PDL NEW DRUG REVIEW

Proprietary Name: Stivarga®
Common Name: regorafenib
PDL Category: Antineoplastics- Protein-Tyrosine Kinase Inhibitors

Comparable Products	Preferred Drug List Status
Avastin	Recommended
Xeloda	Recommended

Summary

Indications and Usage: For the treatment of metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine- oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and if KRAS wild type, an anti-EGFR therapy. This is a pregnancy category D medication. The safety and efficacy of use in children under the age of 18 years have not been established.

Drug Interactions: Concomitant use of Stivarga® with a strong CYP3A4 inducer (rifampin) resulted in a decrease in mean exposure of regorafenib. It is therefore recommended that the combination of strong CYP3A4 inducers (such as rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) with Stivarga® be avoided. Concomitant use of ketoconazole, a strong CYP3A4 inhibitor, with Stivarga® resulted in increased mean exposure of regorafenib. Thus, it is recommended that the combination of strong CYP3A4 inhibitors (such as clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) with Stivarga® be avoided.

Dosage Forms: Film-coated tablet: 40mg

Recommended Dosage: Take 160mg (four- 40mg tablets) once daily for the first 21 days of each 28-day cycle. Treatment is to be continued until disease progression or unacceptable toxicity. Stivarga® should be taken at the same time every day and swallowed whole with a low-fat breakfast that contains less than 30% fat. Two doses of Stivarga® should not be taken on the same day to make up for a missed from the previous day. Several situations exist where Stivarga® therapy should be interrupted, where the dose should be reduced to 120mg or 80mg, or where treatment should be discontinued. Please refer to the prescribing information for additional information.

Dosage adjustment is not required in those with mild or moderate hepatic impairment; however, they should still be closely monitored for adverse events. Stivarga® use is not recommended in those with severe hepatic impairment as use in this population has not been studied. Dose adjustment is not recommended in

those with mild or moderate renal impairment. Use in those with severe renal impairment has not been studied.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most commonly reported adverse events with Stivarga® include asthenia/fatigue (18%), pain (8%), fever (13%), decreased appetite/food intake (19%), hand-foot skin reaction/palmar-plantar erythrodysesthesia (HFSR/PPE; 38%), rash (22%), diarrhea (26%), mucositis (28%), weight loss (22%), infection (14%), hypertension (22%), hemorrhage (13%), dysphonia (24%), and headache (3%).

Other less commonly reported adverse events included alopecia (6%), taste disorder (5.2%), musculoskeletal stiffness (4%), dry mouth (2.8%), hypothyroidism (3.8%), tremor (2%), GERD (1.4%), and GI fistula (0.4%).

Commonly reported laboratory test abnormalities included anemia (13%), thrombocytopenia (24%), neutropenia (3%), lymphopenia (20%), hypocalcemia (41%), hypokalemia (18%), hyponatremia (8%), hypophosphatemia (46%), hyperbilirubinemia (28%), increased AST (19%), increased ALT (15%), proteinuria (26%), increased INR (7%), increased lipase (27%), and increased amylase (9%).

Stivarga® has a warning of hepatotoxicity with use. In one study, fatal hepatic failure occurred in 1.6% of the regorafenib arm as compared with 0.4% in the placebo arm (all with hepatic failure had metastatic disease of the liver). It is therefore recommended that liver function tests be obtained before starting treatment with Stivarga®, be monitored every 2 weeks during the first 2 months of treatment, and then monitored monthly or as clinically indicated thereafter. Depending on the severity and persistence of hepatotoxicity per liver function tests, Stivarga® treatment should be temporarily held or permanently discontinued.

There is a warning regarding hemorrhage with Stivarga® use. Treatment should be permanently discontinued in those with severe or life-threatening hemorrhage. Furthermore, INR levels should be monitored more frequently if taking concomitant warfarin therapy.

Other warnings with Stivarga® include dermatological toxicity, hypertension, cardiac ischemia/infarction, reversible posterior leukoencephalopathy syndrome (RPLS), and gastrointestinal perforation/fistula. It is thus recommended that blood pressure be monitored weekly for the first 6 weeks of treatment and then every cycle. Treatment should be withheld or permanently discontinued for severe or uncontrolled hypertension. Treatment should also be permanently discontinued in those who develop GI perforation/fistula, RPLS, and in those with dermatological toxicity (dependent upon severity and persistence).

Contraindications: There are currently no contraindications listed in the prescribing information.

Manufacturer: Bayer HealthCare Pharmaceuticals, Inc

Analysis: Regorafenib, the active ingredient of Stivarga®, is a small molecule inhibitor of multiple membrane-bound and intracellular kinases that are involved in normal cell functions and in processes such as oncogenesis and tumor angiogenesis. Regorafenib or its metabolites inhibit activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, $BRAF^{V600E}$, SAPK2, PTK5, and Abl.

Stivarga® has a boxed warning discussing the risk of severe and sometimes fatal hepatoxicity. This risk has been reported in clinical trials. It is recommended that hepatic function be monitored prior to and during treatment with Stivarga®. Therapy should be interrupted and then reduced or discontinued for hepatoxicity as deemed per severity and persistence of liver function tests or hepatocellular necrosis.

One multicenter, randomized, double-blind, placebo-controlled study (N=760) included those previously treated for metastatic colorectal cancer to assess for the safety and efficacy of Stivarga®. Patients were randomized to regorafenib once daily plus Best Supportive Care (BSC) or placebo plus BSC. The primary outcome was overall survival (OS), while secondary outcomes included progression-free survival (PFS) and objective tumor response rate.

Results suggest that the death rate was 55% of the Stivarga® group as compared with 62% of the placebo group, which was statistically significantly different (p=0.102). The median overall survival was 6.4 months with Stivarga® as compared with 5 months with placebo. For PFS, the rate was 83% with Stivarga® as compared with 91% with placebo, with the median PFS being 2 months vs 1.7 months, respectively. This difference was statistically significantly different (p<0.0001). The overall response rate was 1% with Stivarga® vs 0.4% with placebo.

It is recommended that Stivarga® be added to the Recommended Drug List as a non-recommended drug, as it is not intended as a first-line treatment option.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended**

References

[1] Stivarga [package insert]. Wayne, NJ: Bayer HealthCare Pharmaceuticals, Inc; 2012.