BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

STIVARGA® (regorafenib)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Stivarga (regorafenib) and/or generic equivalent (if available) is considered ***medically necessary*** when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. Metastatic colon or rectal cancer previously treated with fluoropyrimidine-, oxaloplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy (e.g., Nexavar (sorafenib), Sutent (sunitinib)), and if RAS wild-type an anti-EGFR therapy (e.g., Erbitux (cetuximab), Vectibix (panitumumab))

b. Locally advanced, unresectable, or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib (generic or brand Gleevec) and sunitinib (generic or brand Sutent)

c. Hepatocellular cancer (HCC) who have been previously treated with sorafenib (generic or brand Nexavar)

d. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. Individual has completed **ALL** the following **baseline tests** before initiation of treatment and will have continued monitoring as clinically appropriate:
   a. Liver function tests
   b. Evaluation of blood pressure, and if elevated is adequately controlled with medication
   c. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Will not be used in patients with severe hepatic impairment (total bilirubin > 3 times the ULN)

7. Will not be used in patients with end-stage renal disease on dialysis

8. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as:
   a. Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's wort, others)
   b. Strong CYP3A4 inhibitors (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole, others)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Stivarga (regorafenib) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist

2. Individual has documentation of positive clinical response to therapy defined as there is evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication

4. The dose is at least 80 mg once daily during the 28-day cycle

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
    a. Hepatotoxicity is **ONE** of the following:
        i. AST or ALT > 20 times the ULN
        ii. AST or ALT > 3 times the ULN with concurrent bilirubin more than 2 times the ULN
        iii. Re-occurrence of AST or ALT > 5 times the ULN despite dose reduction
    b. Severe or life-threatening hemorrhage
    c. GI perforation or fistula
    d. Severe and persistent skin toxicity such as hand-foot skin reaction (HFSR) [or palmar-plantar erythrodysesthesia syndrome (PPES)], erythema multiforme, Stevens-Johnson Syndrome, or toxic epidermal necrolysis
    e. Reversible posterior leukoencephalopathy syndrome (RPLS)
    f. Severe or uncontrolled hypertension

7. Will not be used in patients with severe hepatic impairment (total bilirubin > 3 times the ULN)

8. Will not be used in patients with end-stage renal disease on dialysis

9. Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as:
    a. Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's wort, others)
    b. Strong CYP3A4 inhibitors (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole, others)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

    1. **Off-Label Use of Non-Cancer Medications**

    2. **Off-Label Use of Cancer Medications**

Description:

Stivarga (regorafenib) is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wildtype, an anti-EGFR therapy; it is also indicated for the treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated

with imatinib mesylate and sunitinib malate; and it is indicated for the treatment of hepatocellular cancer in patients previously treated with sorafenib.

Stivarga (regorafenib) is a kinase inhibitor. It inhibits 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. Regorafenib demonstrated anti-angiogenic activity and inhibition of tumor growth as well as anti-metastatic activity in several animal models including some for human colorectal carcinoma.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

NCCN recommendation definitions:

Category 1:
Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A:
Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B:
Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3:
Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Resources:

Stivarga (regorafenib) product information, revised by Bayer HealthCare Pharmaceuticals, Inc. 02-2025. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 27, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer Version 4.2025 – Updated June 27, 2025. Available at https://www.nccn.org. Accessed October 09, 2025.

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National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Gastrointestinal Stromal Tumors Version 1.2025 – Updated April 17, 2025 Available at https://www.nccn.org. Accessed October 09, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Hepatocellular Carcinoma Version 1.2025 – March 20, 2025. Available at https://www.nccn.org. Accessed October 09, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Rectal Cancer Version 3.2025 – Updated August 26, 2025. Available at https://www.nccn.org. Accessed October 09, 2025.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

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