Clinical Policy: Regorafenib (Stivarga)

Reference Number: CP.PHAR.107
Effective Date: 12.01.12
Last Review Date: 05.25
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®) 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 (including appendiceal carcinoma);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Previously treated with one of the following (a or b):
   a. For proficient mismatch repair/microsatellite-stable (pMMR/MSS) disease: systemic chemotherapy (*see Appendix B*);
   b. For deficient mismatch repair/microsatellite instability-high (dMMR/MSI-H) or polymerase epsilon/delta (POLE/POLD1) mutation disease: checkpoint inhibitor immunotherapy (*see Appendix B*), unless ineligible;
5. Prescribed as a single agent;
6. For brand Stivarga requests, member must use generic regorafenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 160 mg per day on days 1 to 21 of each 28-day cycle;

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 – 12 months or duration of request, whichever is less

B. Gastrointestinal Stromal Tumor (must meet all)**:**

1. Diagnosis of GIST;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is gross residual (R2 resection), unresectable, tumor rupture, recurrent, metastatic, or locally advanced;
5. Prescribed in one of the following ways (a or b):
   a. As a single agent for one of the following (i or ii):
      i. Disease previously treated with imatinib (Gleevec®)* and sunitinib (Sutent®)* (Qinlock®* if member is intolerant to sunitinib), unless clinically significant adverse effects are experienced or all are contraindicated;
      ii. Succinate dehydrogenase (SDH)-deficient disease (off-label);
   b. In combination with everolimus after progression on approved therapies (i.e., imatinib, sunitinib, and Qinlock)* (off-label);

   **Prior authorization may be required*
6. For brand Stivarga requests, member must use generic regorafenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 160 mg per day on days 1 to 21 of each 28-day cycle;
   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 – 12 months or duration of request, whichever is less

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;
5. Prescribed as a second or subsequent-line therapy (*see Appendix B*);
6. For brand Stivarga requests, member must use generic regorafenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 160 mg per day on days 1 to 21 of each 28-day cycle;
   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 – 12 months or duration of request, whichever is less

D. Soft Tissue Sarcoma (off-label) (must meet all)**:**
1. Diagnosis of one of the following soft tissue sarcomas (a, b, or c):
   a. Non-adipocytic sarcoma as subsequent therapy for advanced, metastatic, recurrent unresectable or recurrent stage IV disease;
   b. Pleomorphic rhabdomyosarcoma as subsequent therapy for advanced or metastatic disease;
   c. Angiosarcoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Prescribed as a single agent;
5. For brand Stivarga requests, member must use generic regorafenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 160 mg per day on days 1 to 21 of each 28-day cycle;
   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 – 12 months or duration of request, whichever is less

E. Bone Cancer (off-label) (must meet all)**:**
1. Diagnosis of one of the following bone cancers (a, b, c, d, or e):
   a. Osteosarcoma;
   b. Ewing sarcoma;
   c. Mesenchymal chondrosarcoma;
   d. Dedifferentiated chondrosarcoma;
   e. High-grade undifferentiated pleomorphic sarcoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Request is for second-line therapy for relapsed/refractory, progressive, or metastatic disease (*see Appendix D*);
5. Prescribed as a single agent;
6. For brand Stivarga requests, member must use generic regorafenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 160 mg per day on days 1 to 21 of each 28-day cycle;
   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 – 12 months or duration of request, whichever is less

F. Central Nervous System Cancer (off-label) (must meet all)**:**
1. Diagnosis of one of the following central nervous system cancers (a, b, or c):
   a. Glioblastoma;
   b. Gliosarcoma;
   c. H3-mutated high-grade glioma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is recurrent or progressive;
5. Prescribed as a single agent;
6. For brand Stivarga requests, member must use generic regorafenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 160 mg per day on days 1 to 21 of each 28-day cycle;
   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 – 12 months or duration of request, whichever is less

G. Uterine Sarcoma (off-label) (must meet all)**:**
1. Diagnosis of one of the following uterine sarcomas (a, b, c, d, or e):
   a. Endometrial stromal sarcoma;
   b. Undifferentiated uterine sarcoma;
   c. Adenosarcoma;
   d. PEGoma;
   e. Leiomyosarcoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is advanced, recurrent/metastatic, or inoperable;
5. Prescribed as a single agent;
6. For brand Stivarga requests, member must use generic regorafenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed 160 mg per day on days 1 to 21 of each 28-day cycle;
   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 – 12 months or duration of request, whichever is less

H. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):

a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: 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. For brand Stivarga requests, member must use generic regorafenib, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. 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 on days 1 to 21 of each 28-day cycle;
   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 – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line

of business: 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
dMMR/MSI-H: deficient mismatch repair/microsatellite instability-high
EGFR: epidermal growth factor receptor
FDA: Food and Drug Administration
GIST: gastrointestinal stromal tumor
HCC: hepatocellular carcinoma
pMMR/MSS: proficient mismatch repair/microsatellite-stable
POLE/POLD1: polymerase epsilon/delta
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 and Checkpoint Inhibitors		
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 PO 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	2,500/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	

Drug	Dosing Regimen	Dose Limit/ Maximum Dose
FOLFOXIRI*	Varies upon protocol and patient tolerance	
IROX*	Varies upon protocol and patient tolerance	
Checkpoint inhibitors: Opdivo® (nivolumab) ± Yervoy® (ipilimumab), Keytruda® (pembrolizumab), Jemperli® (dostarlimab-gxly)	Varies	Varies
Gastrointestinal Stromal Tumor (GIST)		
imatinib (Gleevec®)	400 mg PO daily up to 400 mg PO BID	800 mg/day
sunitinib (Sutent®)	50 mg PO daily for 4 weeks followed by 2 weeks off	87.5 mg/day
Qinlock® (ripretinib)	150 mg PO daily	150 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

	1 Point	2 Points	3 Points
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 January 23, 2025.
2. Regorafenib. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed February 5, 2025.
3. Colon Cancer (Version 6.2024). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2025.
4. Rectal Cancer (Version 5.2024). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2025.
5. Soft Tissue Sarcoma (Version 4.2024). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2025.
6. Hepatocellular Carcinoma (Version 4.2024). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2025.
7. Bone Cancer (Version 1.2025). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2025.
8. Central Nervous System Cancers (Version 4.2024). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2025.
9. Gastrointestinal Stromal Tumors (Version 2.2024). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2025.
10. Uterine Neoplasms (Version 2.2025). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 5, 2025.

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,	02.05.21	05.21

Reviews, Revisions, and Approvals	Date	P&T Approval Date
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.		
2Q 2022 annual review: modified commercial approval duration from length of benefit to "12 months or duration of request, whichever is less"; WCG.CP.PHAR.107 to be retired and approval durations consolidated to 6 months initial and 12 months continuation of therapy; per NCCN added criteria set for off-label use in glioblastoma; per template added generic oral oncology redirection if available language; clarified dosing in each criteria set to allow 160 mg per day on days 1 to 21 of each 28-day cycle; references reviewed and updated.	02.15.22	05.22
Template changes applied to other diagnoses/indications.	09.30.22	
2Q 2023 annual review: for GIST per prescribing information and NCCN clarified previous treatment requiring imatinib *and* Sutent, added per NCCN Compendium off label uses in combination with everolimus and SDH mutation positive disease; for soft tissue sarcoma removed solitary fibrous tumor as this off-label use is no longer NCCN Compendium supported, for pleomorphic rhabdomyosarcoma clarified disease is advanced or metastatic, for non-adipocytic sarcoma clarified use is for subsequent therapy for advanced, metastatic, recurrent unresectable or recurrent stage IV disease; references reviewed and updated.	01.06.23	05.23
2Q 2024 annual review: for CRC, added that appendiceal carcinoma is a coverable diagnosis and specified the prior therapies required based on disease characteristics (pMMR/MSS, dMMR/MSI-H, POLE/POLD1) per NCCN recommendations; for GIST, added additional disease qualifiers, added that Qinlock should be used if intolerant to Sutent when requested for single agent therapy, and revised from SDH mutation-positive to SDH-deficient per NCCN; for soft tissue sarcoma, added that Stivarga should be used as subsequent therapy for pleomorphic rhabdomyosarcoma per NCCN; for bone cancers, added Ewing sarcoma, mesenchymal chondrosarcoma, dedifferentiated chondrosarcoma, and high-grade undifferentiated pleomorphic sarcoma as coverable cancer types and added an additional disease qualifier of progressive per NCCN; revised glioblastoma to central nervous system cancer and added additional coverable cancers (gliosarcoma, H3-mutated high-grade glioma) and disease qualifier of progressive per NCCN; references reviewed and updated.	02.01.24	05.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2025 annual review: for HCC, removed requirement for Child-Pugh class A disease per NCCN; added off-label criteria set for uterine sarcoma per NCCN; references reviewed and updated.	02.05.25	05.25

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.

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.