Clinical Policy: Regorafenib (Stivarga)

Reference Number: CP.PHAR.107
Effective Date: 12.01.12
Last Review Date: 05.21 Revision Log
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/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® that Stivarga is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Colorectal Cancer (must meet all)**:**

1. Diagnosis of advanced or metastatic CRC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Previously treated with systemic chemotherapy (*see Appendix B*);
5. Prescribed as a single agent therapy;
6. 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 Sutent®*, 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 ≥ 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. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as a single agent therapy;
5. Prescribed as a second or subsequent-line therapy (*see Appendix B*);
6. Member has Child-Pugh class A disease (*see Appendix D*);
7. 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 one of the following soft tissue sarcomas (a, b, c, or d):
   a. Non-adipocytic sarcoma;
   b. Pleomorphic rhabdomyosarcoma;
   c. Angiosarcoma;
   d. Solitary fibrous tumor;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as a single agent therapy;
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

E. Bone Cancer (off-label) (must meet all)**:**
1. Diagnosis of osteosarcoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request is for second-line therapy for relapsed/refractory or metastatic disease (*see Appendix D*);
5. Prescribed as a single agent therapy;
6. 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

F. 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.PA.154 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 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.PA.154 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.PA.154 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
Colorectal Cancer (CRC): Examples of Systemic Chemotherapy		
5-FU (fluorouracil)†	Varies upon protocol and patient tolerance	Varies
Avastin® (bevacizumab)	Varies upon protocol and patient tolerance	
Camptosar® (irinotecan)	Varies upon protocol and patient tolerance	
Cyramza® (ramucirumab)	Varies upon protocol and patient tolerance	
Eloxatin® (oxaliplatin)	Varies upon protocol and patient tolerance	
Erbitux® (cetuximab)	Varies upon protocol and patient tolerance	
Lonsurf® (trifluridine and tipiracil)	35 mg/m^2/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^2/day
Vectibix® (panitumumab)	Varies upon protocol and patient tolerance	Varies
Xeloda® (capecitabine)†	1250 mg/m^2 PO BID for 2 weeks followed by a 1-week rest period given as 3-week cycles.	2500/m^2/day
Zaltrap® (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	

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
Gastrointestinal Stromal Tumor (GIST)		
imatinib (Gleevec®)	400 mg PO daily up to 400 mg PO BID	800 mg/day
Sutent® (sunitinib)	50 mg PO daily for 4 weeks followed by 2 weeks off	87.5 mg/day
Hepatocellular Carcinoma (HCC): Examples of Preferred First-line Systemic Therapy		
Nexavar® (sorafenib)	400 mg PO BID	800 mg/day
Lenvima® (lenvatinib)	8-12 mg PO QD	12 mg/day
Tecentriq® (atezolizumab) + bevacizumab	Varies	Varies

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).

Appendix C: Contraindications/Boxed Warnings

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

Appendix D: General Information

- 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
- Child-Pugh Score

	1 Point	2 Points	3 Points
Bilirubin	Less than 2 mg/dL Less than 34 umol/L	2-3 mg/dL 34-50 umol/L	Over 3 mg/dL Over 50 umol/L
Albumin	Over 3.5 g/dL Over 35 g/L	2.8-3.5 g/dL 28-35 g/L	Less than 2.8 g/dL Less than 28 g/L
INR	Less than 1.7	1.7 - 2.2	Over 2.2
Ascites	None	Mild / medically controlled	Moderate-severe / poorly controlled
Encephalopathy	None	Mild / medically controlled Grade I-II	Moderate-severe / poorly controlled. Grade III-IV

Child-Pugh class is determined by the total number of points: A = 5-6 points; B = 7-9 points; C = 10-15 points

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.; December 2020. Available at http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf. Accessed February 8, 2021.
2. Regorafenib. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed February 8, 2021.
3. Colon cancer (Version 2.2021). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2021.
4. Rectal cancer (Version 1.2021). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2021.
5. Soft tissue sarcoma (Version 1.2021). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2021.
6. Hepatobiliary cancers (Version 5.2020). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2021.
7. Bone Cancer (Version 1.2021). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy converted to new template. New indication added for hepatocellular carcinoma. Off-label NCCN recommended uses added across indications where applicable (for GIST, NCCN recommends Stivarga after either imatinib or sunitinib). Therapeutic alternatives added at Appendix B.	06.17	09.17
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.	02.13.18	05.18
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.	02.04.19	05.19
2Q 2020 annual review: added NCCN compendium-supported indication of osteosarcoma; references reviewed and updated.	02.15.20	05.20

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: added NCCN-supported uses to indications, such as regorafenib use as a single agent for most indications, advanced or metastatic disease distinction for CRC, expanded past treatment options for HCC in Appendix B, Child-Pugh class A disease for HCC, and off-label soft-tissue sarcoma additions; added off-label policy references to initial criteria section along with revising references for HIM line of business off-label use from HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	02.05.21	05.21

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.