CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	September 20, 2012
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 203085
Applicant Name	Bayer Healthcare Pharmaceuticals, Inc.
Date of Submission	April 27, 2012
PDUFA Goal Date	October 27, 2012
Proprietary Name / Established (USAN) Name	Stivarga Tablets / regorafenib
Dosage Forms / Strength	Tablets for oral administration/ 40 mg
Proposed Indication(s)	For the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGFR therapy, and, if KRAS wild type, an anti-EGFR therapy
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Monica Hughes
Medical Officer Reviews	Shan Pradhan & Kaushikkumar Shastri
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	M. Anwar Goheer & Andrew McDougal
ONDQA Reviews	Donghao R Lu & Elsbeth Chikhale
Clinical Pharmacology Review	Stacy Shord
OPDP/DPP	Carole Broadnax & Karen Munoz-Nerez
OSI	Janice Pohlman
CDTL Review	Steven Lemery
OSE/DMEPA	James Schlick
OSE/DRISK	Amarylis Vega
Maternal Health Team Consult Review	Carrie Ceresa
Predictive Safety Consult Review	Keith Burkhart & Naomi Kruhlak

OND=Office of New Drugs
ONDQA=Office of New Drugs Quality Assessment
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

Regorafenib (Stivarga Tablets, Bayer) is a small molecule inhibitor of multiple membrane-bound and intracellular kinases (multi-kinase inhibitor) involved in a wide range of normal cellular functions and in pathologic processes, such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. The kinase inhibition profile of regorafenib affect the angiogenic (VEGFR 2/3, TIE2), stromal (PDGFR-ß, FGFR) and oncogenic (KIT, RET and B-RAF) cellular processes and pathways.

The clinical efficacy and safety of regorafenib were primarily supported by a single clinical trial (Protocol 14387; "CORRECT") enrolled 670 patients with metastatic colorectal cancer with disease progression following all FDA-approved therapy. The results of this single trial were considered sufficient to serve as the sole trial in support of this NDA since it was a large multicenter study with consistency of the treatment effects across study subsets; met both the primary endpoint of overall survival as well as one of the key secondary efficacy endpoints, progression-free survival, which involves different events; and the effects on survival and progression-free survival were statistically very persuasive.

CORRECT was an international, multicenter, randomized (2:1), double-blind, placebo-controlled, trial comparing the effect of regorafenib at a dose of 160 mg once daily for 3 weeks (days 1-21) of a 28-day cycle plus best supportive care (BSC) (n=505) to matching placebo plus BSC (n=255) on overall survival (primary endpoint). Key secondary endpoints were progression-free survival, objective response rate, and response duration.

The CORRECT trial demonstrated statistically significant improvements in both overall survival and in progression-free survival for regorafenib treatment patients over those receiving best supportive care alone, however there was inadequate tumor shrinkage among regorafenib-treated patients, as determined by RECIST criteria, to consider this a part of the clinical benefit of this drug.

Efficacy Outcomes	Stivarga + BSC (N=505)	Placebo + BSC (N=255)
Overall Survival		
Number of deaths, n (%)	275 (55%)	157 (62%)
Median Overall Survival (months)	6.4	5.0
95% CI	(5.8, 7.3)	(4.4, 5.8)
HR (95% CI)	0.77 (0.64, 0.94)	
Stratified Log-Rank Test P-value [a,b]	0.01	
Progression-free Survival		
Number of Death or Progression, n (%)	417 (83%)	231 (91%)
Median Progression-free Survival (months)	2.0	1.7
95% CI	(1.9, 2.3)	(1.7, 1.8)
HR (95% CI)	0.49 (0.42, 0.58)	
Stratified Log-Rank Test P-value [a]	<0.0001	
Overall Response Rate		
Overall response, n (%)	5 (1%)	1 (0.4%)
95% CI	0.3%, 2.3%	0%, 2.2%

The most frequently observed adverse drug reactions (≥30%) in regorafenib-treated patients are asthenia/fatigue, decreased appetite and food intake, palmar-plantar erythrodysesthesia (hand-foot syndrome), diarrhea, mucositis, weight loss, infection, hypertension and dysphonia. The most frequent laboratory abnormalities are cytopenias (anemia, thrombocytopenia, and lymphopenia), liver dysfunction (hyperbilirubinemia, transaminitis), and metabolic derangements (hypocalcemia, hypophosphatemia, and hypokalemia). The most serious adverse drug reactions of regorafenib in the CORRECT trial, occurring at an increased incidence in regorafenib-treated patients and placebo-treated patients, respectively, were Grade 3 palmar-plantar erythrodysesthesia (17% vs. 0), fatal hepatotoxicity (1.6% vs. 0.4%), myocardial ischemia and infarction (1.2% vs. 0.4%), and fatal hemorrhage (0.8% vs. 0).

Across the clinical trials safety database of 1100 patients, serious adverse drug reactions with regorafenib were identified at the following rates: gastrointestinal perforation (0.6%), fatal drug-induced liver injury (0.3%), hypertensive crisis (0.18%), and reversible posterior leukoencephalopathy (0.09%). These adverse drug reaction profile for regorafenib appear to be arise primarily from its inhibition of the VEGF pathway (i.e., hypertension, RPLS, cardiac ischemia/infarction, hemorrhage, viscus perforation, fistula formation, dysphonia) and of the EGFR pathway (rash), although some of the common and serious adverse drug reactions of regorafenib are seen in drugs both with and without known kinase inhibition (e.g., hepatotoxicity, asthenia/fatigue, decreased appetite and food intake, palmar-plantar erythrodysesthesia, diarrhea, and mucositis) and cannot be attributed to a specific mechanism.

All review disciplines recommended approval. The approval was based on a single, adequate and well-controlled trial that showed a highly robust effect on 23% relative reduction in the immediate risk of death and 51% relative reduction in the immediate risk of disease progression or death. While the absolute magnitude of the treatment effects on survival (difference of 1.4 months in median survival times) and progression-free survival (difference of 1.2 weeks in median progression-free survival times) are small, the ability of any single

agent to demonstrate efficacy in this heavily pre-treated population represents clinical benefit, when considered in the context of serious adverse drug reactions occurring in fewer than 1% of patients and common toxicities already considered acceptable with other approved agents for the treatment of metastatic colorectal cancer (e.g., palmar-plantar erythrodysesthesia, nausea/vomiting, mucositis, diarrhea, and hypertension) and which are generally manageable with dose modification and symptomatic treatment.

2. Background

Proposed indication

In 2012, there will be an estimated 103, 170 new cases of colon cancer, 40, 290 new cases of rectal cancer,, and an estimated 51, 690 deaths from colon or rectal cancers[1] While the mortality from colorectal cancer has decreased in the past 50 years, approximately half the decline in mortality rates (from 28 deaths per 100,000 to 17 deaths per 100,000) is attributed to screening and early diagnosis[2]. The identification of new systemic treatments for patients with metastatic disease has improved short-term outcomes but not long-term cure rates. The standard of care in the United States for the treatment of metastatic colorectal cancer includes first-line and second-line treatment with fluoropyrimidine-based combination chemotherapy (FOLFOX or FOLFIRI) administered with bevacizumab for the majority of patients. Cetuximab and panitumumab are indicated for the treatment of patients with metastatic colorectal cancer in which the tumor does not contain mutations in the *c* oncogene (*K-Ras* wild-type), either as an addition to combination chemotherapy for initial treatment (cetuximab) or as monotherapy in patients with recurrent, chemotherapy-refractory disease (cetuximab, panitumumab). . The very elderly or those with co-morbid conditions which may render intensive treatment intolerable, are generally treated either with combinations of approved drugs (5-flurouracil and leucovorin, capecitabine, oxaliplatin, irinotecan, with or without anti-EGFR directed antibodies) or with single agent therap.

Bayer has requested approval for the proposed indication:

> "For the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with, (b) (4), fluoropyrimidine-based chemotherapy, an anti-VEGFR therapy, and, if KRAS wild type, an anti-EGFR therapy."

There are no FDA-approved therapies for the proposed indication, which was adequately reflected by the patient population enrolled in the primary efficacy trial. Thus this patient population represents a disease with a clear, unmet medical need.

Regulatory History of NDA

July 19, 2006: Submission for IND 75642

[1] http://www.cancer.gov/cancertopics/types/colon-and-rectal
[2] http://www.cancer.gov/cancertopics/factsheet/cancer-advances-in-focus/colorectal

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