Evolent Clinical Guideline 3020 for Stivarga™ (regorafenib)

Guideline Number:	Applicable Codes	
Evolent_CG_3020		
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Original Date:	**Last Revised Date:**	**Implementation Date:**
December 2012	February 2026	February 2026

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STATEMENT

Purpose

To define and describe the accepted indications for Stivarga (regorafenib) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Colon and Rectal Cancers

- Stivarga (regorafenib) may be used as a single agent for the treatment of advanced or metastatic colon or rectal cancers in members who have disease progression, contraindications, or intolerance to oxaliplatin-based chemotherapy, irinotecan-based chemotherapy, AND, if KRAS wild type, anti-EGFR therapy (e.g. cetuximab/panitumumab).

Gastrointestinal Stromal Tumors (GIST)

- Stivarga (regorafenib) may be used as a single agent in members with recurrent/inoperable/metastatic GIST who have experienced disease progression on imatinib AND sunitinib.

Hepatocellular Carcinoma (HCC)

- Stivarga (regorafenib) may be used as a single agent in members with Child-Pugh Class A unresectable HCC, as second or subsequent line of therapy.

CONTRAINDICATIONS/WARNINGS

- US Boxed Warning
    - Severe and sometimes fatal hepatotoxicity has occurred in clinical trials. Monitor

hepatic function prior to and during treatment. Interrupt and then reduce or discontinue regorafenib for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence.

EXCLUSION CRITERIA

- Disease progression while receiving Stivarga (regorafenib).
- Stivarga (regorafenib) is being used concurrently with other anticancer therapy.
- Dosing exceeds single dose limit of 160 mg.
- Treatment with Stivarga (regorafenib) exceeds the maximum limit of 84 (40 mg) tablets/month.
- Investigational use of Stivarga (regorafenib) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
    - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
    - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
    - Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
    - Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
    - That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
    - That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
    - That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J8999 - regorafenib

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
February 2026	• Updated contraindications/warnings section • Updated references
February 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1232 Stivarga (regorafenib) • Updated exclusion criteria • Updated references
February 2024	• Updated NCH verbiage to Evolent • Updated "continuation request" verbiage

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines

contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

REFERENCES

1. Grothey A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013 Jan 26;381(9863):303-12. doi: 10.1016/S0140-6736(12)61900-X.
2. Demetri GD, et al; GRID study investigators. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013 Jan 26;381(9863):295-302. doi: 10.1016/S0140-6736(12)61857-1.
3. Bruix J, et al; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 7;389(10064):56-66. doi: 10.1016/S0140-6736(16)32453-9. Epub 2016 Dec 6. Erratum in: *Lancet*. 2017 Jan 7;389(10064):36. doi: 10.1016/S0140-6736(16)32615-0.
4. Stivarga prescribing information. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ 2025.
5. Clinical Pharmacology Elsevier Gold Standard 2026.
6. Micromedex® Healthcare Series: Micromedex Drugdex Ann Arbor, Michigan 2026.
7. National Comprehensive Cancer Network. Cancer Guidelines and Drugs and Biologics Compendium 2026.
8. AHFS Drug Information. American Society of Health-Systems Pharmacists or Wolters Kluwer Lexi-Drugs. Bethesda, MD 2026.
9. Ellis LM, et al. American Society of Clinical Oncology perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *J Clin Oncol*. 2014 Apr 20;32(12):1277-80.
10. Medicare Benefit Policy Manual Chapter 15 Covered Medical and Other Health Services: https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/bp102c15.pdf.
11. Current and Resolved Drug Shortages and Discontinuations Reported to the FDA: http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.