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APPLICATION NUMBER:

203085Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	NDA 203-085 \\CDSESUB1\EVSPROD\NDA203085\0000\
Type/Category	NME; Priority
Brand Name	Stivarga
Generic name	Regorafenib
Proposed Indication	Treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) (b) (4), fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, or an anti-EGFR therapy (if KRAS wild type).
Dosage Form	Film-coated tablet, 40 mg
Route of Administration	Oral
Dosing Regimen and Strength	160 mg oral once daily for the first 21 days of each 28-day treatment cycle
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
OCP Division	DCP 5
OND Division	DOP 2
Submission Date	April 27, 2012
PDUFA	October 27, 2012; Internal action goal, September 27, 2012
Primary Reviewer	Stacy S. Shord, Pharm.D.
Team Leader	Hong Zhao, Ph.D.

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1 EXECUTIVE SUMMARY

Regorafenib is a new molecular entity (NME) that inhibits multiple kinases. The proposed indication is for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, or if KRAS wild type, an anti-EGFR therapy. (b) (4) The proposed dose regimen is 160 mg as four 40 mg film-coated tablets administered orally once daily for the first 21 days of each 28-day treatment cycle. The bioequivalence (BE) of regorafenib between the 'to-be-marketed' formulation and clinical trial formulation was demonstrated after a single oral dose, but the exposure of the active metabolites M2 and M5 was clinically insignificantly higher for the 'to-be-marketed' formulation.

A single clinical safety and efficacy trial was conducted in 760 patients with mCRC who were randomized 2:1 to receive oral regorafenib or placebo with best supportive care (BSC) until disease progression or unacceptable toxicity. Regorafenib resulted in a longer overall survival (OS) of 1.4 months compared to placebo [regorafenib: 6.4 mo. vs. placebo: 5.0 mo.; HR = 0.77; 95% CI 0.64, 0.94; p=0.0102]. The OS benefit was independent of age, KRAS mutation status, and the number of previous therapies. Most patients received three or fewer previous therapies for metastatic disease. Regorafenib is associated with several adverse events (AE) commonly seen with drugs that interact with the same kinases: hepatotoxicity, hemorrhage, palmar-plantar erythrodysesias, rash, hypertension, cardiac ischemia or infarction, gut perforation, diarrhea, mucositis, and hypophosphatemia.

The clinical pharmacology studies included in this NDA are two dose escalation studies, three drug interaction studies, one food effect study and one BE study. The clinical safety and efficacy trial was completed earlier than anticipated with demonstrated OS benefit, while several clinical pharmacology studies including exposure-response (E-R) analyses, population pharmacokinetic (PopPK) analyses, an assessment of the risk of QT/QTc interval prolongation and an assessment of a pharmacokinetic (PK) drug interaction with cytochrome P450 probe substrates are still ongoing. Prior to the NDA submission, FDA agreed to the sponsor's proposal to submit the reports of these ongoing studies in November 2012 under post marketing requirements (PMRs) and post marketing commitments (PMCs) if the applicant believes that there are no safety signals or evidence of important but incompletely characterized clinical pharmacologic effects that will preclude an adequate risk-benefit assessment.

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