PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Stivarga Prior Authorization Policy
- Stivarga® (regorafenib tablets – Bayer)

REVIEW DATE: 03/19/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Stivarga, a kinase inhibitor, is indicated for the following uses:[1]

- **Colorectal cancer**, metastatic, in patients 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.
- **Gastrointestinal stromal tumor (GIST)**, locally advanced, unresectable, or metastatic in patients who have been previously treated with imatinib and sunitinib.
- **Hepatocellular carcinoma**, in patients who have been previously treated with sorafenib.

Guidelines

Stivarga is discussed in National Comprehensive Cancer Network (NCCN) guidelines:[2]

- **Bone Cancer**: NCCN guidelines (version 2.2025 – February 28, 2025) recommend Stivarga as a single agent "Preferred Regimen" for second-line therapy for relapsed/refractory or metastatic disease for patients with osteosarcoma (category 1).[3] Stivarga is also recommended under "Other

Recommended Regimens" for second-line treatment (relapsed/refractory or metastatic disease) of Ewing sarcoma (category 2A).

- **Central Nervous System Cancers**: NCCN guidelines (version 4.2024 – January 21, 2025) recommend Stivarga as a single agent "Preferred Regimen" for the treatment of recurrent or progressive glioblastoma (category 2A).[4] NCCN notes in a footnote that the options for recurrent or progressive glioblastoma also apply for H3-mutated high-grade glioma.
- **Colon Cancer and Rectal Cancer**: NCCN guidelines (colon cancer [version 1.2025 – February 7, 2025] and rectal cancer [version 1.2025 – February 7, 2025]) recommend Stivarga as subsequent therapy as a single agent for advanced or metastatic disease not previously treated with Stivarga in patients who have progressed through all available regimens except Stivarga, Fruzaqla® (fruquintinib capsules), or Lonsurf® (trifluridine and tipiracil tablets) with or without bevacizumab.[5,6] Appendiceal adenocarcinoma are treated similarly to colon cancer.
- **Gastrointestinal Stromal Tumors (GIST)**: NCCN guidelines (version 2.2024 – July 31, 2024) recommend Stivarga as a "Preferred Regimen" in the third-line setting (category 1) for treatment of unresectable, progressive, or metastatic disease after single-agent therapy with imatinib or sunitinib [both category 1].[7] Ayvakit® (avapritinib tablets) is a "Preferred Regimen" in the first-line setting for GIST with *PDGFRA* exon 19 mutations that are insensitive to imatinib (including *PDGFRA D842V*). Stivarga in combination with everolimus tablets is recommended as "Useful in Certain Circumstances" for unresectable, recurrent, or metastatic disease after failure on approved therapies. Stivarga is also recommended as "Useful in Certain Circumstances" for unresectable, succinate dehydrogenase (SDH)-deficient disease (category 2A) in the first-line setting.[7]
- **Hepatocellular Carcinoma**: NCCN guidelines (version 4.2024 – January 10, 2025) 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): in patients who are not transplant candidates with unresectable disease; in patients who have liver-confined disease, inoperable by performance status or comorbidity or with minimal or uncertain extrahepatic disease; or in patients who have extensive liver tumor burden or metastatic disease.[8]
- **Soft Tissue Sarcoma**: NCCN guidelines (version 5.2024 – March 10, 2025) recommend Stivarga as a single-agent subsequent therapy for patients with non-adipocytic sarcoma with advanced/metastatic disease, advanced/metastatic pleomorphic rhabdomyosarcoma, or angiosarcoma (all category 2A).[9]
- **Uterine Neoplasms**: NCCN guidelines (version 3.2025 – March 7, 2025) recommend Stivarga as a second-line or subsequent therapy option for uterine sarcoma as one of the "Other Recommended Regimens" for patients with recurrent/metastatic, advanced or inoperable disease (category 2A).[10]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Stivarga. All approvals are provided for the duration noted below.

- **Stivarga® (regorafenib tablets - Bayer)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Colon, Rectal and Appendiceal Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, E, and F):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has advanced or metastatic disease; AND
   - **C)** Patient has been previously treated with a fluoropyrimidine (e.g., capecitabine, 5-fluorouracil [5-FU]); AND
   - **D)** Patient has been previously treated with oxaliplatin; AND
   - **E)** Patient has been previously treated with irinotecan; AND
   - **F)** Patient meets ONE of the following (i or ii):
     - **i.** Patient's tumor or metastases are wild-type *RAS* (*KRAS* wild-type and *NRAS* wild-type) and the patient meets ONE of the following (a or b):
       Note: This includes tumors or metastases that are *KRAS* and *NRAS* mutation-negative.
       - **a)** The patient has tried Erbitux (cetuximab intravenous infusion) or Vectibix (panitumumab intravenous infusion); OR
       - **b)** The patient's tumor did not originate on the left side of the colon (from the splenic fixture to rectum); OR
     - **ii.** The patient's tumor has or metastases have a *RAS* mutation (either *KRAS* mutation or *NRAS* mutation).

2. **Gastrointestinal Stromal Tumor.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has tried BOTH of the following (a and b):
       - **a)** Imatinib or Ayvakit (avapritinib tablets); AND
       - **b)** Sunitinib or Sprycel (dasatinib tablets); OR
     - **ii.** The medication is used as first-line therapy for succinate dehydrogenase (SDH)-deficient disease.

3. **Hepatocellular Carcinoma.** Approve for 1 year if the patient meets BOTH of the following (A and B):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has been previously treated with one systemic regimen.

Note: Examples of a systemic regimen include: Tecentriq (atezolizumab intravenous infusion), bevacizumab, sorafenib, Lenvima (lenvatinib capsules), Opdivo (nivolumab intravenous infusion), Imjudo (tremelimumab-actl intravenous infusion), Imfinzi (durvalumab intravenous infusion).

Other Uses with Supportive Evidence

4. **Central Nervous System Tumors.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has recurrent or progressive disease; AND
   C) Patient has ONE of the following (i or ii):
      i. Glioblastoma; OR
      ii. *H3*-mutated high-grade glioma.

5. **Bone Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has relapsed/refractory or metastatic disease; AND
   C) Patient has tried one systemic chemotherapy regimen; AND
   Note: Examples of a systemic chemotherapy regimen contain one of more of the following: cisplatin, doxorubicin, methotrexate, ifosfamide, cyclophosphamide, etoposide, topotecan, irinotecan, vincristine, temozolomide.
   D) Patient meets ONE of the following (i or ii):
      i. Patient has Ewing sarcoma; OR
      ii. Patient has osteosarcoma.

6. **Soft Tissue Sarcoma.** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   A) Patient is ≥ 18 years of age; AND
   B) Patient has advanced or metastatic disease; AND
   C) Patient has ONE of the following (i, ii, or iii):
      i. Non-adipocytic sarcoma; OR
      ii. Pleomorphic rhabdomyosarcoma; OR
      iii. Angiosarcoma.

7. **Uterine Sarcoma**. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   Note: Examples of uterine sarcoma include endometrial stromal sarcoma, undifferentiated uterine sarcoma, or uterine leiomyosarcomas.
      A) Patient is ≥ 18 years of age; AND
      B) Patient has recurrent, advanced, inoperable, or metastatic disease; AND
      C) Patient has tried at least one systemic regimen.
      Note: Examples of systemic regimen include one or more of the following: doxorubicin, docetaxel, gemcitabine, ifosfamide, dacarbazine, epirubicin, or vinorelbine.

CONDITIONS NOT COVERED

- **Stivarga® (regorafenib tablets - Bayer)**

is(are) considered experimental, investigational or unproven for ANY other use(s) including the following; criteria will be updated as new published data are available

REFERENCES

1. Stivarga® tablets [prescribing information]. Whippany, NJ: Bayer; February 2025.
2. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025. Search term: regorafenib.
3. The NCCN Bone Cancer Clinical Practice Guidelines in Oncology (version 2.2025 – February 28, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
4. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 4.2024 – January 21, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
5. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – February 7, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
6. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 1.2025 – February 7, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
7. The NCCN Gastrointestinal Stromal Tumors Clinical Practice Guidelines in Oncology (version 2.2024 – July 31, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
8. The NCCN Hepatocellular Carcinoma Clinical Practice Guidelines in Oncology (version 4.2024 – January 10, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
9. The NCCN Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (version 5.2024 – March 10, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on March 17, 2025.
10. The NCCN Uterine Neoplasms Clinical Practice Guidelines in Oncology (version 3.2025 – March 7, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed March 17, 2025.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Colon, Rectal, and Appendiceal Cancer:** Appendiceal cancer was added to this condition of approval. **Soft Tissue Sarcoma:** Solitary fibrous tumor was removed from the list of soft tissue sarcomas.	03/08/2023
Annual Revision	**Bone Cancer:** Changed indication name from "Osteosarcoma" to "Bone Cancer". Added new criteria to approve for use in Ewing sarcoma or osteosarcoma. Added more examples of drugs, such as cyclophosphamide, etoposide, irinotecan, topotecan, vincristine, temozolomide, to the Note. **Glioblastoma:** While referring to disease description, added "or progressive" disease, in addition to recurrent disease.	03/06/2024

Annual Revision	**Gastrointestinal Stromal Tumor:** Added criteria for Stivarga use as first-line therapy for succinate dehydrogenase (SDH)-deficient disease. **Central Nervous System Tumors:** Changed indication name from Glioblastoma. Added new criterion to approve for Glioblastoma or *H3*-mutated high-grade glioma. **Uterine Sarcoma:** This condition and criteria for approval were added to the policy.	03/19/2025