvima <sup>®</sup> (lenvatinib)	8-12 mg PO QD	12 mg/day

*Therapeutic alternatives are listed as Brand name<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) 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).

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s): none reported
- Boxed warning(s): hepatotoxicity

*Appendix D: First-line Therapies for Osteosarcoma per NCCN*

- Preferred regimens: cisplatin and doxorubicin, MAP (high-dose methotrexate, cisplatin, and doxorubicin)
- Other recommended regimen: doxorubicin, cisplatin, ifosfamide, and high-dose methotrexate

**V. Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose
CRC, GIST, HCC	160 mg PO QD for the first 21 days of each 28-day cycle	160 mg/day

**VI. Product Availability**

Tablet: 40 mg

**VII. References**

1. Stivarga Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals. Inc.; February 2020. Available at [http://labeling.bayerhealthcare.com/html/products/pi/Stivarga\\_PI.pdf](http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf). Accessed February 15, 2020.
2. Regorafenib. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at [www.nccn.org](http://www.nccn.org). Accessed February 16, 2020.
3. Colon cancer (Version 1.2020). In: National Comprehensive Cancer Network Guidelines. Available at [www.nccn.org](http://www.nccn.org). Accessed February 15, 2020.
4. Rectal cancer (Version 1.2020). In: National Comprehensive Cancer Network Guidelines. Available at [www.nccn.org](http://www.nccn.org). Accessed February 15, 2020.
5. Soft tissue sarcoma (Version 6.2019). In: National Comprehensive Cancer Network Guidelines. Available at [www.nccn.org](http://www.nccn.org). Accessed February 15, 2020
6. Hepatobiliary cancers (Version 4.2019). In: National Comprehensive Cancer Network Guidelines. Available at [www.nccn.org](http://www.nccn.org). Accessed February 15, 2020.
7. Bone Cancer (Version 1.2020). In: National Comprehensive Cancer Network Guidelines. Available at [www.nccn.org](http://www.nccn.org). Accessed February 15, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted policy to new template. Removed prescriber and age requirements. CRC mutations: The RAS family of mutations includes but is not limited to KRAS and NRAS mutations. All mutation designations are represented in the policy per FDA/NCCN language.	11.16	01.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
<p>In initial criteria for CRC and GIST, removed exclusions based on medical conditions if they were presented in the PI as discontinuation recommendations; however, they are maintained under continuation criteria. In continuation criteria, edited reasons to discontinue to those that are permanent discontinues.</p> <p>NCCN recommended uses: For CRC, all NCCN recommended uses are added; for GIST the NCCN uses match the FDA approved uses so NCCN is not listed separately.</p>		
<p>Policy converted to new template.</p> <p>New indication added for hepatocellular carcinoma.</p> <p>Off-label NCCN recommended uses added across indications where applicable (for GIST, NCCN recommends Stivarga after either imatinib or sunitinib).</p> <p>Therapeutic alternatives added at Appendix B.</p>	06.17	09.17
<p>2Q 2018 annual review: no significant changes; policies combined for commercial and Medicaid; added HIM line of business; age added; summarized NCCN and FDA approved uses for improved clarity; added specialist involvement in care; references reviewed and updated.</p>	02.13.18	05.18
<p>2Q 2019 annual review: HCC – added Lenvima as optional first-line treatment required prior to Stivarga; added NCCN compendium supported indications for soft tissue sarcomas; references reviewed and updated.</p>	02.04.19	05.19
<p>2Q 2020 annual review: added NCCN compendium-supported indication of osteosarcoma; references reviewed and updated.</p>	02.15.20	05.20

**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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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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.

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