

## PRIOR AUTHORIZATION POLICY

**POLICY:** Oncology – Stivarga® (regorafenib tablets – Bayer HealthCare Pharmaceuticals, Inc.)

**TAC APPROVAL DATE:** 01/30/2019

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### OVERVIEW

Stivarga, a kinase inhibitor, is indicated for the treatment of patients with the following conditions:<sup>1</sup>

1. Metastatic colorectal cancer (mCRC) 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-epidermal growth factor receptor (EGFR) therapy;
2. Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treatment with Gleevec® (imatinib mesylate tablets) and Sutent® (sunitinib malate capsules);
3. Hepatocellular carcinoma (HCC) who have been previously treated with Nexavar® (sorafenib tablets).

Stivarga 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. In *in vitro* biochemical or cellular assays, Stivarga (or its major active metabolites) inhibited the activity of various receptors, some of which include vascular endothelial growth factor receptor (VEGFR)1, VEGFR2, VEGFR3, platelet-derived growth factor receptor (PDGFR)-alpha, PDGFR-beta, fibroblast growth factor receptor (FGFR)1, FGFR2, BRAF, BRAF<sup>V600E</sup>, and Abl at concentrations of Stivarga that have been achieved clinically.

### Guidelines

#### *Colon and/or Rectal Cancer*

The National Comprehensive Cancer Network (NCCN) guidelines on colon cancer (version 3.2018) and rectal cancer (version 3.2018) recommend Stivarga as subsequent therapy as a single agent for unresectable advanced or metastatic disease not previously treated with Stivarga for the following uses: for first progression (*KRAS/NRAS* mutant only) or second progression for disease previously treated with FOLFOXIRI (5-fluorouracil/leucovorin, irinotecan, oxaliplatin) regimen with or without Avastin® (bevacizumab solution for intravenous injection), for second progression for disease previously treated with irinotecan- and oxaliplatin-based regimens, or for progression for disease that progressed through all available regimens, including Lonsurf® (trifluridine and tipiracil tablets). Stivarga may be given before or after Lonsurf.

#### *Hepatocellular Carcinoma*

The NCCN clinical practice guidelines on hepatobiliary cancers (version 1.2019 – Dec. 17, 2018) recommend Stivarga for subsequent treatment as a single agent for patients with hepatocellular carcinoma (adenocarcinoma) [Child-Pugh Class A only] and disease progression for the following uses (all are category 1): 1) in patients who are not transplant candidates with unresectable disease, 2) in patients who are inoperable by performance status or comorbidity (local disease or local disease with minimal extrahepatic disease only), or in patients who have extensive liver tumor burden or metastatic disease.<sup>6,8</sup>

#### *Soft Tissue Sarcoma*

The NCCN soft tissue sarcoma guidelines (version 1.2019 – Dec. 19, 2018) recommend Stivarga (category 1) for treatment of progressive GIST disease when the patient is no longer receiving benefit from Gleevec or Sutent.<sup>4</sup> If disease is progressing despite prior therapy with Gleevec or Sutent, the following options may be

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considered: Stivarga (category 1), clinical trial, or best supportive care. Discontinuing tyrosine kinase inhibitor (TKI) therapy (i.e., Gleevec, Sutent, or Stivarga) even with progressive disease may accelerate the pace of disease progression and worsen symptoms. In patients with GIST progressing despite Gleevec, Sutent, and Stivarga, other options may be considered or a previously tolerated and effective TKI may be restarted for palliation of symptoms. Stivarga, imatinib (Gleevec® tablets, generics) or Sutent® (sunitinib capsules) can be used in combination with Afinitor® (everolimus tablets). Continuation of life-long TKI therapy should be considered for palliation of symptoms as part of best supportive care.

The NCCN soft tissue guidelines (version 1.2019 – Dec. 19, 2018) recommend Stivarga (all category 2A) as single-agent palliative therapy for patients with: 1) non-adipocytic extremity/superficial trunk, head/neck sarcoma with stage IV or recurrent disease with disseminated metastases, 2) non-adipocytic retroperitoneal/intra-abdominal sarcoma with unresectable or progressive disease, or 3) pleomorphic rhabdomyosarcoma.<sup>4,8</sup>

### **Safety**

Stivarga has Boxed Warnings concerning risks of hepatotoxicity.<sup>1</sup> Hepatic function should be monitored prior to and during treatment. Depending on severity and persistence, therapy with Stivarga should be interrupted and then reduced or discontinued for hepatotoxicity manifested by elevated liver function tests or hepatocellular necrosis.

### **POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of Stivarga. All approvals are provided for 3 years in duration unless otherwise noted below.

**Automation:** None.

### **RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of Stivarga is recommended in those who meet the following criteria:

#### **FDA-Approved Indications**

1. **Colorectal Cancer, Metastatic.** Approve for 3 years if the patient meets the following criteria (A, B, C, and D):
  - A) Patient has been previously treated with a fluoropyrimidine (e.g., capecitabine, 5-fluorouracil [5-FU]);  
AND
  - B) Patient has been previously treated with oxaliplatin; AND
  - C) Patient has been previously treated with irinotecan; AND
  - D) If the patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and/or *NRAS* wild-type) [that is, the tumors or metastases are *KRAS* and/or *NRAS* mutation negative], Erbitux (cetuximab injection for intravenous infusion) or Vectibix (panitumumab injection for intravenous infusion) has been tried.
  
2. **Gastrointestinal Stromal Tumor (GIST), Metastatic and/or Unresectable.** Approve for 3 years if the patient meets the following criteria (A and B):
  - A) Patient has previously tried Gleevec (imatinib mesylate tablets); AND
  - B) Patient has previously tried Sutent (sunitinib malate capsules).

- 3. Hepatocellular Carcinoma.** Approve for 3 years if the patient has previously treated with at least one tyrosine kinase inhibitor (e.g., Nexavar [sorafenib tablets], Lenvima® [lenvatinib capsules]).

In one Phase III trial, patients with hepatocellular carcinoma who tolerated Nexavar and progressed on Nexavar, and had Child-Pugh Class A liver function, were randomized to receive best supportive care plus Stivarga (n = 379) or placebo (n = 194).<sup>7</sup> Median overall survival, the primary endpoint, was 10.6 months (95% confidence interval [CI]: 9.1,12.1) with Stivarga vs. 7.8 months (95% CI: 6.3, 8.8) with placebo (hazard ratio 0.63; 95% CI: 0.50, 0.79; one-sided P < 0.0001).

#### Other Uses with Supportive Evidence

- 4. Soft Tissue Sarcoma.** Approve for 3 years if the patient meets one of the following criteria (A or B):
- A) The patient has non-adipocytic extremity/superficial trunk, head/neck, or retroperitoneal/intra-abdominal sarcoma, OR
  - B) The patient has pleomorphic rhabdomyosarcoma.

#### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Stivarga has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. Renal Cell Carcinoma that is Metastatic and/or Unresectable.** Stivarga has demonstrated clinical benefit in one very small Phase II study in patients (n = 49) with previously untreated metastatic or unresectable renal cell carcinoma.<sup>5</sup> Multiple other oral agents are indicated for the treatment of renal cell carcinoma. Stivarga has not been compared to any currently available treatment for renal cell carcinoma. More data are needed to further define the place in therapy of Stivarga for the treatment of renal cell carcinoma.
- 2.** Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

#### REFERENCES

1. Stivarga® tablets [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; June 2018.
2. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 3.2018 – August 7, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 3, 2018.
3. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (Version 3.2017 – August 7, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on October 3, 2018.
4. The NCCN Soft Tissue Sarcoma Practice Guidelines in Oncology (Version 1.2019 – December 19, 2018). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on December 14, 2019.
5. Eisen T, Joensuu H, Nathan PD, et al. Regorafenib for patients with previously untreated metastatic or unresectable renal-cell carcinoma: a single-group phase 2 trial. *Lancet Oncol.* 2012;13:1055-1062.
6. The NCCN Hepatobiliary Cancers Practice Guidelines in Oncology (Version 1.2019 – December 17, 2018). © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on January 14, 2019.
7. Bruix J, Qin S, Merle P, 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;389(10064):56-66.
8. The NCCN Drugs and Biologics Compendium. © 2019 National Comprehensive Cancer Network, Inc. Available at: <http://www.nccn.org>. Accessed on January 14, 2019. Search term: regorafenib.

### OTHER REFERENCES UTILIZED

- Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol.* 2016;17(12):1732-1742.

### HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	Revised criteria to clarify that the patient's tumor or metastases are wild-type KRAS and/or NRAS, that is, KRAS and/or NRAS mutation negative.	10/14/2015
Annual revision	No criteria changes.	10/05/2016
Selected revision	Criteria added for hepatocellular carcinoma.	05/03/2017
Annual revision	Colorectal Cancer criteria revised to add wild-type RAS. Previously criteria stated KRAS and/or NRAS that are the components of RAS. Wild-type refers to both KRAS and NRAS.	10/25/2017
Annual revision	Removed Other Uses with Supportive Evidence.	10/17/2018
Early annual revisions	Hepatocellular carcinoma criteria revised to require use of at least one TKI prior to Stivarga. Prior criteria required Nexavar specifically. Criteria added for soft tissue sarcoma.	01/30/2019

TAC – Therapeutic Assessment Committee; DEU – Drug Evaluation Unit; \* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>.