Clinical Policy: Regorafenib (Stivarga)

Reference Number: CP.PHAR.107
Effective Date: 12/12 Revision Log
Last Review Date: 11/16

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

Description
The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for regorafenib (Stivarga®).

Policy/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 colorectal cancer (CRC);
2. Meets a or b:
   a. FDA approved use (i and ii):
      i. Disease is metastatic;
      ii. CRC previously has been treated with all of the following:
         a) Fluoropyrimidine-based chemotherapy;
         b) Oxalipolatin-based chemotherapy;
         c) Irinotecan-based chemotherapy;
         d) Anti- vascular endothelial growth factor (VEGF) therapy (e.g., bevacizumab [Avastin], ramucirumab [Cyramza]);
         e) If CRC is RAS* wild type (i.e. no RAS mutation), anti-epidermal growth factor receptor (EGFR) therapy (e.g., cetuximab [Erbitux] or panitumumab [Vectibix]);
   b. Off-label NCCN recommended use (i and ii):
      i. Disease is unresectable, advanced or metastatic;
      ii. Stivarga will be used as a single agent for any of the following:
         a) After first progression for disease that is positive for the KRAS or NRAS mutation;
         b) After second progression for disease previously treated with either of the following:
            1) FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) therapy;
            2) Irinotecan- and oxaliplatin-based therapy;
         c) For disease that is refractory to standard chemotherapy, including trifluridine and tipiracil;
   c. Prescribed daily dose of Stivarga does not exceed 160 mg.

**The RAS family of mutations includes but is not limited to KRAS and NRAS mutations.*

Approval duration: 3 months

B. Gastrointestinal Stromal Tumor (must meet all):
1. Diagnosis of gastrointestinal stromal tumor (GIST);
2. Disease is locally advanced, unresectable or metastatic;
3. GIST previously has been treated with one of the following:
   a. Imatinib (Gleevec);
   b. Sunitinib (Sutent);
4. Prescribed daily dose of Stivarga does not exceed 160 mg.

Approval duration: 3 months

C. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

II. Continued Approval

A. All Indications (must meet all)**:**
1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member has none of the following reasons to discontinue:
   a. Disease progression or unacceptable toxicity;
   b. Failure to tolerate 80 mg dose;
   c. Any occurrence of aspartate amino transferase (AST)/ amino alanine transferase (ALT) >20 times the upper limit of normal (ULN);
   d. Any occurrence of AST/ALT >3 x ULN with concurrent bilirubin >2 x ULN;
   e. Re-occurrence of AST/ALT >5 x ULN despite dose reduction to 120 mg;
   f. Severe or life threatening hemorrhage;
   g. Reversible posterior leukoencephalopathy syndrome;
   h. Gastrointestinal perforation or fistula;
   i. Wound dehiscence (i.e., wound rupture along surgical suture).

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy**.**

Background

Description/Mechanism of Action:

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. In in vitro biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, TrkA, Eph2A, RAF-1, BRAF, BRAF V600E, SAPK2, PTK5, and Abl at concentrations of regorafenib that have been achieved clinically. In in vivo models, regorafenib

demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

Formulations:
Stivarga tablets are for oral administration. Each tablet contains 40 mg of regorafenib in the anhydrous state, which corresponds to 41.49 mg of regorafenib monohydrate.

FDA Approved Indications:
Stivarga is a kinase inhibitor (and VEGF inhibitor)/oral tablet formulation indicated for treatment of patients with:

- Metastatic 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.
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

Appendices

Appendix A: Abbreviation Key

CRC: colorectal cancer
EGFR: epidermal growth factor receptor
GIST: gastrointestinal stromal tumor
KIT: a receptor tyrosine kinase
PDGFR: platelet-derived growth factor receptor
PDGFRA: platelet-derived growth factor receptor alpha (protein coding gene)
ULN: upper limit of normal
VEGF: vascular endothelial growth factor
VEGFR: vascular endothelial growth factor receptor

Reviews, Revisions, and Approvals	Date	Approval Date
Converted to Centene policy template and clarified algorithm language with no criteria changes.	08/13	
Added Stivarga indication for GIST	12/13	01/14
Updated disease state information Added safety and monitoring parameters Added Table 2: Dose modifications	12/14	01/15
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.	12/15	01/16
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	Approval Date
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. 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.		

References

1. Stivarga Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; August 2016. Available at http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf. Accessed November 16, 2016.
2. Regorafenib. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed November 16, 2016.
3. Colon cancer (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed November 16, 2016.
4. Rectal cancer (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed November 16, 2016.
5. Soft tissue sarcoma (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed November 16, 2016.

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.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.