RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	regorafenib
Policy Number:	RxA.485
Drug(s) Applied:	Stivarga®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Regorafenib (Stivarga®) is a kinase inhibitor.
It 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-endothelial 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
regorafenib (Stivarga®)	CRC, GIST, HCC	160 mg PO once daily for the first 21 days of each 28-day cycle	160 mg/day

Dosage Forms

- Tablets: 40 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

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 ≥ 18 Years;
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).

Approval duration
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

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

1. Diagnosis of GIST;
2. Previously treated with imatinib (Gleevec®)* or Sutent®* unless contraindicated or clinically significant adverse effects are experienced;
   **Prior authorization is (or 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/day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

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

1. Diagnosis of HCC;
2. Previously treated with Nexavar®* or Lenvima®* unless contraindicated or clinically significant adverse effects are experienced; **Prior authorization is (or 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/day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

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

1. Diagnosis of non-adipocytic sarcoma, angiosarcoma 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/day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months

Medicaid: 6 months
HIM: 6 months

E. Osteosarcoma (off-label)**:**

1. Diagnosis of relapsed, refractory or metastatic Osteosarcoma;
2. Previously treated with Cisplatin* and Doxorubicin* unless contraindicated or clinically significant adverse effects are experienced; **Prior authorization is (or may be) required*
3. Prescribed by or in consultation with an oncologist;
4. Age ≥ 18 Years;
4. 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).

Approval duration
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

F. Glioblastoma (off-label)**:**

1. Diagnosis of recurrent Glioblastoma;
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/day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 6 months
Medicaid: 6 months
HIM: 6 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all)**:**

1. Currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
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/day;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

Approval duration
Commercial: 12 months
Medicaid: 12 months
HIM: 12 months

I. Appendices

APPENDIX A: Abbreviation/Acronym Key
CRC: colorectal cancer

HCC: hepatocellular carcinoma
EGFR: epidermal growth factor receptor
VEGF: vascular endothelial growth factor
FDA: Food and Drug Administration
VEGFR: vascular endothelial growth factor receptor
GIST: gastrointestinal stromal tumor

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 Name	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	
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® (ziva flibercept)	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)		

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
Lenvima® (lenvatinib)	8-12 mg PO OD	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

- Boxed warning(s):
  - Hepatotoxicity
    - Severe and sometimes fatal hepatotoxicity has occurred in clinical trials.
    - Monitor hepatic function prior to and during treatment.
    - Interrupt and then reduce or discontinue STIVARGA for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence.

APPENDIX D: General Information

- 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, metastasis and tumor immunity.

References

1. Stivarga Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals. Inc.; June 2020. Available at http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf. Accessed September 1, 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Regorafenib. Available at www.nccn.org. Accessed September 1, 2020.
3. National Comprehensive Cancer Network Guidelines. Colon cancer Version 4.2020. Available at www.nccn.org. Accessed September 1, 2020.
4. National Comprehensive Cancer Network Guidelines. Rectal cancer Version 6.2020. Available at www.nccn.org. Accessed September 1, 2020.
5. National Comprehensive Cancer Network Guidelines. Soft tissue sarcoma Version 2.2020. Available at www.nccn.org. Accessed September 1, 2020.
6. National Comprehensive Cancer Network Guidelines. Hepatobiliary cancers Version 5.2020. Available at www.nccn.org. Accessed September 1, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical Policy Title was updated. 2. Line of business policy applies was updated to All lines of business. 3. Drug(s) Applied was updated. 4. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. Initial Approval criteria: Commercial, HIM and Medicaid approval duration were updated from length of benefit to 6 months. 6. Continued Approval criteria: Commercial, HIM and Medicaid approval duration were updated from length of benefit to 12 months. 7. Initial approval criteria is updated for Soft Tissue Sarcoma to include angiosarcoma in criteria. 8. Updated Initial Approval Criteria for Osteosarcoma and Glioblastoma. 9. Appendix D General Information was added. 10. References were updated. 11. Background updated to: Regorafenib (Stivarga®) is a kinase inhibitor	09/01/2020	12/07/2020