09-J1000-83

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Reviewed: 01/09/19

Revised: 02/15/19

Subject: Regorafenib (Stivarga®) Tablets

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Regorafenib (Stivarga) is an oral multikinase inhibitor. It works by inhibiting tyrosine kinases that promote angiogenesis and tumor growth such as vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, VEGFR-3, platelet derived growth factor receptor (PDGFR)-alpha, PDGFR-beta, and TIE2 and oncogenic kinases c-KIT, REF, and BRAF.

Regorafenib was initially approved in 2012 for the treatment of metastatic colorectal cancer (mCRC) in persons who have previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an anti-VEGF therapy; and an anti-EGFR therapy if RAS mutation-negative (wild type). The approval was expanded in 2013 to include treatment of locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) in persons who have previously received imatinib and sunitinib. In April 2017, regorafenib was approved for persons with hepatocellular carcinoma previously treated with sorafenib.

Approval of regorafenib for the treatment of mCRC was based on a single Phase III, multi-center, double-blind, placebo controlled, randomized trial. A total of 760 subjects with documented cancer of the colon or rectum were randomized 2:1 to regorafenib 160 mg orally once daily or placebo. The primary endpoint was overall survival (OS). In a pre-planned interim analysis, the median OS was 6.4 months and 5 months in the regorafenib and placebo arms, respectively. The trial was terminated for efficacy as the primary endpoint of OS was met.

The approval for treatment of GIST was also based on a single Phase III, multi-center, double-blind, placebo-controlled, randomized trial in which 199 subjects were randomized to regorafenib 160 mg daily or placebo. Progression-free survival (PFS), the primary endpoint, was statistically greater in the regorafenib arm when compared to placebo (4.8 months vs. 0.9 months, respectively; $p<0.001$).

The National Comprehensive Cancer Network (NCCN) guidelines recommend the use of regorafenib for colon and rectal cancer, hepatocellular carcinoma, and various types of soft tissue sarcomas.

POSITION STATEMENT:

I. Initiation of regorafenib (Stivarga®) **meets the definition for medical necessity** for members diagnosed with **ANY** of the following conditions when **ALL** associated criteria are met:

A. **Colon or Rectal Cancer**

1. Regorafenib will be used as a single agent
2. Member has metastatic or unresectable advanced disease
3. Member has not previously received regorafenib
4. Member meets **ONE** of the following:
    a. Regorafenib is used following disease progression with FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) +/- bevacizumab **AND** the member's disease is positive for the KRAS/NRAS mutation
    b. Regorafenib is used as third-line or subsequent (i.e., fourth line or greater) therapy for disease progression after previous treatment with **THREE** or more of the following agents (combination use or in separate regimens):
        i. Anti-EGFR therapy (e.g., panitumumab or cetuximab) if KRAS/NRAS gene is normal (i.e., without mutation, also known as wild type).
        ii. Anti-VEGF therapy (e.g., bevacizumab, ziv-aflibercept or ramucirumab).
        iii. Fluoropyrimidine-containing chemotherapy (e.g., fluorouracil or capecitabine).
        iv. Irinotecan-containing chemotherapy
        v. Oxaliplatin-containing chemotherapy
        vi. Trifluridine/tipiracil
5. The dose does not exceed 160 mg daily for 21 days of a 28 day cycle

B. Hepatocellular carcinoma

1. Regorafenib is used as a single agent
2. Member had disease progression on first line systemic treatment
3. Member has Child-Pugh Class A disease
4. **ONE** of the following:
    a. Unresectable disease and is not a candidate for transplant
    b. Metastatic disease
    c. Inoperable due to performance status or comorbidities and has local disease
    d. Extensive tumor burden
5. The dose does not exceed 160 mg daily for 21 days of a 28 day cycle

C. **Soft Tissue Sarcoma**

1. **ONE** of the following:
    a. When used for **Gastrointestinal Stromal Tumors (GIST)** and **ONE** of the following are met:
        i. When used as a single agent for disease progression after therapy with imatinib (Gleevec) or sunitinib (Sutent)
        ii. When used in combination with everolimus (Afinitor) for disease progression after single-agent therapy with imatinib, sunitinib, and regorafenib
    b. When used as a single agent as palliative therapy for non-adipocytic soft tissue sarcoma that is unresectable, recurrent, progressive, or metastatic
    c. When used as a single agent as palliative therapy for pleomorphic rhabdomyosarcoma
2. The dose does not exceed 160 mg daily for 21 days of a 28 day cycle

D. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
1. **ONE** of the following is met:
    a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
    i. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
2. Dose does not exceed the maximum FDA-approved dose

Duration of approval: 180 days (all indications)

I. Continuation of regorafenib (Stivarga®) **meets the definition of medical necessity** for the treatment of colon or rectal cancer, soft tissue sarcoma, hepatocellular carcinoma or other FDA-approved or NCCN supported diagnosis when the following criteria are met:
A. The member's disease has not progressed while receiving treatment with regorafenib*
B. The member has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
C. The dose does not exceed 160 mg daily for 21 days of a 28 day cycle

Approval duration: 1 year

*Exception if use is in combination with everolimus (Afinitor) for Gastrointestinal Stromal Tumor for disease progression after single-agent therapy with regorafenib

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved: regorafenib is indicated for treatment of the following conditions

- Metastatic colorectal cancer in persons who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild type, an anti-EGFR therapy
- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor in persons who have been previously treated with imatinib and sunitinib malate.
- Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib

The recommended dose is 160 mg regorafenib (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle. Regorafenib should be swallowed whole and administered with food at the same time each day (a low-fat meal, less than 30% fat)

Dose adjustments:

Interrupt for the following:

- Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia (PPE)] that is recurrent or does not improve within 7 days despite dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR
- Symptomatic Grade 2 hypertension
- Any CTCAE Grade 3 or 4 adverse reaction
- Worsening infection of any grade

Reduce the dose to 120 mg:

- For the first occurrence of Grade 2 HFSR of any duration
- After recovery of any Grade 3 or 4 adverse reaction except infection
- For Grade 3 aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevation; only resume if the potential benefit outweighs the risk of hepatotoxicity

Reduce the dose to 80 mg:

- For re-occurrence of Grade 2 HFSR at the 120 mg dose
- After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity or infection)

Discontinue permanently for the following:

- Failure to tolerate 80 mg dose
- Any occurrence of AST/ ALT elevation more than 20 times the upper limit of normal (ULN)

- Any occurrence of AST/ ALT elevation more than 3 times the ULN with concurrent bilirubin more than 2 times ULN
- Re-occurrence of AST/ ALT elevation more than 5 times the ULN despite dose reduction to 120 mg
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the risks

Drug Availability: regorafenib is supplied as a 40 mg tablet.

PRECAUTIONS:

Contraindications

None

Boxed Warning

- Severe and sometimes fatal hepatotoxicity has been observed in clinical trials.
- Monitor hepatic function prior to and during treatment.
- Interrupt and then reduce or discontinue regorafenib for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence.

Warnings and Precautions

Hepatotoxicity: Monitor liver function tests and dose reduce or discontinue based on severity and duration.

Infections: Withhold for worsening or severe infections.

- Hemorrhage: Permanently discontinue regorafenib for severe or life-threatening hemorrhage.
- Dermatological toxicity: Interrupt and then reduce or discontinue regorafenib depending on severity and persistence of dermatologic toxicity.
- Hypertension: Temporarily or permanently discontinue regorafenib for severe or uncontrolled hypertension.
- Cardiac ischemia and infarction: Withhold regorafenib for new or acute cardiac ischemia/infarction and resume only after resolution of acute ischemic events.
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue regorafenib
- Gastrointestinal perforation or fistulae: Discontinue regorafenib
- Wound healing complications: Stop regorafenib before surgery. Discontinue in persons with wound dehiscence.
- Embryo-fetal toxicity: Can cause fetal harm. Advise women of potential risk to a fetus.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

C9399	Unclassified drugs or biologicals

J8999	Prescription drug, oral, chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity:

C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C47.0 – C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48.0 – C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 – C49.9	Malignant neoplasm of other connective and soft tissue
C49.A0 – C49.A9	Gastrointestinal stromal tumor, unspecified
C78.00 – 78.02	Secondary malignant neoplasm of unspecified lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

VEGF - Vascular endothelial growth factor.

EGFR - Epidermal growth factor receptor.

RELATED GUIDELINES:

Bevacizumab (Avastin®) Injection, 09-J0000-66

Capecitabine (Xeloda®) Tablets, 09-J1000-42

Everolimus (Afinitor®, Afinitor Disperz®) Tablets, 09-J1000-45

Human EGFR Inhibitors (cetuximab; panitumumab) IV, 09-J0000-94

Imatinib Mesylate (Gleevec®) Tablets, 09-J1000-46

Irinotecan HCl (Camptosar®) IV, 09-J0000-99

KRAS Mutation Analysis, 05-86000-28

Oxaliplatin (Eloxatin®) IV, 09-J1000-00

Ramucirumab (Cyramza™) Injection, 09-J2000-14

Sunitinib Malate (Sutent®) Capsules, 09-J1000-51

Ziv-aflibercept (Zaltrap®) IV, 09-J1000-80

OTHER:

Table 1: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Coverage Committee on 01/09/19.

GUIDELINE UPDATE INFORMATION:

01/15/13	New Medical Coverage Guideline.
05/15/13	Revision to guideline; consisting of adding new indication of GIST to the position statement.
01/15/14	Review and revision to guideline; consisting of updating description, dosage/administration, and precautions sections and revising approval duration.
01/15/15	Review and revision to guideline; consisting of position statement, references
11/01/15	Revision: ICD-9 Codes deleted.
01/15/16	Review and revision to guideline; consisting of updating position statement, dosing, coding and references.
10/01/16	Update to ICD-10 codes.
01/15/17	Review and revision to guideline; consisting of updating position statement, precautions, coding and references.
07/15/17	Review and revision to guideline; consisting of updating position statement, description, dosing, coding and references.
01/15/18	Review and revision to guideline; consisting of updating position statement and references.

02/15/19	Review and revision to guideline; consisting of updating position statement and references.