CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office 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**
Division Director Summary Review	Patricia Keegan
CDTL Review	Steven Lemery
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
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

1. Introduction

On April 27, 2012, Bayer Pharmaceuticals submitted this NDA for Stivarga (regorafenib) tablets in the following 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.

Regorafenib is an 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.

This NDA was primarily supported by a single clinical trial (Protocol 14387; "CORRECT"), which enrolled 670 patients with metastatic colorectal cancer with disease progression following all FDA-approved therapy. 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 OS (primary endpoint). Key secondary endpoints were PFS, objective response rate, and response duration.

The CORRECT trial demonstrated statistically significant improvements in both OS and PFS for regorafenib treatment patients over those receiving best supportive care alone. There was no statistical difference in overall response rates between the arms of the study.

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).

The absolute magnitude of the treatment effects on survival (difference of 1.4 months in median survival times) and PFS (difference of 1.2 weeks in median PFS times) are modest, but the ability of an 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.

2. Background

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

[1] http://www.cancer.gov/cancertopics/types/colon-and-rectal

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 therapy.

3. CMC

There are no outstanding issues that preclude approval. Chemistry reviewers recommended an overall acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 36 months.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding pharmacology/toxicology issues that preclude approval. This application did not contain carcinogenicity studies or a complete battery of reproductive toxicology studies; however, these studies are not required for products indicated for the treatment of advanced, incurable cancers. Similarly, the finding of potential mutagenic effects for a major metabolite (M2) did not require a specific Warning based on the indicated population.

The NDA contained the reports for nonclinical primary pharmacology studies confirming the claimed effects of regorafenib and its two major metabolites (M2 and M5) on kinase inhibition, examining the phosphorylation of downstream targets to establish kinase inhibition at clinically achievable exposures in humans at the recommended dose for multiple kinase targets. Both the M2 and M5 metabolites showed inhibitory activity equal to or greater than the activity of the regorafenib. In addition, *in vivo* evaluation of anti-angiogenic effects were evaluated in rats and mice.

The application also contained reports of repeat dose toxicology studies in rodents and dogs. Toxicologic findings demonstrated both rats and dogs which were also observed in patients with cancer involved the gastrointestinal tract (vomiting, diarrhea, decreased motility), hematopoietic/lymphoid system (marrow hypocellularity, neutropenia, thrombocytopenia, and lymphopenia), atrophy of lymphoid organs, the reproductive system (atrophy), hepatic enzyme elevation with histopathologic changes in the liver, cutaneous toxicity (dyskeratosis, hyperkeratosis, acanthosis, dermatitis, and alopecia), and skeletal system.

Findings identified in animals that have not been confirmed in clinical trials of adults with cancer include renal toxicity (glomerulopathy, tubular degeneration/regeneration, tubular dilation, and interstitial fibrosis), skeletal changes (changes in dentin and epiphyseal growth plates), reproductive toxicity (increased necrotic corpus lutea and atrophy in the ovaries in females and decreased weight of the testes, prostate, and seminal vesicles and retarded maturation of the testes along with aspermia/oligospermia in the epididymides in males), histopathologic changes in the adrenal glands, and hypothyroidism.

A report of a safety pharmacology study did not identify significant cardiotoxicity.

[2] http://www.cancer.gov/cancertopics/factsheet/cancer-advances-in-focus/colorectal

Embryofetal studies conducted in Wistar rats and Himalayan rabbits demonstrated increased post-implantation loss and teratogenic effects including skeletal and cardiovascular malformations and renal findings of dilation of the renal pelvis or hydronephrosis at exposures significantly lower than the human exposure at the recommended daily dose. Based on these findings, and consistent with current practices in the Division of Hematology Oncology Toxicology, Pregnancy category D was recommended.

A distribution study in pregnant rats documented regorafenib exposure in the fetus, with greater regorafenib concentrations in fetal adrenal glands and brain as compared to the maternal blood and increased concentrations of regorafenib or its active metabolites in maternal mammary fluid as compared to the blood. Based on these studies, labeling directs lactating mothers to discontinue nursing while taking regorafenib.

Product labeling identifies the potential risks of impaired fertility in both men and women based on embryofetal and teratogenic effects observed in general toxicology studies in which female rats were administered regorafenib at dose levels resulting in exposures similar to those observed in humans at the clinically recommended dose. Dr. Helms noted that these animals were not followed for a sufficient period to determine reversibility. Given the indicated population, the findings and limitations of the findings (i.e., based on animal data) will be conveyed in product labeling.

5. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that preclude approval.

The NDA contained clinical pharmacology data from two dose-finding trials, evaluating continuous dosing and a three-week on/one-week off dosing schedule, three drug interaction studies, one food effect study and one bioequivalence trial comparing the pharmacokinetic of the tablet form used in the major efficacy trial with that of the "to-be-marketed" tablet.

Following oral administration, regorafenib undergoes enterohepatic circulation. It is highly protein bound (99.5%), as are the two major metabolites (M2 and M5) of regorafenib, both of which are clinically active. Regorafenib is primarily metabolized by CYP3A4 and UGT1A9 and about 71% of a single radiolabeled dose (24% as metabolites) was excreted in feces. The mean elimination half-lives of regorafenib, M2, and M5 are 28 hours, 25 hrs and 51 hrs, respectively. Hepatic elimination appears to be the major route of elimination for regorafenib.

The bioavailability of regorafenib and its active metabolites are affected by the presence of food (fasted vs. fed) and the fat content (low vs. high-fat meal). Since the major efficacy trial which provides substantial evidence of effectiveness of regorafenib was performed with the direction to take regorafenib following a low-fat meal, and in light of the food-effects, product labeling recommends that regorafenib be administered following a low-fat meal.

Pharmacokinetic data obtained in patients with mild renal impairment (n=10) or mild, Child-Pugh A (n=4) or moderate Child-Pugh B (n=10) hepatic impairment do not suggest altered clearance requiring dose adjustments. However, Bayer will be required to conduct trials assessing pharmacokinetics in patients with severe renal impairment and severe hepatic impairment.

Pharmacokinetic studies were conducted to evaluate for interactions between regorafenib and irinotecan, between regorafenib and 5-fluorouracil, and between regorafenib and oxaliplatin. There was no evidence of a pharmacokinetic interaction with fluoropyrimidines. Regorafenib and its metabolites inhibited UGT1A9 and inhibited UGT1A1 *in vitro*; exposure to irinotecan and its major active metabolite, SN-38, were increased by 28% and 44%, respectively when irinotecan was administered following regorafenib. Exposure to oxaliplatin was increased by 39% when oxaliplatin was administered following regorafenib. The mechanism for this apparent

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