

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204369Orig1s000

**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 Evaluation and Mitigation Strategy (REMS) Review

Date: January 30, 2013

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Subject: Evaluate the need for a REMS

Drug Name(s): Regorafenib (Stivarga)

Therapeutic Class: Anti-neoplastic protein kinase inhibitors

Dosage and Route: 160 mg (40 mg oral tablets)

Application Type/Number: NDA 204369

Submission Number: Original application-1, sequence 0000 Applicant/sponsor:
Bayer HealthCare Pharmaceuticals

OSE RCM #: 2012-2259

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1 INTRODUCTION

This review documents DRISK's evaluation of the proposed Risk Management Plan (RMP) and evaluates if a REMS is needed for regorafenib (Stivarga). The proposed indication for regorafenib is (b) (4)

1.1 BACKGROUND

Regorafenib is an oral multiple kinase inhibitor that is proposed for the treatment of patients with GIST who have been previously treated with 2 tyrosine kinase inhibitors. Regorafenib is currently approved for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

Regorafenib potentially blocks multiple protein kinases, including angiogenic (VEGFR, -2, -3, TIE2), oncogenic (KIT, RET), and stromal (PDGFR, FGFR) receptor tyrosine kinases (RTK), and intracellular signaling protein kinases (RAF-1, BRAF, BRAFV600E).

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

1.2 PHARMACOLOGICAL CLASS EFFECTS

As described above regorafenib is a multiple protein kinase inhibitor. Approved drugs that belong to the same ATC class are:

- Afatinib
- Axitinib
- Bosutinib
- Crizotinib
- Dasatinib
- Erlotinib
- Everolimus
- Gefitinib
- Imatinib
- Lapatinib
- Nilotinib
- Pazopanib
- Ponatinib¹
- Ruxolitinib
- Sorafenib
- Sunitinib
- Temsirolimus
- Vandetanib
- Vemurafenib

¹ Ponatinib, recently approved by FDA on December 14, 2012, has been given a temporary ATC code which would place it in this class. However, the ATC code will not be considered final and implemented in the ATC/DDD index until 2014.

The sponsor provided clinically relevant class adverse effects, discussed in the scientific literature, related to VEGF blockage, KIT inhibition, and combined VEGF blockage and other kinase inhibition.

VEGF blockage: Hypertension, proteinuria, arterial thromboembolic events, cardiomyopathy, hemorrhage, wound complications, gastrointestinal perforation/fistula formation, and reversible posterior leukoencephalopathy syndrome.

KIT inhibition: Dermatological toxicity (skin rash) and myelosuppression (neutropenia, thrombocytopenia, and anemia).

Combined VEGF blockage and other kinases: Hand-Foot Skin Reaction (HFSR)

1.3 REGULATORY HISTORY

On September 27, 2012, regorafenib was approved for the treatment of patients with mCRC, who have been previously treated with fluopyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. Although a new molecular entity (NME), the application for regorafenib for treatment of mCRC was not referred to an FDA advisory committee because there were no significant safety or efficacy issues that were unexpected for a drug of this class in the intended population.

On August 30, 2012 the final portion of a rolling NDA was received, from Bayer HealthCare Pharmaceuticals, for regorafenib for the treatment of GIST in patients who have been previously treated with 2 tyrosine kinase inhibitors. The application was filed 60 days later and classified as a priority review with a user fee goal date of February 28, 2013.

2 MATERIALS REVIEWED

2.1 DATA AND INFORMATION SOURCES

- Regorafenib, Clinical Study Report No. A53306, Bayer HealthCare Pharmaceuticals, March 19, 2012
- Regorafenib, Clinical Study Report No. A59137, Bayer HealthCare Pharmaceuticals, July 25, 2012
- Regorafenib, Safety Risk Management Plan, Bayer HealthCare Pharmaceuticals, August 30, 2012
- Regorafenib, draft labeling, Bayer HealthCare Pharmaceuticals, October 23, 2012
- Regorafenib, 90 Day Safety Update Report, Bayer HealthCare Pharmaceuticals, November 6, 2012
- Jennie Chang and Amir Shahlaee, Regorafenib, midcycle clinical reviewers' slide presentation, November 29, 2012

3 REVIEW FINDINGS FOR STIVARGA

3.1 NON-CLINICAL FINDINGS

Reproductive Toxicity: Specific fertility studies were not performed; however, morphological changes were observed in the testes, ovaries, and uterus in rats and dogs after repeated dosing of regorafenib. Also, potential for effects on intrauterine development was confirmed in rabbits at exposures below the anticipated clinical exposure. The urinary system, the heart and major vessels, and the skeleton were affected. The current label (regorafenib approved for mCRC) lists a pregnancy category D as is consistent with other drugs in this class.

Hepatotoxicity: Liver transaminases (aspartate transaminase (AST) and alanine transaminase (ALT)) were increased in repeated dose toxicity studies with regorafenib in mice, rats, and dogs. A treatment-related effect on liver function is indicated by clinical chemistry findings, but was not accompanied by severe morphological findings. Hepatotoxicity is a boxed warning in the currently approved label (regorafenib approved for mCRC) and appears in section 5, Warnings and Precautions.

3.2 OVERVIEW OF CLINICAL PROGRAM

The clinical safety and efficacy of regorafenib were studied in patients with metastatic and/or unresectable GIST after progression of disease despite prior treatment with imatinib and sunitinib in a randomized, double-blind, placebo controlled phase III study, “GRID” (study 14874). One hundred, ninety nine patients were randomized 2:1 to receive regorafenib 160mg daily for three weeks on therapy and one week off therapy plus best supportive care (BSC) (n=133) or placebo plus BSC (n=66). The primary endpoint of this study was progression free survival (PFS) and the secondary endpoints were time to progression (TTP), overall survival (OS), disease control rate (DCR), tumor response rate (RR), and duration of response (DOR). Data from study 14874 were analyzed using two different time points; the time point when 122 PFS events had occurred (the number of PFS events specified in the original protocol) and the time point when 144 PFS events had occurred (the Jan. 26, 2012 primary completion date).

Clinical safety was also supported by “CORRECT,” (study 14387; 500 patients treated with regorafenib and 253 who received placebo) the pivotal study used for approval of the indication of mCRC, two phase 2 studies (study 11726 in renal cell carcinoma and study 14596 in hepatocellular carcinoma), and several other phase 1 studies.

Key Efficacy Findings. The reported Hazard Ratio (HR) for PFS in study 14874 (disease progression event or death with regorafenib + BSC versus placebo + BSC) was 0.272 for 122 PFS events and 0.268 for 144 PFS events. This corresponds to a reduction of relative risk of disease progression or death by approximately 72.8% for 122 PFS events and 73.2% for 144 PFS events in regorafenib treated patients compared to placebo treated patients. Median PFS was longer for the regorafenib group versus the placebo group; 4.2 months versus 0.9 months for 122 PFS events and 4.8 months versus 0.9 months for 144 PFS events. The difference between treatment groups was statistically significant ($p < 0.000001$) for both 122 and 144 PFS events.

Key Safety Findings. The most frequent treatment-emergent adverse events (TEAEs) that occurred at a >10% higher frequency in the regorafenib + BSC compared to placebo + BSC in study 14874 were:

- hypertension (59.1% vs 27.3%)
- hand-foot-skin reaction (HFSR) (56.8% vs 13.6%)
- fatigue (50.0% vs 37.9%)
- diarrhea (46.2% vs 9.1%)
- mucositis oral (40.9% vs 7.6%)
- hypothyroidism (14.4% vs 3.0%)
- abdominal pain (26.5% vs 15.2%)
- rash maculopapular (18.2% vs 3.0%)
- alopecia (24.2% vs 1.5%)
- hoarseness (24.2% vs 6.1%).

In study 14874, grade 3 TEAE occurred in 64.4% of patients treated with regorafenib versus 25.8% of patients treated with placebo; hypertension, palmar-plantar erythrodysesthesia syndrome, diarrhea, and rash were the most common. Grade 4 TEAE occurred at similar rates in patients treated with regorafenib (6.8%) and patients treated with placebo (6.1%).

Dose modifications were more common, in study 14874, among patients who received regorafenib (75.0%) versus those who received placebo (25.8%) and were mainly due to HFSR. However, no difference in permanent treatment discontinuation, due to TEAE, was observed in the regorafenib versus placebo groups (6.1% and 7.6% respectively).

Reviewer Comments: This indicates that most TEAEs could be managed by dose modification and may not result in a permanent discontinuation of study drug.

Deaths (during treatment and up to 30 days post permanent treatment discontinuation) occurred at similar rates in the regorafenib group (7 patients, 5.3%) and placebo group (3 patients, 4.5%) in study 14874. All deaths in the placebo group and 4 of the 7 deaths in the regorafenib group were reported as progressive disease. Of the 3 deaths in the regorafenib group not associated with clinical disease progression, 2 were from AEs (1 from cardiac arrest and 1 from hepatic failure) and 1 was of other cause (azotemia and metabolic acidosis).

Results from study 14874 were pooled with results from study 14387 and all other company-sponsored and investigator-sponsored studies (phase 1-3). The most common AEs in regorafenib treated patients from all studies were: palmar-plantar erythrodysesthesia syndrome, hypertension, diarrhea, dysphonia, fatigue, and decreased appetite. Thus, a similar AE pattern is demonstrated when compared to study 14874 alone.

On November 6, 2012, Bayer HealthCare Pharmaceuticals, submitted a 90 day safety update report that covered the period after the NDA cut-off date (March 31, 2012) until July 31, 2012. The data in the update was pooled from all company-sponsored and investigator-sponsored studies (phase 1-3). The safety data reported was consistent with the known regorafenib safety profile as presented in the original NDA. However, there were two reports of grade 3 exfoliative rash, four reports of erythema multiforme, two reports of toxic epidermal necrolysis (TEN), and one report of Stevens-Johnson syndrome (SJS). Although many of these cases were confounded, the Sponsor considered it appropriate to update the proposed label to include exfoliative rash, erythema multiforme, TEN, and SJS as adverse drug reactions (ADRs). Also, there were 20 new deaths reported, three of which were considered drug-related by the investigators. The reported causes were blood bilirubin increased, possible bowel perforation, and acute coronary syndrome. These events are reported as adverse reactions in the NDA;

therefore, they do not change the overall safety profile of regorafenib as presented in the NDA.

3.3 RISK MINIMIZATION ACTIVITIES PROPOSED BY THE SPONSOR

The sponsor proposes to minimize risk by utilizing the *Warnings and Precautions* of the label to address the risks of: severe drug-induced liver injury, cardiac ischemic events, hypertension and hypertensive crisis, hemorrhage, hand-foot skin reaction, reversible posterior leukoencephalopathy syndrome, gastrointestinal perforation and fistula, and wound healing complications.

The sponsor is proposing to [REDACTED] (b) (4)

4 DISCUSSION

The benefits associated with the use of regorafenib, for the treatment of GIST in patients who have been previously treated with 2 tyrosine kinase inhibitors, appear to outweigh the risks. The safety profile of regorafenib is similar to that of other multiple protein kinase inhibitors in the same ATC class and has similar product label warnings of hepatotoxicity, hemorrhage, dermatological toxicity, hypertension, cardiac ischemia and infarction, RPLS, gastrointestinal perforation or fistula, wound healing complications, and embryo-fetal toxicity. The 90-day safety update report showed that there may be a greater risk of exfoliative rash, erythema multiforme, TEN, and SJS with regorafenib treatment and these can be appropriately managed in the label as ADRs. Regorafenib, currently approved for mCRC, has a similar risk-benefit profile for the treatment of GIST; therefore, the risk mitigation can be accomplished through labeling.

5 CONCLUSION AND RECOMMENDATIONS

In conclusion, DRISK concurs with the DOP2 recommendation that a REMS is not required for regorafenib, for the treatment of GIST in patients who have been previously treated with 2 tyrosine kinase inhibitors, and that the risks associated with regorafenib can be managed through labeling. DRISK bases this conclusion on the provided efficacy and safety data, potential benefit of the drug, the intended prescribers, and the target population. If new safety information becomes available, additional measures beyond labeling may be considered.

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/s/

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01/30/2013

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