BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/01/16**
SECTION: DRUGS	**LAST REVIEW DATE: 11/16/17**
	LAST CRITERIA REVISION DATE: 11/16/17
	ARCHIVE DATE:

STIVARGA® (regorafenib) oral tablet

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.

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) oral tablet (cont.)

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.

Stivarga (regorafenib)

Medication class:
Antineoplastic agent, tyrosine kinase inhibitor, vascular endothelial growth factor (VEGRF) inhibitor

FDA-approved indication(s):
- Treatment of metastatic colorectal cancer in patients previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, antivascular endothelial growth factor (VEGF) therapy, and if RAS wild type, an antiepidermal growth factor receptor (EGFR) therapy
- Treatment of locally advanced, unresectable or metastatic GI stromal tumor (GIST) in patients previously treated with imatinib and sunitinib
- Treatment of hepatocellular cancer (HCC) in patients previously treated with sorafenib

Recommended Dose:
- 160 mg once daily for the first 21-days of each 28-day cycle

Maximum dosage
- Not stated

Available Dosage Forms:
- 40 mg tablets

Warnings, Precautions, and other Clinical Information:
- Permanently discontinue for failure to tolerate 80mg dose
- Stivarga is not recommended for use in patients with severe hepatic impairment (total bilirubin > 3x ULN)
- Interrupt and reduce dose or discontinue for hepatotoxicity
- Permanently discontinue for any occurrence of AST or ALT > 20x ULN
- Permanently discontinue for any occurrence of AST or ALT > 3x ULN with concurrent bilirubin > 2x ULN
- Permanently discontinue for re-occurrence of AST or ALT > 5x ULN despite dose reduction to 120mg
- Permanently discontinue for severe of life-threatening hemorrhage
- Permanently discontinue for gastrointestinal perforation or fistula

STIVARGA® (regorafenib) oral tablet (cont.)

- Interrupt and reduce dose or permanently discontinue for severe and persistent dermatologic toxicity such as hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome (PPES), erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis
- Blood pressure should be well controlled before starting therapy
- Interrupt or permanently discontinue for severe or uncontrolled hypertension occurs
- Interrupt therapy in patients who develop new or acute onset cardiac ischemia or infarction, restart after resolution of acute event
- Discontinue if reversible posterior leukoencephalopathy syndrome (RPLS) occurs
- Woman who is breast feeding an infant or child should stop breast feeding
- Woman of child bearing potential should use effective contraception
- Male on Stivarga with female partners of reproductive potential should use effective contraception
- Avoid use with strong CYP3A4 inducers such as carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's wort
- Avoid use with strong CYP3A4 inhibitors such as clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and voriconazole

Criteria:

- **Criteria for initial therapy:** Stivarga (regorafenib) is considered ***medically necessary*** when **ALL** of the following criteria are met:

1. Prescriber is an Oncologist

2. Individual is 18 years of age or older

3. A confirmed diagnosis of **ONE** of the following:
    - Metastatic colorectal cancer (CRC) who has been previously treated with the following:
        - Flouropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy
        - Anti-VEGF therapy – bevacizumab
        - If KRAS wild type, an anti-EGFR therapy – cetuximab, panitumumab
            - Example regimens include:
                - FOLFOX with or without bevacizumab
                - CAPEOX with or without bevacizumab
                - FOLFOX with cetuximab or panitumumab
                - FOLFIRI with or without bevacizumab
                - FOLFIRI with cetuximab or panitumumab
                - FOLFOXIRI with or without bevacizumab
                - 5FU/leucovorin with or without bevacizumab
                - Capecitabine with or without bevacizumab

    - Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who has progressed after previous treatment with **both** of the following:
        - Imatinib
        - Sunitinib

STIVARGA® (regorafenib) oral tablet (cont.)

- Hepatocellular cancer (HCC) patient who is Child-Pugh Class A who has progressed on or after previous treatment with sorafenib

4. **ALL** of the following baseline tests have been completed before initiation of treatment:
   - Liver function tests

Initial approval duration: 6 months with initial fills of 14 days per fill for first 3 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 an Oncologist

2. Individual's condition has not worsened while on therapy
   - Worsening is defined as:
     - Disease progressed while on Stivarga

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use such as:
   - Liver toxicity
     - Signs and symptoms may include:
       - Right sided abdominal pain, bruising, yellow skin or eyes, dark brown urine, severe nausea or vomiting, fatigue, light colored pale stools, itching, confusion
   - Hemorrhage
     - Signs and symptoms may include:
       - Rectal bleeding, bleeding gums, coughing up blood, vomiting blood, blood in urine, blood in stools, nose bleeds, unusual bleeding, easy bruising
   - GI perforation or fistula
     - Signs and symptoms may include:
       - Abdominal tenderness or severe pain in abdomen, nausea, vomiting
   - Skin toxicity
     - Signs and symptoms may include:
       - Rashes, redness, pain, swelling, or blisters on palms of hands or soles of feet, hives, oral ulcers
   - Reversible posterior leukoencephalopathy syndrome (RPLS)
     - Signs and symptoms may include:
       - Rapid onset of headache, seizures, altered consciousness, and visual disturbance, often but not always associated with acute hypertension

5. There are no significant interacting drugs

Renewal duration: 12 months

STIVARGA® (regorafenib) oral tablet (cont.)

Resources:

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.

Stivarga. Package Insert. Revised by manufacturer 04/2015. Accessed 09-04-2015.

Stivarga. Package Insert. Revised by manufacturer 08/2016. Accessed 10-20-2016

NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary cancers. Version 4.2017, Oct 9, 2017. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf

NCCN Clinical Practice Guidelines in Oncology: Soft tissue sarcoma. Version 1.2018, Oct 31, 2017. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf

UpToDate: Systemic chemotherapy for metastatic colorectal cancer: General principles. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/systemic-chemotherapy-for-metastatic-colorectal-cancer-general-principles?source=see_link#H9659249

NCCN Clinical Practice Guidelines in Oncology: Rectal cancer. Version 3.2017, Mar 13, 2017. https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf

NCCN Clinical Practice Guidelines in Oncology: Colon cancer. Version 2.2017, Mar 13 2017. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

UpToDate: Systemic chemotherapy for nonoperable metastatic colorectal cancer: Treatment recommendations. Current through Oct 2017. https://www-uptodate-com.mwu.idm.oclc.org/contents/systemic-chemotherapy-for-nonoperable-metastatic-colorectal-cancer-treatment-recommendations?source=search_result&search=colorectal%20cancer&selectedTitle=8~150

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Fax completed prior authorization request form to 602-864-3126 or email to pharmacyprecert@azblue.com.
Call 866-325-1794 to check the status of a request.
All requested data must be provided. **Incomplete forms or forms without the chart notes will be returned.**
Pharmacy Coverage Guidelines are available at www.azblue.com/pharmacy.

Pharmacy Prior Authorization Request Form

Do not copy for future use. Forms are updated frequently.
REQUIRED: Office notes, labs, and medical testing relevant to the request that show medical justification are required.

Member Information

Member Name (first & last):	Date of Birth:	Gender:	BCBSAZ ID#:
Address:	City:	State:	Zip Code:

Prescribing Provider Information

Provider Name (first & last):	Specialty:	NPI#:	DEA#:
Office Address:	City:	State:	Zip Code:
Office Contact:	Office Phone:	Office Fax:	

Dispensing Pharmacy Information

Pharmacy Name:	Pharmacy Phone:	Pharmacy Fax:

Requested Medication Information

Medication Name:	Strength:		Dosage Form:
Directions for Use:	Quantity:	Refills:	Duration of Therapy/Use:

☐ Check if requesting **brand** only ☐ Check if requesting **generic**

☐ Check if requesting continuation of therapy (prior authorization approved by BCBSAZ expired)

Turn-Around Time For Review

☐ Standard ☐ Urgent. Sign here: _____ ☐ Exigent (requires prescriber to include a written statement)

Clinical Information

1. **What is the diagnosis? Please specify below.**

   ICD-10 Code: _____ **Diagnosis Description:** _____

2. ☐ Yes ☐ No **Was this medication started on a recent hospital discharge or emergency room visit?**

3. ☐ Yes ☐ No **There is absence of ALL contraindications.**

4. **What medication(s) has the individual tried and failed for this diagnosis? Please specify below.**
Important note: Samples provided by the provider are not accepted as continuation of therapy or as an adequate trial and failure.

Medication Name, Strength, Frequency	Dates started and stopped or Approximate Duration	Describe response, reason for failure, or allergy

5. **Are there any supporting labs or test results? Please specify below.**

Date	Test	Value

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Pharmacy Prior Authorization Request Form

6. Is there any additional information the prescribing provider feels is important to this review? Please specify below.
For example, explain the negative impact on medical condition, safety issue, reason formulary agent is not suitable to a specific medical condition, expected adverse clinical outcome from use of formulary agent, or reason different dosage form or dose is needed.

Signature affirms that information given on this form is true and accurate and reflects office notes

Prescribing Provider's Signature: Date:

Please note: Some medications may require completion of a drug-specific request form.

Incomplete forms or forms without the chart notes will be returned.

Office notes, labs, and medical testing relevant to the request that show medical justification are required.