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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:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
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 Burkhardt & 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- β , 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 ($\geq 30\%$) 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 cancers¹. 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 diagnosis². 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-fluorouracil 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

interaction is unknown. Because regorafenib is indicated for use as a single agent, these interactions are not included in product labeling.

Additional pharmacokinetic trials demonstrated interactions between regorafenib and ketoconazole and between regorafenib and rifampin. Administration of ketoconazole increased the exposure of regorafenib by 33% and decreased the mean AUC of M2 and M5 each by 93%. Information on drug interactions is described in product labeling based on the potential for co-administration with regorafenib of drugs that are strong inhibitors or strong inducers the CYP3A4 enzyme.

Regorafenib or its active metabolites M2 or M5 inhibited CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 *in vitro*. The effect of regorafenib on the PK of CYP2C8, CYP2C9, and CYP3A4 substrates are under evaluation in an ongoing study. Regorafenib did not induce cytochrome P450 activity *in vitro*.

See action letter for PMRs and PMCs.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The data supporting this NDA are from Protocol 14387 (CORRECT trial), titled "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care (BSC) versus placebo plus BSC in patients with metastatic colorectal cancer (CRC) who have progressed after standard therapy".

Key inclusion criteria were age 18 years or older, ECOG performance status of 0 or 1, metastatic adenocarcinoma of colon or rectum with disease progression during or within 3 months after the last administration of an FDA-approved drug(s) for colorectal cancer or intolerance to such drugs.

Patients were randomized to regorafenib 160 mg or matching placebo, administered orally, once daily on days 1-21 of each 28-day treatment cycle. Study drug administration continued until objective disease progression (per RECIST), clinical progression, unacceptable toxicity, or death.

The planned sample size of 690 patients was designed to detect a hazard ratio (HR) of 0.75 for OS after 582 deaths, with a two-sided alpha of 0.05 and 90% power, given the 2:1 randomization ratio. This was based on the assumed median OS times of 6 months and 4.5 months for the regorafenib- and placebo-treated arms, respectively.

Results

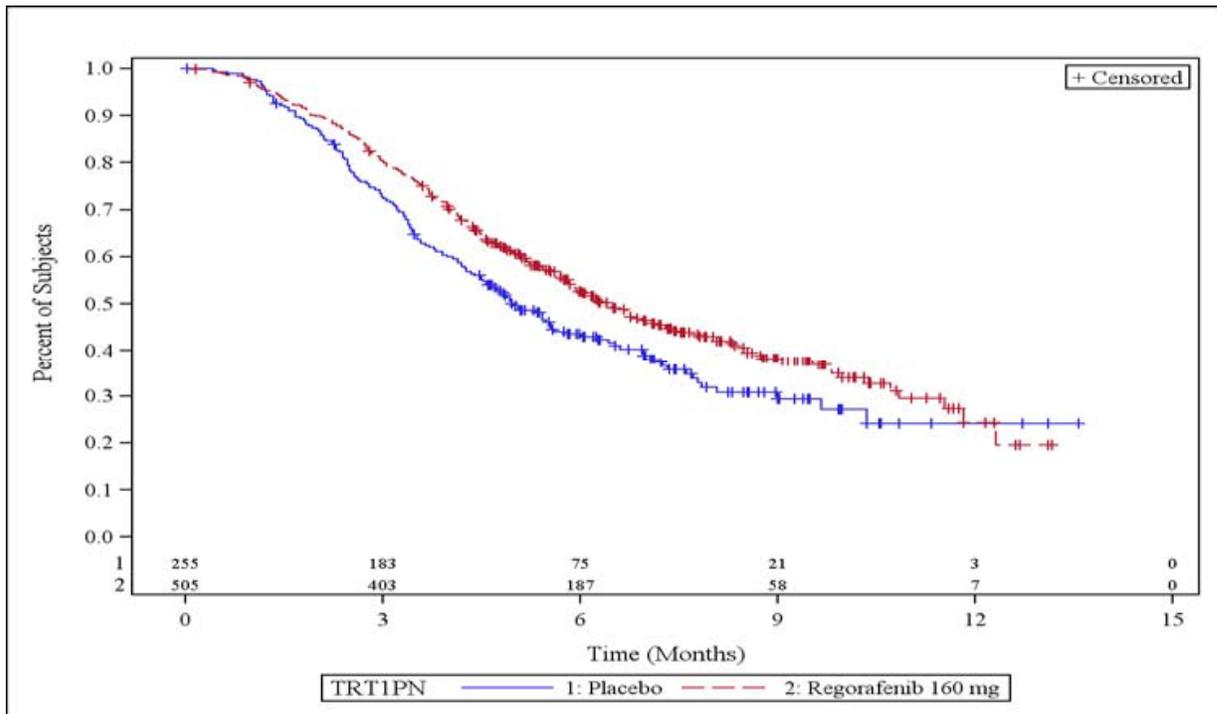
Protocol 14387 enrolled 780 patients at 105 clinical sites across 15 countries; there were 505 patients randomized to regorafenib and 255 patients randomized to placebo. The trial was terminated at the first interim analysis of OS for efficacy, after 432 deaths (74% of the planned 582 deaths for the final analysis). Based on the O'Brien-Fleming-type error spending function, the boundary was considered to have been crossed ($p=0.018$) at the interim analysis which yielded a hazard ratio of 0.77, $p=0.0102$ stratified log-rank test. Efficacy was tested for the secondary endpoints of PFS, which was also statistically significant, and for overall response rate, which was not significantly different between arms. The results of the key efficacy analyses are summarized in the table below.

Efficacy Results from the CORRECT Trial		
Efficacy Endpoint	Regorafenib (n=505)	Placebo (n=255)
Overall Survival		
Number of deaths, n (% of all ITT)	275 (55%)	157 (62%)
# of deaths - Region 1 (% of all deaths)	238 (86.5%)	135 (86%)
# of deaths - Region 2 (% of all deaths)	29 (10.5%)	16 (10%)
# of deaths - Region 3 (% of all deaths)	8 (3%)	6 (4%)
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	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%

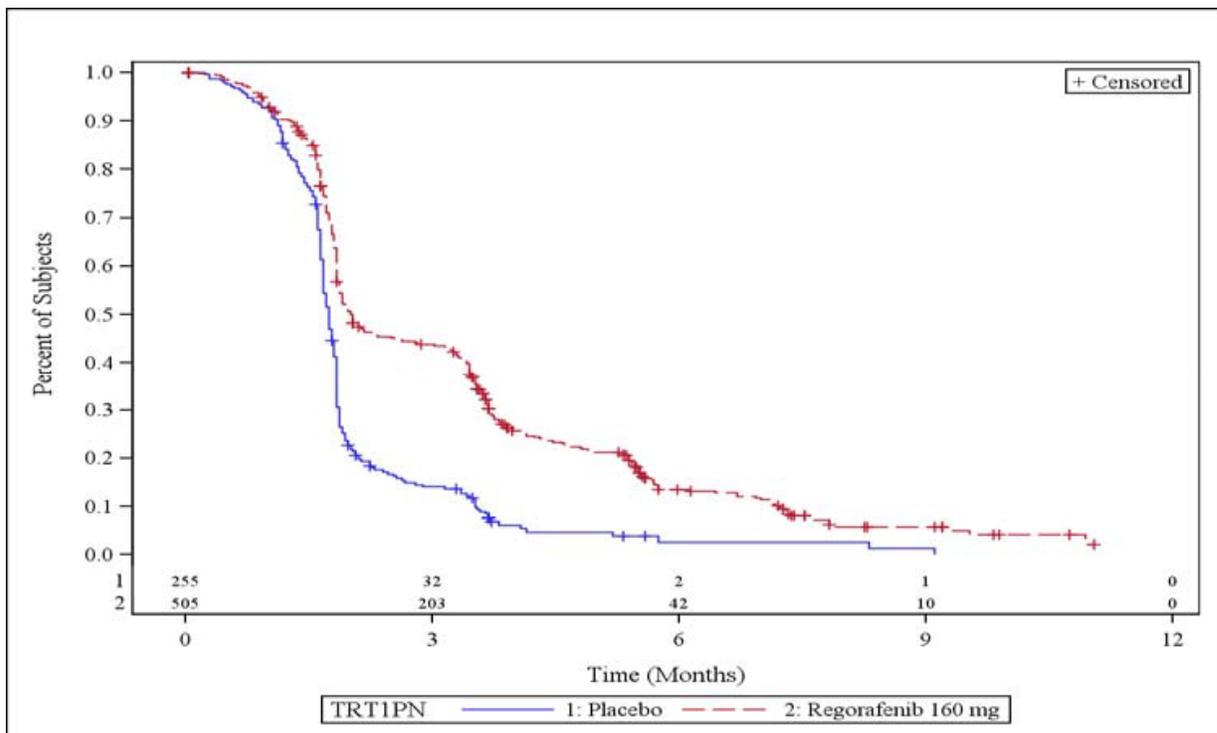
In exploratory subset analyses based on demographic parameters (age, gender, race) and on prognostic factors (ECOG performance status, *K-Ras* mutation status, time from metastatic cancer diagnosis of less than 18 months or 18 months or longer, number of prior lines of chemotherapy), there was consistent evidence of a treatment effect favoring the regorafenib arm for OS.

Kaplan-Meier curves for the two treatment arms for OS and for PFS, respectively, are below.

Kaplan-Meier Curves for Overall Survival, by Treatment Arm, for the CORRECT trial



Kaplan-Meier Curves for Progression-Free Survival, by Treatment Arm, for the CORRECT trial



The results described above, demonstrate a statistically persuasive and clinically meaningful increase in OS in patients for whom there is no FDA-approved treatment. The effects were supported by consistent trends in improved OS in relevant patient subgroups and evidence of a significant improvement in PFS.

8. Safety

Safety evaluation across multiple trials

There was adequate data in the application to assess the risks of regorafenib treatment. The evaluation of safety in this application was supported primarily by data from the CORRECT trial in which 500 patients with mCRC received regorafenib and safety was compared with the 253 patients with mCRC who received placebo.

Evaluation of serious adverse reactions was evaluated across the 1,145 patients with cancer, which included 621 regorafenib-treated patients with mCRC in Phase 1-2 and Phase 3 trials, a Phase 3 study (Protocol 11726) in patients with renal cell carcinoma, a Phase 2 study (Protocol 14596) in patients with hepatocellular carcinoma, and 12 Phase 1 studies (7 studies in patients with advanced solid tumors and 5 studies enrolling 124 healthy volunteers).

Across the pooled safety database, there were 138 deaths occurring during or within 30 days of drug treatment; the majority of these deaths (n=111) were attributed to disease progression by the medical reviewer after evaluation of the case narratives. The most common causes of death after disease progression in regorafenib-treated patients were hemorrhage (4 patients: upper GI hemorrhage; rectal and vaginal hemorrhage, pulmonary hemorrhage; and intracranial hemorrhage), cardiac arrest (3 patients), and pneumonia (3 patients).

There were 13 patients (1 in the placebo group and 12 treated with regorafenib) in the safety database with evidence of hepatotoxicity [AST/ALT > 3 times the upper limit of normal (ULN), alkaline phosphatase < 2 times the ULN, and total bilirubin 2 times ULN]. Of the 12 regorafenib-treated patients, only 2 of the 13 met all of the Hy's law criteria as the other eleven had underlying liver disease (hepatocellular carcinoma or liver metastases).

Safety evaluation in the CORRECT trial

In Protocol 14387, the evaluation of adverse reaction profile was based on 500 patients with mCRC received at least one dose of regorafenib and 253 patients with mCRC who received at least one dose of matching placebo. The demographic and baseline characteristics for this safety population were similar to that for the efficacy population. The mean duration of therapy was 12 weeks for patients receiving regorafenib and 8 weeks for patients receiving placebo; 16% of the regorafenib-treated patients (n=80) in the safety population received 6 or more cycles of protocol-specified treatment. Treatment-emergent adverse events resulted in dose interruptions in 61% of the patients receiving regorafenib and 38% of the patients had their dose reduced. In placebo group, the incidences of dose interruption and dose reduction were 22% and 3%, respectively. Drug-related adverse reactions that resulted in treatment discontinuation were reported in 8.2% of regorafenib-treated patients compared to 1.2% of patients who received placebo. The most common adverse reactions leading to drug discontinuation were general health deterioration (4%) and palmar-plantar erythrodysesthesia, hepatic failure, decreased appetite, pneumonia and rash (1% for each). The most common adverse reactions leading to dose reduction were palmar-plantar erythrodysesthesia (18%), diarrhea (3.8%), hypertension (3.2%), fatigue (2%), rash (2%), mucositis (1.2%), abdominal pain (1%) and asthenia (1%).

Most frequent treatment-emergent adverse drug reactions, i.e., occurring at a higher rate among regorafenib patients as compared to those receiving placebo, reported in CORRECT trial were: decreased appetite, palmar-plantar erythrodysesthesia (PPE), diarrhea, fatigue, decreased weight, hypertension, dysphonia, pyrexia, asthenia,

constipation, and rash. The incidence of both Grade 3 (56% vs. 26.5%) and Grade 4 (8.6% vs. 7.9%) toxicities were higher among regorafenib-treated patients as compared to those receiving placebo in the CORRECT trial. The most common of grades 3 and 4 adverse drug reactions of regorafenib observed in the CORRECT trial were palmar-plantar erythrodysesthesia, fatigue, diarrhea, hypertension, asthenia, rash, and hyperbilirubinemia.

Other adverse drug reactions of special interest, based on the toxicity spectrum of other agents with similar mechanism of action, which occurred at higher rate in regorafenib-treated patients in the CORRECT trial were: hemorrhage (regorafenib 13% vs. 4.3% placebo), cardiac ischemia (regorafenib 1.2% vs. 0.4% placebo), and hypertension (regorafenib 30% vs. 8% placebo).

Based on evaluation of EKG findings obtained serially in the CORRECT trial, there was no evidence of QTc prolongation in regorafenib-treated patients. The final results of an ongoing dedicated cardiac safety study (study 14814), are pending.

9. Advisory Committee Meeting

The NDA for this new molecular entity was not presented to the Oncologic Drugs Advisory Committee for all of the following reasons: the safety profile is similar to that of other drugs approved for this indication; the clinical study design was acceptable; the application did not raise significant safety or efficacy issues that were unexpected for a drug indicated for the treatment of metastatic colorectal cancer; the application did not raise significant public health questions on the role of regorafenib in the treatment of metastatic colorectal cancer; and there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

A full waiver is granted because the disease/condition (metastatic colorectal cancer) does not exist in children.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

▪ Proprietary name:

The proposed proprietary name, Stivarga, was found to be acceptable by the Office of Prescription Drug Promotion (OPDP), the Division of Medication Error and Prevention Analysis (DMEP), and the Office of Hematology and Oncology Products.

- Physician labeling, Carton & container, Patient Labeling: There are no outstanding issues that preclude approval.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval.
- Risk Benefit Assessment

The CORRECT trial demonstrated a statistically persuasive and clinically meaningful increase in OS in patients for whom there is no FDA-approved treatment. The effects were supported by consistent trends in improved OS in relevant patient subgroups and evidence of a significant improvement in PFS. While both effects are modest, judged in the context of the very short survival and PFS expected these improvements are clinically meaningful in this population for which there are currently no FDA-approved treatments. Furthermore, the clinical benefits are meaningful in light of the adverse drug reaction profile. The adverse drug reaction profile of regorafenib is qualitatively similar to that observed with drugs previously approved for the treatment of metastatic solid tumors and which have been deemed acceptable by the patient and medical community in light of the potential benefits. The risk-benefit profile, which was also discussed by Drs. Keegan, Lemery, Pradhan and Shastri, is acceptable. In addition, the review team recommends approval of this NDA, and I concur.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
A REMS is not needed to ensure safe and effective use of regorafenib.
- Recommendation for other Postmarketing Requirements and Commitments: See action letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMY E KIM
09/26/2012

RICHARD PAZDUR
09/26/2012