# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**204369Orig1s000**

# SUMMARY REVIEW

# Summary Review for Regulatory Action

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|---|---|
| **Date** | February 25, 2013 |
| **From** | Patricia Keegan |
| **Subject** | Division Director Summary Review |
| **NDA** | 204369 |
| **Applicant Name** | Bayer HealthCare Pharmaceuticals Inc. |
| **Date of Submission** | August 30, 2012 |
| **PDUFA Goal Date** | February 28, 2013 |
| **Proprietary Name / Established (USAN) Name** | Stivarga film-coated tablets/ Regorafenib, tablets for oral administration |
| **Dosage Forms / Strength** | Film-coated tablets: 40 mg |
| **Proposed Indication(s)** | (b) (4) [redacted] |
| **Action:** | *Approval* |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Regulatory Project Manager Review | Monica Hughes |
| Medical Officer Reviews | Jenny Chang & Amir Shahlaee |
| Statistical Review | Xiaoping (Janet) Jiang |
| Pharmacology Toxicology Review | Anwar Goheer |
| Quality Review | Josephine Jee & Vinayak Pawar |
| Quality Biopharmaceutics Review | Elsbeth Chikhale |
| Clinical Pharmacology Review | Stacy Shord |
| OND/DMPP Consult | Karen Dowdy |
| OPDP/DPDP Consult | Carole Broadnax |
| OPDP/DCDP Consult | L. Shenee Toombs |
| OSE/DRISK Consult | Jason Bunting |

OND=Office of New Drugs
DMPP=Division of Medical Policy Programs
OPDP= Office of Prescription Drug Promotion
DPDP= Division of Professional Drug Promotion
DCDP= Division of Consumer Drug Promotion
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management

# Division Director Summary Review

## 1. Introduction

This Type 9 NDA for Stivarga (regorafenib, Bayer Healthcare Pharmaceuticals) was submitted under a rolling review, with the last module for the NDA submitted August 30, 2012. FDA review of this NDA overlapped with the review of NDA 203085 for Stivarga for the treatment of patients with metastatic colorectal cancer (CRC) 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. NDA 203085 approved on September 12, 2012; the NDA for the GIST indication (NDA 204369) will be administratively closed following its approval and all submissions relating to this indication will be submitted to NDA 203085 after the approval of NDA 204369.

Bayer Healthcare Pharmaceuticals (Bayer) requested and received priority review for this application, seeking approval for the following proposed indication

(b)(4)

The major safety and efficacy data supporting the proposed indication are derived from a single international, multi-center, randomized, double-blind, placebo-controlled trial (Protocol 14874), which investigated the efficacy of regorafenib in patients with unresectable, locally advanced or metastatic gastrointestinal stromal tumor (GIST), who had been previously treated with imatinib mesylate and sunitinib malate. Randomization was stratified by line of therapy (third vs. four or more) and geographic region (Asia vs. rest of the world).The major efficacy outcome measure was progression-free survival (PFS) based on disease assessment by independent radiological review using modified RECIST 1.1 criteria and the key secondary outcome measure was overall survival. Patients were randomized (2:1) to receive 160 mg regorafenib orally once daily or placebo for the first 21 days of each 28-day cycle. Treatment continued until disease progression or unacceptable toxicity.

A total of 199 patients were enrolled and randomized in Protocol 14874 to regorafenib (n=133) or placebo (n=66), with the following demographic and baseline entry characteristics: median age of 60 years, 64% were men, 68% were White, and all patients had baseline ECOG performance status of 0 (55%) or 1 (45%). At the time of disease progression as assessed by central review, the study blind was broken and all patients were offered the opportunity to take regorafenib at the investigator's discretion. Fifty-six (85%) patients randomized to placebo and 41 (31%) patients randomized to regorafenib received open-label regorafenib.

A statistically significant improvement in PFS was demonstrated for regorafenib-treated patients compared to placebo {HR 0.27 (95% CI: 0.19, 0.39); $p < 0.0001$], with median survival times of 4.8 months for the regorafenib arm and 0.9 months for the placebo arm. There was no statistically significant difference in overall survival at the time of the planned interim analysis based on 29% of the total events for the final analysis {HR 0.77 (95% CI:

0.42, 1.41); P = 0.2], however survival results may have been confounded by the high rate of cross-over for patients in the placebo arm upon disease progression together with the short median progression-free survival time (0.9 months) in the placebo arm.

The adverse event profile of regorafenib in Protocol 14874 was similar to that observed in a placebo-controlled trial of regorafenib in 760 patients with previously treated metastatic colorectal cancer and in the overall safety database consisting of 1200 patients enrolled in Bayer-sponsored clinical trials. The toxicity profile reflects the pharmacodynamic effects of regorafenib with the majority of adverse reactions attributable to the EGFR- and VEGFR-inhibiting properties of this molecule. The most common serious adverse reactions with regorafenib across the entire safety database were fatal hemorrhage, gastrointestinal perforation, fatal hepatotoxicity, hypertensive crisis, and Stevens Johnson Syndrome. New reports of toxic epidermal necrolysis were identified in the safety database with a reported rate of 0.17%

The most common adverse reactions of regorafenib observed in regorafenib-treated patients in Protocol 14874 were hand-foot syndrome (67%), hypertension (59%), asthenia/fatigue (52%), diarrhea (47%), mucositis (40%), dysphonia (39%), infection (32%), decreased appetite and food intake (31%), rash (30%), alopecia (24%), fever (21%), nausea (20%), hypothyroidism (18%), vomiting (17%), headache (16%), weight loss and musculoskeletal stiffness (14% each) and hemorrhage (11%). With the exception of hypothyroidism, all of these events were identified in the approved labeling for NDA 203085. The most common laboratory abnormalities among regorafenib-treated patients in the Protocol 14874 which were increased by more than 5% over observed rate in the placebo-treated arm were hypophosphatemia (55% vs. 3%), elevations in AST (58% vs. 47%), hyperbilirubinemia (33% vs. 12%), lymphopenia (30% vs. 12%), hypokalemia (21% vs. 3%), hypocalcemia (17% vs. 5%), increased lipase (14% vs. 5%) and thrombocytopenia (13% vs. 2%).

# 2. Background

*Gastrointestinal Stromal Tumors (GIST*

Gastrointestinal stromal tumors (GIST) are mesenchymal tumors arising in the gastrointestinal tract (from the esophagus to the rectum). These tumors have characteristic mutations in the KIT gene or platelet-derived growth factor receptor alpha (PDGFRA) gene. The estimated annual incidence is 3,300 to 6,000 new GIST cases in the United States[1]. However this incidence may not include incidental small GIST tumors. Sixty percent of GIST tumors present in the gastric wall, 30% in the small intestine and the remainder throughout the GI tract. While most GIST tumors are sporadic, there are rare familial forms with the characteristic heritable mutations in the KIT gene or succinate dehydrogenase genes.

Based on an epidemiologic assessment of 1,458 cases of GIST from 1992 to 2000, the diagnosis of GIST was rare in patients less than 50 years of age with an increasing incidence with increasing age. There was a slight male predominance (54% male and 46% female)[2]. The

[1] http://www.cancer.gov/cancertopics/pdq/treatment/gist/HealthProfessional/page1 (accessed Feb. 25. 2013)
[2] Tran T, Davila JA, El-Serag HB: The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 100 (1): 162-8, 2005.

highest incidence was in Blacks, followed by a composite "other group" (Asians, Pacific Islanders, Native Americans, and Alaska Natives0, with the lowest incidence in Whites.

Prognosis is related to stage of disease and has been altered by the introduction of effective treatment since 2002. Prior to 2002, the estimated 1-year survival rate for patients with advanced (metastatic) GIST was 49% and the 5-year survival rate was 11%.

*Regulatory background- Available therapy for GIST*

Prior to 2002, there were no FDA-approved drugs indicated for the treatment of GIST, the reported response rates with off-label chemotherapy regimens were approximately 5%, radiotherapy was felt to be ineffective and there was a substantial risk of relapse following surgical resection. As of the date of this summary review, there are now two drugs with FDA-approval for the treatment of metastatic or unresectable GIST, imatinib mesylate (Gleevec) and sunitinib malate (Sutent). The details of the approved indications and basis for approval are summarized below.

**Imatinib mesylate** (Gleevec; Novartis Pharmaceuticals Corporation) is a kinase inhibitor, which inhibits tyrosine kinase signaling via the bcr-*abl* fusion protein, platetet-derived growth factor (PDGF), and c-kit tyrosine kinase pathways. Gleevec capsule was approved, under 21 CFR 314.510 subpart H, for the treatment of patients with Kit (CD117) positive, unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) on February 1, 2002 (NDA 21335/001); approval for this indication for Gleevec tablets occurred on April 18, 2003 (NDA 21588/000). The original approval for this indication was based on the results of an open-label, two-arm, randomized (1:1), dose-comparison (400 mg vs 600 mg administered for up to 36 months), multicenter trial (Study 106) conducted in 147 patients with GIST, demonstrating durable objective responses (ORR of 33% in the 400 mg arm and 43% in the 600 mg arm); with a median follow-up time of 7 months, there was insufficient follow-up to determine the median duration of response.

Verification of clinical benefit was to be performed under the following post-marketing requirements

- Complete the follow-up of sNDA trial B2222 and submit mature response rate, response duration and survival data. The suggested timeline for submission of the overall response rate and response duration is December 31, 2002. The suggested timeline for submission of the survival analysis is when either 70% of events have occurred or there has been 5 years follow-up is March 31, 2007.
- An updated report of the central pathology review for sNDA trial B2222 should be submitted when review of the 13 pending cases is complete (June 2002).
- Submit data from the two ongoing multicenter trials of imatinib that are testing 400 mg/day versus 800 mg/day in patients with GIST (EORTC and NCI sponsored trials). Response rate, duration of response, safety and survival data should be submitted. The data should be submitted in a timeline consistent with the statistical analysis plan of each respective protocol (est. June 2003).

NDA 21588/S-008: Gleevec product labeling was amended on October 20, 2005 to include the updated results of Study B2222, which demonstrated overall response rates of 68.5% (400 mg) and 67.6% (600 mg) with a median duration of response of 118 weeks. FDA noted that although the survival data was not mature, with only 37% of events having occurred, it was not likely that a subsequent survival analysis will be more informative given the limited sample size (147 patients) and the lack of a placebo or active comparator. Therefore, FDA released Novartis from the requirement to provide an updated analysis of overall survival at 5 years or 70% of the planned events in this trial.

NDA 21588/S-024: Regular approval was granted on September 26, 2008, for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors based on verification of clinical benefit (durable treatment effects on tumor as measured by time-to-progression) in the required post-marketing trials. Based on similarity of trial design for the NCI- and EORTC-sponsored trials (open-label, dose-comparison (400 mg vs. 800 mg), randomized (1:1), multicenter trials), the data were pooled. Across the two trials, 1640 patients were enrolled. The pooled analysis demonstrated median progression-free survival times of 18.9 (400 mg) and 23.2 (800 mg) months, supported by demonstration of prolonged survival with median survival times (49.0 months and 48.7 months), and objective responses of approximately 50% [complete response rates (5.3% and 5.0%) and partial response rates (46.1% and 48.0%)] for the 400mg and 800 mg arms, respectively.

In addition, imatinib is approved for the adjuvant treatment of GIST following gross surgical resection

- NDA 21588/S-025: Accelerated approval granted on December 19, 2008, for the adjuvant treatment of adult patients following complete gross resection of Kit (CD117)-positive gastrointestinal stromal tumors (GIST).

- NDA 21588/S-035: Accelerated approval granted on January 31, 2012, to modify the recommended duration of treatment from 1 year of treatment to at least 3 years of treatment for the adjuvant treatment of patients with GIST at high-risk for recurrence following surgical resection.

**Sunitinib malate** (Sutent; Pfizer, Inc.) is a multi-kinase inhibitor, which inhibits activation of the PDGF receptors alpha and beta, the vascular endothelial growth factor receptors 1, 2, and 3, the stem-cell receptor/c-Kit, the fms-like tyrosine kinase 3 (FLT3), the colony-stimulating factor-Type 1 receptor (CSF-1R), and/or the glial cell line-derived neurotrophic factor receptor (RET) signaling pathways.

NDA 21938 was approved on January 26, 2006 for the treatment of gastrointestinal stromal tumor after disease progression on, or intolerance to, imatinib mesylate. This approval was based on the results of two trials. The major efficacy trial (Protocol A6181004) was a randomized (2:1), double-blind, placebo-controlled trial of sunitinib versus placebo conducted in 312 patients with metastatic GIST who had suffered disease progression on, or were intolerant to, imatinib. Protocol A6181004 was terminated at the planned interim analysis (147 events) of the primary endpoint (time-to-tumor progression (TTP) when the O'Brien-Fleming boundary ($p<0.0042$) was crossed. demonstrating a statistically significant improvement in

TTP for patients in the sunitinib arm [HR 0.33 (95% CI: 0.23, 0.47); p <0.0001] with median TTP of 27.3 months and 6.4 months and higher overall response rates (6.8% for sunitinib vs. no responses for placebo arm, p<0.006). The results of Protocol A681004 were supported by demonstration of durable objective tumor responses in a single arm trial of 55 patients, demonstrating a partial response rate of 9.1% patients with metastatic GIST who had suffered disease progression on, or were intolerant to, imatinib.

NDA 21938/S-010 was approved on July 1, 2010, to include updated information on Protocol A6181004 on survival. After the interim analysis of TTP, treatment assignment was unblinded and 99 of the 118 patients randomized to placebo received open-label sunitinib. At the protocol-specified final analysis of overall survival, there was no significant difference in survival [HR 0.78 (95% CI: 0.68, 1.13}], with median survival times of 72.7 and 64.9 weeks in the sunitinib and placebo-arms, respectively.

*Pre-Submission History for regorafenib*

July 19, 2006: IND 75642 submitted for clinical investigations of regorafenib. As a result of the re-organization of the Office of Hematology and Oncology Products, a separate IND was submitted for the development program for GIST, IND 113896, on February 7, 2012.

August 25, 2010: EOP2 meeting held to discuss use of a single Phase 3, multinational placebo-controlled trial to support a development program for GIST for the treatment of patients with metastatic and/or unresectable GIST whose disease has progressed despite at least imatinib and sunitinib as prior treatments. Key agreements reached

- The proposed safety database from ≥400 subjects would be adequate
- Since side effects of regorafenib may compromise the study blind, central radiology review of the primary endpoint of progression-free survival (PFS) would be required.
- A six-week improvement in median PFS would be unlikely to establish clinical benefit and a statistically significant, clinically important improvement must be shown
- The trial should be powered for overall survival; an interim analysis of overall survival should be performed at the time of the final analysis of PFS
- The proposed stratification criteria for randomization and frequency of tumor assessments for the planned Phase 3 trial and the development plan for characterization of pharmacokinetics and the non-clinical development plans to be submitted to support an NDA were acceptable

October 13, 2010: Protocol 14874 was submitted to IND 75,642; based on the August 25, 2010 EOP2 meeting, Bayer modified the design of the trial to power the study for overall survival (80% power to detect a 66.7% increase) as a secondary endpoint, adding an interim analysis for OS, and using an O'Brien-Fleming type alpha spend to control the overall type I error rate. The protocol was amended on February 18, 2011, August 15, 2011, and October 12, 2011.

January 12, 2011: Orphan drug designation granted for "treatment of patients with metastatic and/or unresectable GIST whose disease has progressed despite at least imatinib and sunitinib as prior treatments."

April 17, 2011: Fast track designation granted for "the investigation of regorafenib for the treatment of patients with metastatic and/or unresectable GIST whose disease has progressed despite at least imatinib and sunitinib as prior treatments."

February 7, 2012: The statistical analysis plan (SAP) for Protocol 14874 was submitted to IND 113,896.

March 9, 2012: FDA letter providing advice on proposed changes to the statistical analysis plan for Protocol 14874. In this letter, FDA advised that

- The number of the events for the final analyses of PFS and overall survival should not be increased due to lack of adequate rationale for such modifications.
- Details on the assumptions underlying the analyses of PFS and overall survival were requested as well as the planned assumptions regarding the interim analysis of survival (projected number of events, corresponding O'Brien-Fleming boundary and alpha level)
- Results for disease control rate (DCR) would not be included in the label.
- If labeling claims for other secondary endpoints would be sought, the proposed plan for analysis of secondary endpoints would need to be replaced with a statistical plan controlling overall alpha at 0.05 for those secondary endpoints.

April 2012: Bayer submitted the revised, final SAP for Protocol 14874.

May 3, 2012: Pre-NDA meeting held. Agreements were reached on the contents of a complete NDA and further discussion occurred regarding the components of modules in the rolling NDA. Bayer also agreed to provide analyses of PFS based on the protocol-specified number of events (122 events) and based on over-enrollment with 144 events; Bayer acknowledged that both analyses would be required to be statistically significant to support the application.

May 24, 2012: FDA granted request for Rolling Review/

*NDA 204369 Submission History*

- The first module was submitted May 31, 2012 and the final module was submitted August 30, 2012
- The application was filed on October 29, 2012 with a review classification of Priority.

# 3. CMC

There is no new quality information contained in this Type 9 NDA that has not been previously submitted for review under NDA 203085. Bayer's microbial testing for drug product release testing approved under NDA 203085 was re-evaluated by the Product Quality

Microbiology Reviewer during the review of NDA 204369. Based upon this re-evaluation and at FDA's request, Bayer agreed to modify the approved microbial release test method and to conduct a post-marketing commitment to establish the acceptance criteria for the new test under a voluntary post-marketing commitment. There are no outstanding quality issues that preclude approval.

# 4. Nonclinical Pharmacology/Toxicology

Not applicable. There is no new non-clinical pharmacology or toxicology information contained in this Type 9 NDA that has not already been submitted to and reviewed under NDA 203085. There are no outstanding non-clinical pharmacology or toxicology issues that preclude approval.

# 5. Clinical Pharmacology

Clinical pharmacology data were provided from two trials (Protocols 14874 and 14935) conducted in patients with gastrointestinal stromal tumors (GIST) previously treated with imatinib and sunitinib; these data were not submitted and reviewed under NDA 203-085. As noted by Dr. Shord, there were no clinically meaningful differences in exposure to regorafenib or its active metabolites (M2 and M5) in patients with GIST as compared to patients with colorectal cancer or other solid tumors. There are no outstanding non-clinical pharmacology or toxicology issues that preclude approval.

Bayer did not provide adequate clinical pharmacology data to fully characterize the PK profile of regorafenib but will provide this as a post-marketing commitment (PMC), as agreed-upon during the pre-NDA meeting, given the results of Protocol 14874 which demonstrated that regorafenib fulfilled an unmet medical need in this serious and life-threatening disease. Bayer has proposed to conduct a PMC to submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 using relevant available data collected in patients with metastatic or unresectable GIST. As noted by the clinical pharmacology reviewer, this analysis will explore the relationship between exposure of regorafenib and its active metabolites (M2 and M5) and relevant clinical endpoints in patients with unresectable or metastatic GIST. This analysis might help support the proposed dose modifications for adverse events listed in the labeling and potential dose modifications for organ impairment or drug interactions in which dose modifications are typically recommended based on identified exposure differences.

# 6. Clinical Microbiology

Not applicable. There is no new clinical microbiology information contained in this Type 9 NDA that has not already been submitted to and reviewed under NDA 203085.

# 7. Clinical/Statistical-Efficacy

The pre-submission regulatory history for this application is summarized in Section 2 of this review. During the EOP2 meeting, FDA agreed with the design and primary endpoint (PFS) of the clinical trial, noting that the magnitude of the treatment effect would need to be both statistically significant and clinical important. The proposed indication is supported primarily by a single, randomized, placebo-controlled trial demonstrating a clinically meaningful improvement in progression-free survival in patients with GIST has received prior imatinib and sunitinib.

*Protocol 14984 – Trial Design*
The primary efficacy trial supporting this NDA is Protocol 14874 (also known as the "GRID" trial) entitled "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatments with at least imatinib and sunitinib."

The trial was a randomized (2:1), double-blind, placebo-controlled study of regorafenib versus placebo in patients with metastatic and/or unresectable gastrointestinal stromal tumor whose disease has progressed despite prior treatment with at least imatinib and sunitinib. Key eligibility criteria were age ≥ 18 years, histologically confirmed GIST, at least one measurable lesion per RECIST 1.1, objective disease progression or intolerance to prior imatinib treatment and disease progression while on sunitinib therapy, disease progression or intolerance to other systemic therapy if administered, no prior treatment with any other vascular endothelial growth factor receptor (VEGFR) inhibitor. ECOG PS 0 or 1, adequate end-organ function and recovery from toxicity of prior therapy. Patients were randomized to regorafenib 160 mg (as four 40 mg tablets) or matching placebo orally with a low-fat breakfast, once daily for the first 21 days of each 28-day cycle. Treatment continued until disease progression or unacceptable toxicity. Randomization was stratified by line of therapy (third vs. four or more) and geographic region (Asia vs. rest of the world). The randomization procedures were designed to ensure that no more than 50% of the study population had received more than 3 prior lines of systemic therapy.

The primary study endpoint was progression-free survival (PFS) based on disease assessment by independent radiological review using modified RECIST 1.1 criteria, in which lymph nodes and bone lesions were not target lesions and progressively growing new tumor nodule within a pre-existing tumor mass was progression. The key secondary outcome measure was overall survival; additional secondary endpoints were time to progression, disease control rate, response rate, safety and duration of response. Tumor assessment were to be performed every 4 weeks (or less weeks, if clinically indicated) for the first 3 months, every 6 weeks (or less weeks, if clinically indicated) for the next 3 months (through month 6), and every 8 weeks (or less weeks, if clinically indicated) until the end of treatment (> 6 months on treatment). Tumor assessments were to be performed until progressive disease as determined by blinded central radiology review).

The sample size originally proposed was 170 patients, based on the assumptions that 122 PFS events as determined by a blinded central review committee (IRC) would be required to detect a hazard ratio would be 0.5 (a 6-week difference in median PFS) with 90% power at a significance level of 0.01, two-sided, using the stratified log-rank test. In addition, with a sample size of 170 patients and 136 deaths, the trial was powered to detect a significant difference in overall survival, assuming a hazard ratio of 0.6 and median survival in the control arm of 6 months, with 80% power and a significance level of 0.05, two-sided. The analysis plan was revised on September 27, 2011, when accrual reached 199 patients due to higher than expected accrual rates in the last week of study accrual, to modify the timing of the analysis of PFS to occur after 144 IRC-determined PFS events and of overall survival to occur after at least 160 deaths. As discussed in Section 2 of this review, the revised analysis plan was submitted to IND 113,896 on February 7, 2012 and FDA informed Bayer (advice letter dated March 9, 2012) that this additional PFS analysis would be considered acceptable only if the analysis of PFS with 122 was also statistically significant.

The key secondary endpoints of time-to-progression and overall survival, were to be tested using a gate-keeping procedure to preserve type 1 error (alpha level of 0.025, one-sided for TTP and for OS), with time-to-progression tested first and then overall survival. The analysis of time-to-progression and an interim analysis of survival would be conducted at the final analysis of PFS, while the final analysis of survival would be conducted when a minimum of 160 deaths were observed (per the revised analysis plan of September 27, 2011). An O'Brien-Fleming alpha spending function would be used to determine the significance levels based on the actual number of events.

*Trial results*

Protocol 14874 enrolled a total of 199 patients, with 133 randomized to receive regorafenib and 66 to receive placebo. The first patient was enrolled January 4, 2011 and the last patient initiated treatment in August 2011. The baseline entry characteristics were similar between the two arms, with a median age of 60 years, 64% were men, 68% were White, and all patients had baseline ECOG performance status of 0 (55%) or 1 (45%).

At the time of disease progression as assessed by central review, the study blind was broken and all patients were offered the opportunity to take regorafenib at the investigator's discretion. Fifty-six (85%) patients randomized to placebo and 41 (31%) patients randomized to regorafenib received open-label regorafenib.

A statistically significant improvement in PFS was demonstrated for regorafenib arm as compared to the placebo arm. The effect on PFS was consistent in exploratory subgroup analyses based on extent of prior therapy ($3^{rd}$-line, $\geq 4^{th}$- line), ECOG performance status, duration of treatment with imatinib, and KIT mutation (exon 11, exon 9) by an non-validated assay There was also a statistically significant improvement in time-to-progression [HR 0.25 (95% CI 0.17, 0.36), $p < 0.0001$], however there was no statistically significant difference in overall survival at the time of the planned interim analysis based on 29% of the total events for the final analysis.

Efficacy Results for Protocol 14874 (from physician package insert)

| | Stivarga (N=133) | Placebo (N=66) |
|---|---|---|
| **Progression-free Survival** | | |
| Number of Death or Progression, N (%) | 82 (62%) | 63 (96%) |
| Median Progression-free Survival (months) | 4.8 | 0.9 |
| 95% CI | (3.9, 5.7) | (0.9, 1.1) |
| HR (95% CI) | 0.27 (0.19, 0.39) | |
| Stratified Log-Rank Test P-value [a] | <0.0001 | |
| **Overall Survival** | | |
| Number of Deaths, N (%) | 29 (22%) | 17 (26%) |
| Median Overall Survival (months) | NR[b] | NR[b] |
| HR (95% CI) | 0.77 (0.42, 1.41) | |
| Stratified Log-Rank Test P-value [a, b] | 0.2 | |

[a] Stratified by line of treatment and geographical region.
[b] NR: Not Reached.

*Supportive information*
Bayer also provided the summary results of an investigator-sponsored trial, Protocol 14935, a non-randomized, open label, multi-center trial investigating the anti-tumor activity and safety of regorafenib in patients with metastatic or unresectable GIST, previously treated with imatinib and sunitinib. As noted by the clinical reviewer, Bayer did not have access to primary data for this trial and submitted only summary results in the study report.

The trial was conducted at four clinical sties in the United States. Protocol-specified treatment was the same as in Protocol 14874: regorafenib 160 mg orally once daily for 21 consecutive days of each 28-day cycle.

The primary endpoint was clinical benefit rate (CBR) defined as the percentage of patients with complete responses, partial responses, or stable disease for at least 16 weeks.
The reported clinical benefit rate was 79% (95% CI: 61%-91%), based on four patients who achieved a partial response and 22 patients with stable disease for at least 16 weeks.

# 8. Safety

The size of the clinical trials experience supporting this application, consisting of 1200 regorafenib-treated patients across multiple trials, is adequate to assess for uncommon but serious risks. As of the date of this review, there is inadequate marketing experience to characterize post-marketing adverse reactions.

Significant new safety findings identified during the review of this application included the risk of toxic epidermal necrolysis, which was reported in 0.17% of the 1200 regorafenib-treated patients all Bayer-sponsored clinical trials, but not reported in Protocol 14874. In addition, an increased risk of hypothyroidism, based on treatment-emergent elevations in TSH or requirement for thyroid supplementation at patients who were euthyroid at baseline, was identified in regorafenib-treated patients in Protocol 14874.

The safety database from Protocol 14874 consisted of 132 patients treated with regorafenib at a dose of 160 mg daily for the first 21 days of each 28-day cycle and 66 patients placebo-treated patients. The median duration of therapy was 22.9 (range 0.1, 50.9) weeks in regorafenib-treated patients. Dose interruptions for adverse events were required in 58% of regorafenib-treated patients, while 50% of regorafenib-treated patients required dose reductions. Drug-related adverse reactions that resulted in treatment discontinuation were reported in 2.3% of regorafenib-treated patients compared to 1.5% of patients who received placebo.

The following tables, abstracted from the package insert, summarize the adverse reactions of regorafenib identified in Protocol 14874. The adverse reactions of regorafenib identified in Protocol 14874, with the exception of toxic epidermal necrolysis, were previously identified in the package insert based on the approval of NDA 203085.

Adverse reactions (≥10%) of regorafenib in Protocol 14874, which occurred at a higher incidence in regorafenib-treated patients than in patients receiving placebo (≥ 5% between arm difference for all grades or ≥ 2% between arm difference for Grade 3-4 events).

| **Adverse Reactions** | **Stivarga (N=132)** | | **Placebo (N=66)** | |
|---|---|---|---|---|
| | **Grade** | | **Grade** | |
| | **All %** | **≥ 3 %** | **All %** | **≥ 3 %** |
| **Skin and subcutaneous tissue disorders** | | | | |
| HFSR/PPE | 67 | 22 | 15 | 2 |
| Rash [a] | 30 | 7 | 3 | 0 |
| Alopecia | 24 | 2 | 2 | 0 |
| **General disorders and administration site conditions** | | | | |
| Asthenia/Fatigue | 52 | 4 | 39 | 2 |
| Fever | 21 | 0 | 11 | 2 |
| **Vascular disorders** | | | | |
| Hypertension | 59 | 28 | 27 | 5 |
| Hemorrhage | 11 | 4 | 3 | 0 |
| **Gastrointestinal disorders** | 47 | 8 | 9 | 0 |
| Diarrhea | 40 | 2 | 8 | 2 |
| Mucositis | 20 | 2 | 12 | 2 |

| Adverse Reactions | Stivarga (N=132) | | Placebo (N=66) | |
|---|---|---|---|---|
| | Grade | | Grade | |
| | All % | ≥ 3 % | All % | ≥ 3 % |
| Nausea<br>Vomiting | 17 | <1 | 8 | 0 |
| **Respiratory, thoracic and mediastinal disorders**<br>Dysphonia | 39 | 0 | 9 | 0 |
| **Infections and infestations**<br>Infection | 32 | 5 | 5 | 0 |
| **Metabolism and nutrition disorders**<br>Decreased appetite and food intake<br>Hypothyroidism [b] | 31<br>18 | <1<br>0 | 21<br>6 | 3<br>0 |
| **Nervous system disorders**<br>Headache | 16 | 0 | 9 | 0 |
| **Investigations**<br>Weight loss | 14 | 0 | 8 | 0 |
| **Musculoskeletal and connective tissue disorders**<br>Musculoskeletal stiffness | 14 | 0 | 3 | 0 |

[a] The term rash represents reports of events of rash, erythematous rash, macular rash, maculo-papular rash, papular rash and pruritic rash.
[b] Hypothyroidism incidence based on subset of patients with normal TSH and no thyroid supplementation at baseline.

*Laboratory Abnormalities*

Laboratory test abnormalities in Protocol 14874 that were reported at a higher incidence in regorafenib-treated patients than in patients receiving placebo (≥ 5% between arm differences for all grades or ≥ 2% between arm differences for Grade 3-4 events).

| Laboratory Parameter | Stivarga (N=132 [a]) | | | Placebo (N=66 [a]) | | |
|---|---|---|---|---|---|---|
| | Grade [b] | | | Grade [b] | | |
| | All % | 3 % | 4 % | All % | 3 % | 4 % |
| **Blood and lymphatic system disorders** | | | | | | |
| Thrombocytopenia | 13 | 1 | 0 | 2 | 0 | 2 |
| Neutropenia | 16 | 2 | 0 | 12 | 3 | 0 |
| Lymphopenia | 30 | 8 | 0 | 24 | 3 | 0 |
| **Metabolism and nutrition disorders** | | | | | | |
| Hypocalcemia | 17 | 2 | 0 | 5 | 0 | 0 |
| Hypokalemia | 21 | 3 | 0 | 3 | 0 | 0 |
| Hypophosphatemia | 55 | 20 | 2 | 3 | 2 | 0 |
| **Hepatobiliary disorders** | | | | | | |
| Hyperbilirubinemia | 33 | 3 | 1 | 12 | 2 | 0 |
| Increased AST | 58 | 3 | 1 | 47 | 3 | 0 |
| Increased ALT | 39 | 4 | 1 | 39 | 2 | 0 |
| **Renal and urinary disorders** | | | | | | |
| Proteinuria | 33 | 3 | - [c] | 30 | 3 | - [c] |
| **Investigations** | | | | | | |
| Increased Lipase | 14 | 0 | 1 | 5 | 0 | 0 |

[a] % based on number of patients with post-baseline samples which may be less than 132 (regorafenib) or 66 (placebo).
[b] CTCAE, v4.0.
[c] No Grade 4 denoted in CTCAE, v4.0.

I concur with the DRISK consultant's and clinical reviewer's determination that a REMS is not required to ensure safe and effective use of regorafenib for the treatment of GIST in patients who have been previously treated with imatinib and sunitinib, and that the risks of regorafenib can be managed through labeling. As noted by the DRISK consultant, this determination is based on the demonstrated clinical benefit, the observed toxicity, the intended prescribers, and the target population.

There were no recommend PMRs based on safety findings.

## 9. Advisory Committee Meeting

The application was not referred for review to the Oncologic Drugs Advisory Committee because it did not raise significant safety or efficacy issues that were unexpected for a drug of this class in the intended population. The study design, primary endpoint, and magnitude of the treatment effect are similar to those supporting approval for sunitinib for treatment of GIST. FDA staff sought the advice from an Special Government Employee (SGE) consultant regarding demonstration of a positive risk:benefit analysis and regarding product labeling.

## 10. Pediatrics

Bayer was granted orphan drug designation on January 12, 2011 for regorafenib for the "treatment of patients with metastatic and/or unresectable GIST whose disease has progressed despite at least imatinib and sunitinib as prior treatments." Therefore, Bayer is exempt from the requirements under the Pediatric Research Equity Act (PREA) for this indication for regorafenib.

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues. As noted in the clinical review, clinical study site inspections were not conducted due to the small number of patients enrolled at each site (less than 10 patients), such that no single site could have a major influence on study outcomes.

## 12. Labeling

- Proprietary name: Not applicable- no changes proposed by Bayer or FDA to proprietary name.

- Physician labeling
  - Indications and Usage: The proposed new indication was modified to specify (b) (4)
  - Dosage and Administration: FDA accepted Bayer's proposal to remove the version of the CTCAE from this section because data from Protocol 14874 were obtained using CTCAE version 4.0.
  - Warnings and Precautions
    - Subsections 5.1 updated to include information obtained in Protocol 14874 and to reflect larger safety experience (data from 1200 rather than 1100 patients across the clinical trials experience) supporting this supplement.
    - Subsections 5.2 updated to include information obtained in Protocol 14874.
    - Subsection 5.3 updated to include information obtained in Protocol 14874; editorial revisions for clarity; replaced incidence of Grade 1-2 HFST during first cycle with

the proportion of patients with HFSR who presented during the first-cycle of treatment, as more informative to healthcare professionals. Added information on the incidence of serious adverse skin reactions (Study 1 and 2) and on Stevens-Johnson Syndrome for Study 1), and incidence of toxic epidermal necrolysis (TEN) across all clinical trials experience (1200 patients) based on new data provided in the supplement.

- Subsection 5.4 updated to include information obtained in Protocol 14874 and editorial revisions for clarity.
- Editorial revisions in Subsection 5.5 for clarity; there were no events of cardiac ischemia or infarction in Protocol 14874.
- Editorial revisions in Subsection 5.6 for clarity; there were no events of RPLS in Protocol 14874.
- Subsections 5.7 updated to include information obtained in Protocol 14874 and to reflect larger safety experience (data from 1200 patients across the clinical trials experience)

- Adverse Reactions
  - Updated initial paragraphs preceding section 6.1 as recommended by SEALD consultant for PLR labeling; increased list of most common adverse events to include those occurring in ≥ 20% rather than in ≥30% as in original labeling, taking into account additional clinical trials experience and results of Protocol 14874.
  - [redacted] (b) (4) colorectal cancer and [redacted] (b) (4) GIST); data from clinical studies for both indications now included in section 6.1 under appropriate subheadings; description of exposure changed from mean to median duration of treatment for both colorectal and GIST populations [redacted] (b) (4) Added information on preferred terms used to generate incidence data for composite term "rash" for both Studies 1 and 2. [redacted] (b) (4)
  - [redacted] (b) (4)
- Use in specific populations: Updated to include information on geriatric patients from Protocol 14874.
- Overdosage: Edited for brevity (adverse events listed are the same as those identified with the recommended dose)
- Clinical Studies: Revised this section to include details on the study protocol by identifying the required prior treatment (imatinib and sunitinib) for study eligibility, stratification variables used for randomization, and inclusion of the modifications to RECIST 1.1 used to determine tumor-based endpoints. [redacted] (b) (4)

[redacted] (b) (4) All data values in the table rounded in accordance with scientific standards for significant values (e.g., HR 0.268 rounded to HR 0.27). Replaced [redacted] (b) (4) with the factual statement that "There was no statistically significant difference in overall survival at the time of the planned interim analysis…" [redacted] (b) (4)

- Carton and immediate container labels: Not applicable – no changes proposed by Bayer or FDA to approved carton/container labeling

- Patient labeling/Medication guide:
  - Modified to include information on new indication; expanded description of RPLS and on bowel perforation for consistency with other patient labels and to provide adequate information; reordered information on most common side effects to reflect decreasing incidence and consistency with section 6 of physician label.

# 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  GIST is an uncommon but serious malignancy involving the gastrointestinal tract. FDA-approved therapy has been effective in prolonging progression-free survival in the adjuvant and metastatic setting but has not resulted in cures for patients with metastatic disease. Therefore, patients who have progressed following treatment with FDA-approved drugs have unmet needs. The data provided in this NDA demonstrated that treatment with regorafenib results in a statistically robust and clinically important prolongation in progression-free survival for patients with GIST whose tumors are no longer controlled with imatinib and sunitinib. The risks of regorafenib are also clinically important but are also similar to other drugs, notably sunitinib, used for the treatment of GIST and would be considered acceptable in light of the observed benefits by patients and the oncology community.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies:
  No new post-marketing requirements were identified by the FDA reviewers. A REMS was not required to ensure safe and effective use for this new indication.

- Recommendation for other Postmarketing Requirements and Commitments
  There were two post-marketing requirements identified by FDA reviewers:

  - Submit the results of the protocol-specified final analysis of overall survival, along with datasets and analysis programs, from Study 14874, "A randomized, double-blind, placebo-controlled phase III study of regorafenib plus best supportive care versus placebo plus best supportive care for subjects with metastatic and/or unresectable gastrointestinal stromal tumors (GIST) whose disease has progressed despite prior treatment with at least imatinib and sunitinib."

  - Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 using relevant available data collected in patients with metastatic or unresectable gastrointestinal stromal tumor (GIST).

  - Submit a CMC CBE-30 supplement that includes the addition of a microbial purity test as a drug product specification and test each batch prior to release and the addition of X-Ray Powder Diffraction (XRPD) testing methodology & specifications to test any batches that do not meet the dissolution acceptance criterion of NLT (b) (4) dissolved at 45 minutes.

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

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/s/

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PATRICIA KEEGAN
02/25/2013