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*APPLICATION NUMBER:*

**203085Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Review

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<b>NDA</b>	NDA 203-085  \\CDSESUB1\EVSPROD\NDA203085\0000\
<b>Type/Category</b>	NME; Priority
<b>Brand Name</b>	Stivarga
<b>Generic name</b>	Regorafenib
<b>Proposed Indication</b>	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).
<b>Dosage Form</b>	Film-coated tablet, 40 mg
<b>Route of Administration</b>	Oral
<b>Dosing Regimen and Strength</b>	160 mg oral once daily for the first 21 days of each 28-day treatment cycle
<b>Applicant</b>	Bayer HealthCare Pharmaceuticals, Inc.
<b>OCP Division</b>	DCP 5
<b>OND Division</b>	DOP 2
<b>Submission Date</b>	April 27, 2012
<b>PDUFA</b>	October 27, 2012; Internal action goal, September 27, 2012
<b>Primary Reviewer</b>	Stacy S. Shord, Pharm.D.
<b>Team Leader</b>	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 erythrodysesthesias, 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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