Clinical Policy: Regorafenib (Stivarga)

Reference Number: ERX.SPA.93
Effective Date: 03.01.14
Last Review Date: 05.20
Line of Business: Commercial, 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 (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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Previously treated with systemic chemotherapy;
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:
Commercial – Length of Benefit
Medicaid – 6 months

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. Previously treated with imatinib (Gleevec®)* or Sutent®*, unless clinically significant adverse effects are experienced or both are contraindicated;

**Prior authorization may be required for imatinib and Sutent*

5. Request meets one of the following (a or b):*
   c. Dose does not exceed 160 mg per day;

d. 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:
Commercial – Length of Benefit
Medicaid – 6 months

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

1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Previously treated with Nexavar®* or Lenvima®*, unless clinically significant adverse effects are experienced or both are contraindicated;
   **Prior authorization may be required for Nexavar and Lenvima*
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:
Commercial – Length of Benefit
Medicaid – 6 months

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 ≥ 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:
Commercial – Length of Benefit
Medicaid – 6 months

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. Request meets one of the following (a or b):*
   a. Dose does not exceed 160 mg/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:
Commercial – Length of Benefit
Medicaid – 6 months

F. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, 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:
Commercial – Length of Benefit
Medicaid – 12 months

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 policy – ERX.PA.01 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 and may require prior authorization.

Drug Names	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 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	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	
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)		
Nexavar (sorafenib)	400 mg PO BID	800 mg/day

Drug Names	Dosing Regimen	Dose Limit/ Maximum Dose
Lenvima (lenvatinib)	8-12 mg PO QD	12 mg/day

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: First-line Therapies for Osteosarcoma per NCCN
- Preferred regimens: cisplatin and doxorubicin, MAP (hig-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. Accessed February 15, 2020.
2. Regorafenib. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at www.nccn.org. Accessed February 16, 2020.
3. Colon cancer (Version 1.2020). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 15, 2020.
4. Rectal cancer (Version 1.2020). In: National Comprehensive Cancer Network Guidelines. Available at 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. Accessed February 15, 2020.
6. Hepatobiliary cancers (Version 4.2019). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 15, 2020.
7. Bone Cancer (Version 1.2020). In: National Comprehensive Cancer Network Guidelines. Available at www.nccn.org. Accessed February 15, 2020.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy converted to new template. Removed safety criteria. Added age restriction and max dose criteria. Changed initial approval period to 3 months.	07.16	09.16
Policy converted to new template. Age removed. New indication added for hepatocellular carcinoma. Off-label NCCN recommended uses added across indications where applicable. Increased approval duration from 3/6 months to 6/12 months. Alternative therapy added at Appendix B. References updated.	06.17	08.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2018 annual review: no significant changes; age added; NCCN and FDA approved uses summarized for improved clarity; specialist involvement in care added; approval durations increased to length of benefit; 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; added Medicaid line of business with 6/12 month approval durations; references reviewed and updated.	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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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