PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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STIVARGA® (regorafenib)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

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This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

STIVARGA® (regorafenib)

Criteria:

- **Criteria for initial therapy:** Stivarga (regorafenib) 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. A confirmed diagnosis of **ONE** of the following:
     a. Colon cancer or Rectal cancer as single agent subsequent therapy for disease that is unresectable advanced or metastatic in patients not previously treated with Stivarga (regorafenib) who have progressed through all available regimens besides Stivarga (regorafenib) or Lonsurf (trifluridine/tipiracil)

     b. Any of the following soft tissue sarcomas:
        i. Gastrointestinal Stromal Tumors (GIST) as preferred third-line therapy for unresectable or metastatic disease, with generalized (widespread, systemic) treatment for disease progression after single-agent therapy with imatinib (Gleevec or generic) and Sutent (sunitinib)

        ii. Gastrointestinal Stromal Tumors (GIST) as fourth-line therapy in combination with Afinitore (everolimus) for unresectable or metastatic disease progression after single-agent therapy with imatinib (Gleevec or generic), and Sutent (sunitinib), and Stivarga (regorafenib)

        iii. Angiosarcoma as single-agent therapy

        iv. Extremity/Superficial Trunk, Head/Neck as single-agent palliative therapy for non-adipocytic sarcoma as subsequent lines of therapy with stage IV or recurrent for advanced/metastatic disease with disseminated metastases

        v. Retroperitoneal/Intra-Abdominal as single-agent palliative therapy for non-adipocytic sarcoma as subsequent lines of therapy for recurrent unresectable or progressive Stage IV disease

        vi. Rhabdomyosarcoma as single-agent palliative subsequent line of therapy for advanced/metastatic pleomorphic rhabdomyosarcoma

        vii. Solitary fibrous tumor as single-agent therapy

        viii. Undifferentiated pleomorphic sarcoma (UPS) as preferred single-agent therapy

     c. Hepatocellular cancer (HCC) as single agent subsequent therapy for progressive disease in patients (Child-Pugh Class A only) in any of the following:
        i. Unresectable disease and are not a transplant candidate

ii. Inoperable by performance status or comorbidity, or have local disease or local disease with minimal extrahepatic disease only

iii. Metastatic disease or extensive liver tumor burden

d. Osteosarcoma as second-line single agent therapy for relapsed/refractory or metastatic disease (preferred)

e. Glioblastoma as a preferred single agent for recurrent disease

f. 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. **ALL** of the following baseline tests have been completed before initiation of treatment with continued monitoring as clinically appropriate:
   a. Liver function tests
   b. Evaluation of blood pressure, and if elevated is adequately controlled with medication

5. Will not be used in patients with severe hepatic impairment (total bilirubin > 3x ULN)

6. Will not be used with strong CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's wort

7. Will not be used with strong CYP3A4 inhibitors such as clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and voriconazole

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Stivarga (regorafenib) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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

2. Individual's condition has not worsened while on therapy
   a. Worsening is defined as:
      i. Disease progressed while on Stivarga
      ii. There is no 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. Individual has not developed any significant level 4 adverse drug effects that may exclude continued use

STIVARGA® (regorafenib)

a. Significant adverse effect such as:
   i. Liver toxicity
   ii. Hemorrhage
   iii. GI perforation or fistula
   iv. Skin toxicity
   v. Reversible posterior leukoencephalopathy syndrome (RPLS)
   vi. Uncontrolled hypertension

6. There are no significant interacting drugs

Renewal duration: 12 months

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 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.

Resources:

Stivarga (regorafenib) product information, revised by manufacturer 06-2020, at DailyMed http://dailymed.nlm.nih.gov accessed 09-01-2020

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Colon Cancer Version 4.2020 – June 15, 2020 ; https://www.nccn.org. Accessed September 2, 2020

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Soft Tissue Sarcoma Version 2.2020 – May 28, 2020 ; https://www.nccn.org. Accessed September 2, 2020

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Hepatobiliary Cancers Version 5.2020 – August 4, 2020 ; https://www.nccn.org. Accessed September 2, 2020

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Rectal Cancer Version 6.2020 – June 25, 2020 ; https://www.nccn.org. Accessed September 2, 2020

STIVARGA® (regorafenib)

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Bone Cancer Version 1.2020 – August 12, 2019 ; https://www.nccn.org. Accessed September 2, 2020

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers Version 2.2020 – April 30,2020 ; https://www.nccn.org. Accessed September 2, 2020

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.