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RESEARCH**

APPLICATION NUMBER:

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**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Management Options Review

Date: 8/28/2012

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Drug Name(s): Regorafenib (Stivarga™)

Therapeutic Class: Anti-neoplastic protein kinase inhibitors

Dosage and Route: 160 mg tablets, oral use

Application Type/Number: NDA 203085

Submission Number: Sequence 0005

Applicant/sponsor: Bayer HealthCare Pharmaceuticals Inc.

OSE RCM #: 2012-1124

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1 INTRODUCTION

This review documents DRISK's evaluation of the proposed Risk Management Plan (RMP) for regorafenib (Stivarga™).

1.1 BACKGROUND

Regorafenib is an oral multi kinase inhibitor is proposed 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, and, if KRAS wild type, and anti-EGFR therapy.

Regorafenib targets cancer cells and the tumor microenvironment. Its kinase inhibition profile includes angiogenic (VEGFR 2/3, TIE2), stromal (PDGFR-β, FGFR) and oncogenic (KIT, RET and B-RAF) (receptor tyrosine) kinases. Regorafenib demonstrated anti-tumor activity – mediated by its anti-angiogenic and anti-proliferative effects – and anti-metastatic effects.

Regorafenib is formulated as a 40 mg film-coated tablet. The recommended dose is 160 mg (4 tablets, each containing 40 mg of regorafenib) taken orally once daily after a light meal for 3 weeks (21 days) followed by 1 week (7 days) off therapy to comprise a cycle of 4 weeks.

1.2 OTHER PRODUCTS IN THE SAME THERAPEUTIC CLASS

The World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system classifies Regorafenib as an anti-neoplastic protein kinase inhibitor (ATC code L01XE21). Other products in this same class include:

- Afatinib
- Axitinib
- Bosutinib
- Crizotinib
- Dasatinib
- Erlotinib
- Everolimus
- Gefitinib
- Imatinib
- Lapatinib
- Nilotinib
- Pazopanib
- Ruxolitinib
- Sorafenib
- Sunitinib
- Temsirolimus
- Vandetanib
- Vemurafenib

Products in this ATC class that inhibit at least 3 of the main tyrosine kinases targeted by regorafenib (VEGFR, PDGFR and KIT) include sorafenib (Nexavar), sunitinib (Sutent) and pazopanib (Votrient). A side-by-side comparison of pazopanib, sorafenib, and sunitinib is included in the Appendix.

1.2.1 Known Class Adverse Events

The sponsor provided the following list of the most clinically relevant adverse events for this class of drugs based on the medical literature.

Related to VEGF blockage. Hypertension, proteinuria, arterial thromboembolic events, cardiomyopathy, hemorrhage, wound complications, gastrointestinal perforation/fistula formation, and reversible posterior leukoencephalopathy syndrome (RPLS).

Related to KIT Inhibition. Skin rash and myelosuppression.

Related to combined VEGF and other kinase inhibition. Hand-Foot Skin Reaction (HFSR)

1.3 REGULATORY HISTORY

Following are pertinent milestones in the regulatory history of regorafenib:

- **July 19, 2006:** IND 75642 submitted
- **September 3, 2009:** End-of-phase 2 and pre-phase 3 meetings for metastatic colorectal cancer (mCRC) study
- **January 22, 2010:** Special Protocol Assessment (SPA) not Accepted for mCRC study
- **June 10, 2011:** Fast-track granted
- **August 23, 2011:** Pre-NDA meeting
- **April 27 2012:** NDA application receipt date
- **June 25, 2012:** Filed with deficiencies identified; priority review

2 MATERIALS REVIEWED

- Regorafenib, Risk Management Plan, Bayer Healthcare, April 27, 2012 and revised document submitted June 4, 2012.
- Regorafenib, Clinical Overview, Bayer Healthcare, April 27, 2012.
- Regorafenib, draft labeling, Bayer Healthcare, June 4, 2012.
- Shan Pradhan, MD (efficacy), Kaushik Shastri, MD (safety), Regorafenib, midcycle clinical reviewers' slide presentation.
- Anwar Goheer, Ph.D. (Primary reviewer), Regorafenib, midcycle pharmacology/toxicology reviewer's slide presentation.

3 REVIEW FINDINGS

3.1 RELEVANT NON-CLINICAL FINDINGS

Reproductive Toxicity. Regorafenib demonstrated a similar toxicological profile in mice, rats, and dogs, which was characterized by degenerative changes, and frequently accompanied by regenerative and inflammatory processes in multiple organs at clinically relevant doses. In rabbits, there was a dose response for increased late resorptions and

teratogenicity (cardiovascular, renal, and skeletal) at exposures below the anticipated human exposure. These findings are consistent with regorafenib's mechanism of action and were confirmed in rats as a second species (increased resorptions and teratogenicity including cardiovascular, renal, thyroid, and skeletal defects). The sponsor proposed pregnancy labeling category D; the pharmacology/toxicology reviewer concurs with this recommendation.¹ In summary, regorafenib has the potential to be embryo-fetotoxic.

Hepatotoxicity. Studies in mice, rats and dogs identified the liver as a potential target for toxicity, as demonstrated by increase in transaminases (primarily aspartate transaminase (AST) and alanine transaminase (ALT)) in serum.

3.2 OVERVIEW OF CLINICAL PROGRAM

The clinical efficacy and safety of regorafenib were studied in patients with metastatic colorectal cancer who have progressed after failure of standard therapy in an international, multicenter, randomized, double-blind, placebo-controlled phase III study (CORRECT, study 14387). Seven hundred, sixty patients were randomized 2:1 to receive regorafenib 160 mg once a day orally for 3 weeks on therapy followed by 1 week off therapy plus best supportive care (BSC) (n=505) or placebo plus BSC (n=255). The primary endpoint of this study was overall survival (OS) and the secondary endpoints were progression-free survival (PFS), disease control rate (DCR), and objective response rate (ORR). Efficacy was also supported by a Phase 1 study (Study 11650), which provided evidence of the anti-tumor activity of regorafenib in a similar patient population. Study 11650 was a single-center, open-label, nonrandomized, single-agent, dose-escalation study to determine the safety, tolerability, maximum tolerated dose, recommended Phase 2 dose, pharmacokinetics, and biomarker status of regorafenib and to evaluate biomarkers in 76 subjects with advanced solid tumors. After a dose escalation phase, an expansion cohort was conducted in patients with CRC at dose level 160 mg once a day regorafenib on an intermittent dosing schedule.

Sources of safety data included a Phase 3 pivotal study (study 14387; 500 patients treated with regorafenib and 253 who received placebo) in mCRC patients, two Phase 2 studies (Study 11726 in renal cell carcinoma (RCC) and Study 14596 in hepatocellular carcinoma (HCC)), and 12 Phase 1 studies (7 studies in patients with advanced solid tumors and 5 studies in healthy volunteers).² Since the inception of the clinical development program to December 31, 2011, approximately 1,145 patients with cancer, including 621 patients with CRC, and 124 healthy volunteers have been exposed to regorafenib.

¹ Anwar Goheer, Ph.D. (Primary reviewer), Regorafenib, midcycle pharmacology/toxicology reviewer's slide presentation.

² Exposure and event rate analyses are based on two pools:

- Phase III controlled trial population - includes safety data from study 14387 (a randomized controlled design) which allows direct analytical comparisons between the regorafenib 160 mg daily and placebo.
- Phase I-III pooled monotherapy safety set - includes safety data from patients with a variety of malignancies in all phase I to III studies using the intermittent or continuous dosing schedule (also including data from study 14387). Patient populations were comparable because they all had metastatic and/or unresectable solid tumors. The starting dose of regorafenib was 160 mg in these trials, with the exception of the dose escalation studies 11650 and 11651.

Key Efficacy Findings. Study 11650 provided initial evidence of the anti-tumor activity of regorafenib in the CRC patient population. In the subgroup analysis of metastatic CRC patients in study 11650, 1 patient (4%) out of 27 patients evaluable for response according to RECIST (v 1.0) had confirmed partial response (PR) and 19 patients (70%) had stable disease (SD), resulting in a disease control rate (DCR) of 74%.

The reported Hazard Ratio (HR) for OS in the pivotal study (risk of death with regorafenib + BSC versus placebo + BSC) was 0.77 (95% CI, 0.64-0.94, p=0.005] which translates to a 29.2% increase in survival time over placebo + BSC. In addition, the HR for PFS was 0.49, P<0.001 representing a 50.6% reduction in hazard for regorafenib over placebo. The clinical review team in the Office of New Drugs (OND), Division of Oncology Products 2 (DOP 2), concluded that the pivotal study (Study 14387) demonstrated a clinically meaningful, statistically significant OS benefit in patients receiving regorafenib.³

Key Safety Findings. Most frequent treatment emergent adverse events (AEs) identified in the pivotal Phase 3 study (study 14387) were: decreased appetite (regorafenib 47% vs. 28% placebo), palmar-plantar erythrodysesthesia (45% vs 7%), diarrhea (43% vs. 17%), fatigue 40% vs. 29%), decreased weight (32% vs. 10%), hypertension (30% vs. 8%), dysphonia (30% vs. 6%), pyrexia (28% vs. 15%), asthenia (26% vs. 18%), constipation (24% vs. 19%), and rash (22% vs. 3%).

Grade 3 and grade 4 AEs identified in study 14387 occurred at a rate of 56% vs. 26.5% and 8.6% vs. 7.9% respectively. The most common of grades 3 and 4 AEs were Palmar-plantar erythrodysesthesia, fatigue, diarrhea, hypertension, asthenia, rash, and hyperbilirubinemia.

The most serious adverse events were hemorrhage and severe liver injury. There were 138 deaths in the clinically complete pooled studies; the majority (111 deaths) were associated with clinical disease progression.⁴ The most common cause of death other than disease progression in regorafenib-treated patients was 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 that met Hy's law criteria (AST/ALT > 3x ULN, alkaline phosphatase < 2x ULN, total bilirubin 2x ULN); only 2 out of the 13 did not have malignant hepatic lesions (hepatocellular carcinoma or liver metastases). Other AEs of special interest identified in the pivotal study (14387) include hemorrhage (regorafenib 13% vs. 4.3% placebo), cardiac ischemia (regorafenib 1.2% vs. 0.4% placebo), and hypertension (regorafenib 30% vs. 8% placebo). Other serious AEs based from ongoing studies and included in the proposed label include impaired wound healing (6 cases), gastrointestinal perforation (7 cases), and Reversible Posterior Leukoencephalopathy Syndrome (RPLS, 1 case).

³ Shan Pradhan, MD (efficacy), Kaushik Shastri, MD (safety), Regorafenib, midcycle clinical reviewers' slide presentation.

⁴ Deaths occurring during treatment and up to within 30 days post permanent treatment discontinuation.

The sponsor evaluated the potential risk of QTc prolongation through a cardiac safety study (study 14814). No QTc prolonging effects were observed after administration of 160 mg regorafenib at steady state to male and female cancer patients.

The clinical reviewers in the DOP 2 concluded that the safety profile of regorafenib is acceptable in the proposed patient population and typical of drugs with similar mechanism of action. A safety signal for hepatotoxicity is present in the safety database.

3.3 RISK MANAGEMENT PLAN PROPOSED BY THE SPONSOR

Following is a list of adverse events identified by the sponsor as confirmed or potential risks associated with the use of regorafenib and their proposed risk management approach.

Identified risks

- **Severe drug-induced liver injury:** risk management through routine pharmacovigilance, labeling (Warnings and Precautions), and further characterization of incidence, severity, and management in an open label Phase IIIb study (Study 15967).
- **Cardiac ischemic events:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).
- **Hypertension:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).
- **Hemorrhage:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).
- **Hand-foot skin reaction:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).
- **Reversible posterior leukoencephalopathy syndrome:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).
- **Gastrointestinal perforation and fistulas:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).

Potential Risks

-  (b) (4)
- **Wound healing complications:** risk management through routine pharmacovigilance and labeling (Warnings and Precautions).
-  (b) (4)

A Patient Labeling section is included in the proposed product label.

4 DISCUSSION

The risks identified by the sponsor and included in their proposed Risk Management Plan are consistent with those identified by FDA reviewers. The safety profile of regorafenib is similar to that of pazopanib, sorafenib, and sunitinib, including warnings in the product label for teratogenicity, hypertension, hemorrhagic events, and QTc prolongation. In contrast to pazopanib and sunitinib, sorafenib is not labeled for hepatotoxicity. However, postmarketing cases of drug-induced hepatitis, including reports of hepatic failure and death, have been reported with the use of sorafenib.

Based on the available data and the potential benefit of regorafenib, DOP 2 believes that that the potential increased risk of hepatotoxicity can be adequately addressed through labeling.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, DRISK concurs with DOP 2 recommendation that a Risk Evaluation and Mitigation Strategy is not required for regorafenib and the risks associated with regorafenib can be managed through labeling based on the data available and potential benefit. If new safety information becomes available, additional measures beyond labeling will need to be re-considered.

APPENDIX

Appendix 1. A side-by-side Comparison of Pazopanib, Sorafenib, and Sunitinib

	PAZOPANIB	SORAFENIB	SUNITINIB
Generic Name:	Pazopanib	Sorafenib	Sunitinib
Trade Name:	Votrient	Nexavar	Sutent
NDA:	22564	21923	21938
Sponsor:	GlaxoSmithKline	Onyx/Bayer	Sugen/Pfizer
FDA Approval:	2009	2005	2006
Class:	Small Molecule	Small Molecule	Small Molecule
Target:	VEGFR2/PDGFR/c-kit	Multiple Targets	Multiple Targets
Indication:	<ul style="list-style-type: none"> - Advanced renal cell carcinoma - Advanced soft tissue sarcoma who have received prior chemotherapy 	<ul style="list-style-type: none"> -Unresectable hepatocellular carcinoma -Advanced renal cell carcinoma 	<ul style="list-style-type: none"> - Gastrointestinal stromal tumor - Advanced renal cell carcinoma - Pancreatic neuroendocrine tumors
Risk Management	Labeling (Medication Guide)	Labeling (Patient Labeling)	Labeling (Medication Guide)
Labeling			
o Box Warning	Hepatotoxicity	None	Hepatotoxicity
o Warning & Precautions	Increases in serum transaminase levels and bilirubin; Prolonged QT intervals and torsades de pointes; Cardiac dysfunction such as congestive heart failure and decreased left ventricular ejection fraction; Fatal hemorrhagic events; Arterial thrombotic events; Venous thrombotic events (VTE); Gastrointestinal perforation or fistula has occurred; Reversible Posterior Leukoencephalopathy Syndrome (RPLS); Hypertension; Hypothyroidism; Proteinuria; Infection; Fetal harm	Cardiac ischemia and/or infarction; Bleeding; Hypertension; Hand-foot skin reaction and rash; Gastrointestinal perforation; QT Prolongation; Fetal harm	Hepatotoxicity; Cardiac toxicity; Prolonged QT Intervals and Torsade de Pointes; Hypertension; Hemorrhagic events; Osteonecrosis of the jaw; Tumor Lysis Syndrome (TLS); Thyroid dysfunction; Adrenal hemorrhage; Fetal harm
o Pregnancy Category	D	D	D

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