CENTENE PHARMACY AND THERAPEUTICS
DRUG REVIEW
3Q17 July – August

BRAND NAME
Stivarga®

GENERIC NAME
Regorafenib

MANUFACTURER
Bayer HealthCare Pharmaceuticals, Inc.

DATE OF APPROVAL
April 27, 2017 (new indication)

PRODUCT LAUNCH DATE
April 27, 2017

REVIEW TYPE

☐ Review type 1 (RT1): New Drug Review
Full review of new chemical or biologic agents

☒ Review type 2 (RT2): New Indication Review
Abbreviated review of new dosage forms of existing agents that are approved for a new indication or use

☐ Review type 3 (RT3): Expedited CMS Protected Class Drug Review
Expedited abbreviated review of Centers for Medicare & Medicaid Services protected class drugs (anticonvulsants, antidepressants, antineoplastics, antipsychotics, antiretrovirals, and immunosuppressants)

☐ Review type 5 (RT5): Abbreviated Review for Intravenous Chemotherapy Agents
Abbreviated review for intravenous chemotherapy agents which are usually covered under the medical benefit

FDA APPROVED INDICATION(S)[1]
Current Indications
Stivarga is a kinase/VEGFR inhibitor indicated for 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 wild-type, an anti-EGFR therapy;

- Locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib mesylate and sunitinib malate.

New Indication
Treatment of patients with:
- Hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

OFF-LABEL USES[2]
As monotherapy for unresectable, advanced or metastatic CRC:
- After first progression for disease that is positive for the KRAS or NRAS mutation (KRAS and NRAS are members of the RAS family of mutations);
- After second progression for disease previously treated with either of the following:
    - FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen with or without bevacizumab;
    - Irinotecan- and oxaliplatin-based therapy;
- For disease that is refractory to standard chemotherapy, including trifluridine and tipiracil.

CLINICAL EFFICACY

RESORCE Trial[3]

- **Overview:** Clinical efficacy and safety of Stivarga were evaluated in an international, multicenter, randomized (2:1), double-blind, placebo-controlled trial [Study "REgorafenib after SORafenib in patients with hepatoCEllular carcinoma" (RESORCE); NCT 01774344].
- **Inclusion/exclusion criteria:** The study enrolled adults with Child-Pugh A and Barcelona Clinic Liver Cancer Stage Category B or C hepatocellular carcinoma, with documented disease progression following sorafenib. The median duration of previous sorafenib treatment was 7.8 months. Patients who permanently discontinued sorafenib due to toxicity or were unable to tolerate sorafenib doses of 400 mg once daily were ineligible.
- **Trial design:** Patients were randomized to receive Stivarga 160 mg orally once daily plus best supportive care (BSC) (n=379) or matching placebo plus BSC (n=194) for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographical region (Asia vs. rest of world), ECOG performance status (0 vs. 1), alphafetoprotein levels (<400 ng/mL vs. ≥400 ng/mL), extrahepatic disease (presence vs. absence), and macrovascular invasion (presence vs. absence).
- **Demographics:** Study population characteristics were as follows: median age of 63 years (range 19 to 85 years); 88% male; 41% Asian, 36% White, and 21% not reported; 66% had ECOG performance status (PS) of 0 and 34% had ECOG PS of 1; 98% had Child-Pugh A and 2% had Child-Pugh B. Risk factors for underlying cirrhosis included hepatitis B (38%), alcohol use (25%), hepatitis C (21%), and non-alcoholic steatohepatitis (7%). Macroscopic vascular invasion or extra-hepatic tumor spread was present in 81% of patients. Barcelona Clinic Liver Cancer (BCLC) was stage C in 87% and stage B in 13% of patients. All patients

received prior sorafenib and 61% received prior loco-regional transarterial embolization or chemoinfusion procedures.

- **Primary outcome:** The major efficacy outcome measure was overall survival (OS).
- **Secondary outcomes:** Additional outcome measures were progression-free survival (PFS), overall tumor response rate (ORR) and duration of response as assessed by investigators using RECIST 1.1 and using modified RECIST (mRECIST) for HCC. Patients continued therapy with Stivarga until clinical or radiological disease progression or unacceptable toxicity.
- **Results:** Median overall survival in months: 10.6 vs. 7.8 ($p<0.001$). Progression-free survival in months: 3.1 versus 1.5 ($p<0.0001$) [mRECIST].
- **Withdrawals from study:** Of patients who started treatment, 309 (83%) receiving Stivarga and 183 (95%) receiving placebo discontinued study treatment. The most common reason for discontinuation was disease progression (226 [60%] in the Stivarga group and 162 [84%] in the placebo group). Excluding treatment delays or interruptions, almost half of the Stivarga group (184 [49%] of 374) received the full protocol dose (160 mg/day) with no reductions.

CONTRAINDICATIONS
None reported.

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

DRUG INTERACTIONS
- Strong CYP3A4 inducers: Avoid strong CYP3A4 inducers.
- Strong CYP3A4 inhibitors: Avoid strong CYP3A4 inhibitors.
- Breast Cancer Resistance Protein (BCRP) substrates: Monitor patients closely for symptoms of increased exposure to BCRP substrates (e.g., methotrexate, fluvastatin, atorvastatin).

ADVERSE REACTIONS
The most common adverse reactions (≥20%) are pain (including gastrointestinal and abdominal pain), hand-foot skin reaction (HFSR), asthenia/fatigue, diarrhea, decreased appetite/food intake, hypertension, infection, dysphonia, hyperbilirubinemia, fever, mucositis, weight loss, rash, and nausea.

DOSAGE AND ADMINISTRATION

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The recommended dose is Stivarga 160 mg (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle. Continue treatment until disease progression or unacceptable toxicity.

PRODUCT AVAILABILITY
Stivarga oral tablets: 40 mg

THERAPEUTIC ALTERNATIVES
NA

Utilization Management Recommendation
• There is significant potential for inappropriate use and utilization management should be considered for the following reason(s): i) To ensure appropriate use of medications that have a significant potential for use that may lead to inferior or unpredictable outcomes. (1) Evidence-based national treatment guidelines recommend first-line agents or step therapy ahead of the drug that is being reviewed.[4] (a) Stivarga is FDA-approved for use in HCC after previous treatment with sorafenib. ii) Recommended utilization management tool(s): (check all that apply) (1) ☒ Prior authorization (2) ☐ Quantity limits (3) ☐ Provider newsletter (4) ☐ Hard block (plan exclusion) (5) ☐ Messaging (6) ☐ Electronic step therapy (7) ☐ Clinical Program
Product Comparison
• Only available second line therapy for hepatocellular carcinoma.

REFERENCES

[1] Stivarga Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; April 2017. Available at http://labeling.bayerhealthcare.com/html/products/pi/Stivarga_PI.pdf. Accessed May 10, 2017.
[2] Regorafenib. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at nccn.org. Accessed May 10, 2017.
[3] Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): A randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017; 389: 56-66.
[4] Hepatobiliary cancers (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at nccn.org. Accessed May 10, 2017.

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