

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
204369Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA	204-369
Type/Category	Type 9 NDA
Brand Name	Stivarga®
Generic name	Regorafenib
Proposed Indication	(b) (4)
Dosage Form	Film-coated tablet, 40 mg
Route of Administration	Oral
Dosing Regimen and Strength	160 mg oral once daily for the first 21 days of each 28-day treatment cycle
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
OCP Division	DCPV
OND Division	DOP2
Submission Date	August 30, 2012
PDUFA	February 28, 2013
Primary Reviewer	Stacy S. Shord, Pharm.D.
Team Leader	Hong Zhao, Ph.D.

Table of Contents

1	EXECUTIVE SUMMARY	2
1.1	RECOMMENDATIONS	2
1.2	SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS	4
2	QUESTION BASED REVIEW	4
2.1	GENERAL ATTRIBUTES	4
2.2	GENERAL CLINICAL PHARMACOLOGY	5
2.3	INTRINSIC FACTORS	8
2.4	EXTRINSIC FACTORS	8
2.5	GENERAL BIOPHARMACEUTICS	8
2.6	ANALYTICAL SECTION	9
3	DETAILED LABELING RECOMMENDATIONS	10

List of Tables

Table 1.	Description of Study 14874 and Study 14935	6
Table 2.	Primary efficacy analysis of Study 14874	6
Table 3.	The repeat dose mean (% coefficient variation) pharmacokinetic parameters of regorafenib, M2 and M5 in patients administered 160 mg daily from Study 14935 (on cycle 1, day 15) and Study 11650 (on cycle 1, day 21)	8
Table 4.	The accuracy and precision estimated for the quality control samples	10

1 EXECUTIVE SUMMARY

Regorafenib as Stivarga[®] was approved on September 27, 2012 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. This NDA has been identified as a type 9 NDA (new indication submitted as distinct NDA) and it will be converted to an efficacy supplement of NDA 203-085 upon its approval. Only two studies were included in this submission to support an indication for the treatment of patients with gastrointestinal stromal tumors (GIST) that were not submitted and reviewed under NDA 203-085: Study 14935 (phase 2) and Study 14874 (phase 3). In Study 14874, 199 patients with metastatic and/or unresectable GIST after prior treatment with at least imatinib and sunitinib were randomized 2:1 to best supportive care (BSC) with regorafenib or placebo. Regorafenib was administered at a dose of 160 mg (4 x 40 mg tablets) once daily with a low fat breakfast for the first 21 days of a 28 day treatment cycle. The median progression free survival (PFS) time was statistically significantly longer for patients randomized to regorafenib + BSC than for patients randomized to placebo + BSC (4.2 vs. 0.9 months) with a hazard ratio (HR) 0.27 (0.19, 0.40) (P<0.0001). The safety profile appears similar in patients with GIST compared to patients with mCRC.

No clinically meaningful differences in exposure of regorafenib and the active metabolites M2 and M5 were observed for patients with GIST enrolled in Study 14935 as compared with patients with solid tumors or colorectal cancer enrolled in Study 11650 (reviewed under NDA 203-085).

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective provided that the applicant and the FDA come to an agreement regarding the labeling language and the identified Post Marketing Commitment (PMC).

1.1.1 Post Marketing Commitments

The Office of Clinical Pharmacology requires the applicant to conduct the following PMC. This study will be included in the action letter with milestones agreed upon after negotiation with the applicant.

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).

Signatures:

Stacy S. Shord, Pharm.D.
Reviewer
Division of Clinical Pharmacology 5

Hong Zhao, Ph.D.
Team Leader
Division of Clinical Pharmacology 5

Nam Atiqur Rahman, Ph.D.
Division Director
Division of Clinical Pharmacology 5

Cc: DOP2: RPM-**M Hughes**; MO- **J Chang, A Shahlaee**; MTL- **S Demko**
DCP-5: DDD - **B Booth**

****An OCP Office Level Briefing was not held.****

1.2 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

The submission includes a clinical study report, a PK summary with an analytical report and a publication describing a clinical study to support an indication for the treatment of patients with GIST. No clinically important differences in the exposure of regorafenib and the active metabolites M2 and M5 were observed using a cross study comparison of patients with solid tumors or colorectal cancer enrolled in Study 11650 (reviewed as part of NDA 203-085) and Study 14935 (phase 2 trial). Sparse pharmacokinetic (PK) samples were collected in the clinical safety and efficacy trial (Study 14874); a post marketing commitment (PMC) will be requested for the applicant to conduct exposure-response (E-R) analyses.

2 QUESTION BASED REVIEW

On September 27, 2012, regorafenib as Stivarga was 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. The following Post Marketing Requirements (PMRs) and Post Marketing Commitments (PMCs) pertinent to clinical pharmacology were included in the approval letter:

- 1925-1 Complete a clinical trial evaluating the potential for regorafenib to prolong the QT/QTc interval in an adequate number of patients administered repeated doses of 160 mg of regorafenib and submit the final report, along with a thorough review of cardiac safety data.
- 1925-2 Complete a clinical trial and submit the final report to evaluate the effect of repeated doses of 160 mg of regorafenib on the pharmacokinetics of a probe substrate of CYP2C8, CYP2C9, CYP3A4 and CYP2C19.
- 1925-3 Conduct a multiple dose trial to determine the appropriate regorafenib dose in patients with severe renal impairment. Submit the final protocol for FDA review before conducting the trial.
- 1925-4 Submit an integrative population pharmacokinetic analysis report to evaluate the effect of intrinsic and extrinsic factors on the pharmacokinetics of regorafenib and its active metabolites M2 and M5.
- 1925-5 Submit an exposure-response analysis for regorafenib and its active metabolites M2 and M5 using data collected from the CORRECT trial (Study 14387) in patients with metastatic colorectal cancer (mCRC) who have progressed after standard therapy.

This submission includes the nonclinical and clinical studies submitted and reviewed under NDA 203-085. Two additional studies relevant to clinical pharmacology included in this NDA were Study 14935 and Study 14874. Orphan drug designation was granted on January 12, 2011.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they related to clinical pharmacology and biopharmaceutics review?

As stated in the approved labeling, regorafenib has a molecular formula of $C_{21}H_{15}ClF_4N_4O_3 \cdot H_2O$ and a molecular weight of 501 g/mol. Regorafenib is practically insoluble in water, slightly soluble in acetonitrile, methanol, ethanol, and ethyl acetate and sparingly soluble in acetone.

Each tablet contains 40 mg of regorafenib in the anhydrous state, which corresponds to 41.49 mg of regorafenib monohydrate.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

As stated in the approved labeling, regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In *in vitro* biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Abl at concentrations of regorafenib that have been achieved clinically. In *in vivo* models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended dose as listed in the approved labeling is 160 mg (4 x 40 mg tablets) once daily for the first 21 days of each 28-day treatment cycle. Stivarga is to be taken with a low-fat breakfast that contains less than 30% fat.

The proposed dose and route of administration for GIST is the same as in the approved labeling for mCRC.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

This NDA includes a final study report, a PK summary with an analytical report and a publication describing a clinical trial to support the indication for the treatment of patients with GIST that were not submitted under NDA 203-085. The remaining nonclinical and clinical studies appear to have been submitted and reviewed as part of NDA 203-085.

Table 1. Description of Study 14874 and Study 14935		
Study	Study 14874 (phase 3)	Study 14935 (phase 2)
Study Design	Randomized, double blind, placebo controlled followed by open label (cross over permitted)	Non-randomized, open label, multicenter
Objectives	Efficacy Safety	Efficacy Safety Pharmacokinetics Biomarkers
Treatment	160 mg once daily for the first 21 days of a 28-day treatment cycle with a low fat breakfast	160 mg once daily for the first 21 days of a 28-day treatment cycle with a light breakfast
Population	199 patients with metastatic and/or unresectable GIST after prior treatment with at least imatinib and sunitinib	33 patients with metastatic and/or unresectable GIST refractory or intolerant to at least imatinib and sunitinib

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary endpoint of the clinical safety and efficacy trial Study 14874 was progression free survival (PFS) defined as the time (days) from randomization to objective tumor progression or death. As stated in the FDA Guidance for Industry “*Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*”, PFS has served as a primary endpoint for drug approval, but role of PFS as an endpoint to support licensing approval varies in different cancer settings. The secondary endpoints included overall survival (OS), time to progression (TTP), disease control rate (DCR), tumor response rate (RR), and duration of response (DOR).

Table 2. Primary efficacy analysis of Study 14874 (Applicant’s analysis)		
	Placebo + BSC (N = 66)	Regorafenib + BSC (N = 133)
Number of patients (%) with event	63 (95.5%)	81 (60.9%)
Median PFS, days (95% CI)	28 (28, 32)	147 (122, 173)
Median PFS, months	0.9	4.8
Hazard ratio (regor/pl) (95% CI)	0.268 (0.185,0.388)	
p-value (one sided from log rank test)	<0.000001	

Historical Biomarker Analyses - Study 14874

Historical mutation data is available from 48% (N=96) of all randomized patients: 53% (N=51) mutation in KIT exon 11, 16% (N=15) mutation in KIT exon 9, and 8% (N= 8) had no KIT and no PDGFR α mutation. The applicant stated that descriptive subgroup analyses evaluating PFS by historical KIT mutational status demonstrated a strong and consistent benefit in favor of regorafenib over placebo for patients with tumors mutated in KIT exon 11 (HR of 0.21; 95% CI: 0.10, 0.46) and in KIT exon 9 (HR of 0.24; 95% CI: 0.06, 0.88). The mutation frequency reported appears consistent with published data (exon 11, 67% and exon 9, 10% to 15%).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The concentrations of regorafenib and its metabolites in the PK samples collected as part of Study 14935 were determined using a LCMS assay which is different from the assay submitted and reviewed under NDA 203-085.

The PK data collected as part of Study 14874 were not included in the study report submitted under this NDA, but will be submitted to address the proposed PMC to conduct E-R analyses. It is not known which assay was used to measure the concentrations of regorafenib or its metabolites in this study.

2.2.4 Exposure-response

The applicant did not provide E-R analyses in this submission. The applicant will be requested to conduct E-R-response analyses using data collected in the patients with GIST under a PMC.

A final study report of an ongoing cardiovascular safety study was submitted under NDA 203-085 in November 2012 to address PMR 1925-1 to assess the potential for regorafenib to prolong the QT/QTc interval and it is being reviewed under NDA 203-085.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

Sparse PK samples were collected from all patients in Study 14874 pre-dose on day 15. A summary of these PK data were not included in the clinical study report, but will be submitted to address the proposed PMC to conduct E-R analyses.

Sixteen patients enrolled in the Study 14935 provided serial PK samples up to 24 hrs after the dose administered on cycle 1, day 15 to determine concentrations of regorafenib and its metabolites as stated in the analytical report. Additional PK samples were drawn to measure plasma trough concentrations on the day of each ¹⁸F-DG-PET/CT, with the exception of the baseline scan, to correlate metabolic tumor activity with drug trough level. The PK report did not include a summary of these additional trough concentrations.

The exposure of regorafenib appears similar between patients enrolled into Study 11650 (reviewed under NDA 203-085) and Study 14935 using a cross study comparison; however, the exposure to M2 and M5 metabolites appears lower (**Table 3**). Two different assays were used to measure the plasma concentrations in the PK samples collected in these studies; a bridging study was not conducted to compare these methods.

The M2 metabolite has a geometric mean (range) elimination half-life of 25 hours (14 to 32 hours) and its plasma concentrations have likely reached steady-state on day 15. The mean exposure of M2 metabolite appears lower (~40%) for the patients enrolled in Study 14935 as compared with patients enrolled in Study 11650. It is not clear if these differences are partly resulted from any difference between the two assays used.

The M5 metabolite has a relatively long-half life (geometric mean of 51 hours) and its plasma concentrations have not reached steady-state on day 15. Therefore, the plasma concentrations measured on cycle 1, day 21 during Study 11650 are expectedly higher.

Since no clinically meaning differences have been observed between patients with GIST and solid tumors or colorectal cancer, no revisions to the clinical pharmacology section of the

approved labeling are recommended.

Table 3. The repeat dose mean (% coefficient variation) pharmacokinetic parameters of regorafenib, M2 and M5 in patients administered 160 mg daily from Study 14935 (on cycle 1, day 15) and Study 11650 (on cycle 1, day 21)

	AUC _{0-24h,ss} µg·h/mL	C _{max} µg/mL	AUC _{0-24h,ss} µg·h/mL	C _{max,ss} µg/mL	AUC _{0-24h,ss} µg·h/mL	C _{max,ss} µg/mL
	Study 14935 GIST N=16		Study 11650 - Cohort 7 Solid Tumors N=10		Study 11650 - Cohort 9 Colorectal Cancer N=19	
Regorafenib	59.7 (63%)	4.0 (61%)	58.3 (43%)	3.9 (44%)	50.3 (86%)	3.4 (63%)
M2	33.6 (110%)	2.1 (106%)	53.7 (78%)	3.3 (69%)	48.1 (89%)	3.2 (72%)
M5	18.1 (144%)	1.2 (140%)	48.7 (89%)	2.9 (83%)	64.6 (162%)	4.0 (174%)

2.3 INTRINSIC FACTORS

The applicant did not provide population PK analyses or dedicated studies to assess intrinsic factors in this submission. As stated in the original NDA approval letter, an integrative population PK analysis report to evaluate the effect of intrinsic and extrinsic factors on the PK of regorafenib and its active metabolites M2 and M5 should be submitted in June 2013 to address PMC 1925-4. In addition, a final study report should be submitted in June 2015 to address PMR 1925-3 to assess the PK of regorafenib and the metabolites M2 and M5 in patients with severe renal impairment.

Biomarker Analyses- Study 14935

When available, tumor tissue was analyzed for mutations in KIT and PDGFR α genes. Tumors with no identifiable mutation in either KIT or PDGFR α were genotyped for BRAF mutation. Patients who consented to optional tumor biopsies underwent tumor biopsy before the first dose of study drug, and a second biopsy was performed between days 10 and 21 of cycle one. Mutation data is available from 30 patients included in this study; KIT exon 11 mutations were identified in 19 tissues, KIT exon 9 mutations were identified in 3 tissues and no KIT or PDGFR α mutations were identified in 8 tissues. The mutation frequency appears consistent with the published literature.

Biomarker Analyses- Study 14874

DNA isolated from archival tumor tissue specimens and fresh plasma samples is being evaluated for mutations in KIT, PDGFR α , KRAS and BRAF. The applicant stated that these analyses will be provided in a separate report; this report is not included in the current submission. The frequency of the KIT mutation was reported as part of the efficacy analyses.

2.4 EXTRINSIC FACTORS

The applicant did not provide population PK analyses or dedicated studies to assess extrinsic factors in this submission.

To address PMR 1925-2 to assess the potential for regorafenib to inhibit multiple cytochrome P450 enzymes as stated in the original NDA approval letter, a final study report of a drug interaction study was submitted in November 2012 and it is being reviewed under NDA 203-085.

2.5 GENERAL BIOPHARMACEUTICS

Please refer to the clinical pharmacology review of the NDA 203-085.

The dose of 160 mg in each clinical trial was administered as 4 x 40 mg tablets. The 40 mg tablets are the currently approved dosage form and strength.

2.6 ANALYTICAL SECTION

A different analytical assay was used to estimate the plasma concentrations of regorafenib and its metabolites for PK samples collected from Study 14935 as compared to the assay submitted and reviewed under NDA 203-085. The analytical report does not fully describe the performance characteristics of the assay. Since no new PK data will be included in the approved labeling, additional characterization of the analytical assay was not requested.

2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?

Regorafenib, M2, M4 and M5 were identified in human plasma using LCMS.

2.6.2 Which metabolites have been selected for analysis and why?

M2, M4 and M5 were selected for analysis in Study 14935 along with regorafenib. M2 and M5 metabolites are major circulating metabolites at steady-state and exhibit similar anticancer activity compared to regorafenib in tumor models and inhibition of the same protein kinases as regorafenib which were reviewed under NDA 203-085.

2.6.3 For all moieties measured is free, bound or total measured?

Total plasma concentrations were measured for all active moieties (regorafenib and the two active metabolites M2 and M5).

2.6.4 What bioanalytical methods are used to assess concentrations?

LCMS was used to measure the concentrations of regorafenib, M2, M4 and M5 in human plasma collected from patients enrolled in Study 14935.

As stated earlier, the assay used to measure the concentrations of regorafenib and its metabolites in Study 14874 was not specified. The bioanalytical methods used to measure these concentrations in the PK samples collected as part of this study will be evaluated when the applicant submits the PK data to address the proposed PMC.

2.6.4.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

Calibration and QC samples were prepared by spiking human plasma with appropriate volumes of serially diluted working standard solutions of regorafenib or a metabolite. The calibration curve extended from LLOQ to 2,010 ng/mL or 5,176 ng/mL for regorafenib and from LLOQ to ~2,000 ng/mL for M2 and M5. The analytical report does not state why the calibration range for regorafenib was changed.

Calibration functions were validated for relative peak areas which were obtained by weighted ($1/x^2$) linear regression of the nominal concentration or by fitting to an exponential function. The calibration range reasonably represents the concentrations of regorafenib, M2 and M5 in humans.

2.6.4.2 *What are the lower and upper limits of quantification?*

The LLOQ for regorafenib in plasma was 4 ng/mL or 10 ng/mL and for M2 and M5 was ~4

ng/mL. The analytical report did not state why the LLOQ was changed for regorafenib.

2.6.4.3 *What are the accuracy, precision and selectivity at these limits?*

The accuracy and precision of the QC samples for regorafenib, M2 and M5 in human plasma appear adequate based on the current FDA Guidance for Industry *Bioanalytical Method Validation*.

Table 4. The accuracy and precision estimated for the quality control samples		
Compound	Accuracy	Precision
Regorafenib	98 % to 105 %	2.7 % to 8.1 %
M2	98 % to 108 %	1.4 % to 12.4 %
M5	89 % to 107 %	1.8 % to 8.6 %

2.6.4.4 *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

The sample stability under the conditions used in the study was not described in the study report.

2.6.4.5 *What is the QC sample plan?*

QC samples were prepared at a concentrations range of 12 ng/mL to 4,000 ng/mL for regorafenib and 12 ng/mL to 1,500 ng/mL for M2 and M5 by spiking human plasma with an appropriate volume of working solutions. The QC samples were included in duplicate in each run.

3 DETAILED LABELING RECOMMENDATIONS

The applicant proposed the addition of the underlined text to section 12.3 of the approved labeling. The change is acceptable. No other changes were proposed or appear to be warranted to the clinical pharmacology relevant sections of the approved labeling.

12.3 Pharmacokinetics

Absorption

... Stivarga was administered with a low-fat meal in Studies 1 and 2 [see *Dosage and Administration (2.1), Clinical Studies (14)*]...

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

/s/

STACY S SHORD
01/24/2013

HONG ZHAO
01/25/2013

NAM ATIQR RAHMAN
01/28/2013

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204369	Reviewer: Elsbeth Chikhale, Ph.D.	
Submission Date:	August 30, 2012 (last date to complete rolling submission)		
Division:	Division of Oncology Products	Team Leader: Angelica Dorantes, Ph.D.	
Applicant:	Bayer Healthcare Pharmaceuticals, Inc.	Acting Supervisor: Richard Lostritto, Ph.D.	
Trade Name:	Stivarga Tablets	Date Assigned:	August 23, 2012
Generic Name:	Regorafenib	Date of Review:	November 19, 2012
Indication:	Treatment of patients with (b) (4)	Type of Submission: 505(b)(1) Original New Drug Application	
Formulation/ strengths	Film coated IR tablet/ 40 mg		
Route of Administration	Oral		

SUBMISSION:

This 505(b)(1) New Drug Application 204369 is for a (non-functional) film coated immediate release tablet, containing 40 mg of regorafenib as the active ingredient. The proposed indication is for the treatment of patients with (b) (4)

(b) (4) Regorafenib is an orally active, multikinase inhibitor that has been shown to target the following receptor tyrosine kinases: VEGFR1-3, TIE2, PDGFR-β, FGFR, KIT, RET, RAF-1, BRAF, BRAFV600E.

Previous NDA 203085 for Stivarga (regorafenib) Tablets 40 mg for the treatment of patients with metastatic colorectal cancer (CRC) was approved on September 27, 2012. The current NDA 204-369 is a type 9 NDA, which by definition will be converted to an efficacy supplement (ES) under NDA 203085 upon approval of NDA 204369.

The Biopharmaceutics information/data submitted in the current NDA 204369 is the same as that submitted under NDA 203085. For reference, see the Biopharmaceutics review of NDA 203085 by Elsbeth Chikhale, Ph.D. dated 8/28/2012 in DARRTS.

BIOPHARMACEUTICS INFORMATION:

The formulation and method of manufacturing of the proposed 40 mg regorafenib tablets are exactly the same as those for the 40 mg regorafenib tablets recently approved under NDA 203085. The Biopharmaceutics review for this NDA is referring to the Biopharmaceutics review

of NDA 203085 by Elsbeth Chikhale, Ph.D. dated 8/28/2012 for the evaluation and acceptability of 1) the proposed dissolution methodology and 2) the proposed dissolution acceptance criteria.

DISSOLUTION METHOD:

The proposed dissolution method that was found acceptable during the review of NDA 203085 is as follows:

USP Apparatus II (paddle)

Dissolution medium: 900 mL acetate buffer pH 4.5 containing 0.1% sodium dodecyl sulfate

Temperature: 37 °C

Rotation speed: 75 rpm

Analysis: UV at 265 nm

DISSOLUTION ACCEPTANCE CRITERIA:

The final dissolution acceptance criteria that were found acceptable during the review of NDA 203085 are as follows:

USP Apparatus/ RPM	Medium	Volume	Acceptance Criteria
Apparatus II/ 75 rpm	Acetate buffer pH 4.5 containing 0.1% sodium dodecyl sulfate	900 mL	a) QC testing: $Q = \frac{(b)(4)}{t=30}$ min with stage testing according to USP, EP, JP. b) Testing for absence of crystalline drug substance: dissolution after 45 min with not less than $(b)(4)$ (mean of 6 individual samples) and without stage testing

Note: The following is not part of the final drug product specifications, but suggested by the Applicant as a post-approval action to NDA 203085:

If a mean dissolution rate of $(b)(4)$ is not met, then XRPD testing is required confirming that $(b)(4)$ XRPD testing will not be implemented until validated XRPD methodology and revised specifications (with XRPD) have been submitted to the Division (post-approval).

The acceptability of the XRPD method and validation will be a review issue when the information is submitted to NDA 203085 (post-approval). The suggested XRPD acceptance criterion of $(b)(4)$ has not been agreed upon and will need to be evaluated when submitted to NDA 203085 (post-approval).

RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 204369 for Regorafenib Tablets, 40 mg is recommended for APPROVAL.

Elsbeth Chikhale, Ph.D.

Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.

Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

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

/s/

ELSBETH G CHIKHALE
11/19/2012

ANGELICA DORANTES
11/19/2012

Office of Clinical Pharmacology

Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	204-369	Brand Name	Stivarga
OCP Division (I, II, III, IV, V)	V	Generic Name	Regorafenib
Medical Division	DOP2	Drug Class	Kinase inhibitor
OCP Reviewer	Stacy S. Shord, Pharm.D.	Indication(s)	Gastrointestinal stromal tumor
OCP Team Leader	Hong Zhao, PhD	Dosage Form	Film-coated tablets
Pharmacometrics Reviewer	None	Dosing Regimen	160 mg
Date of Submission	08/30/2012	Route of Administration	Oral
Estimated Due Date of OCP Review	01/31/2013	Sponsor	Bayer HealthCare Pharmaceuticals, Inc
Medical Division Due Date	02/28/2013	Priority Classification	Priority
PDUFA Due Date	02/28/2013	eCTD link	\\CDSESUB1\EVSPROD\NDA204369\204369.enx

Clinical Pharmacology and Biopharmaceutics Information

	“X” if included at filing	Number of studies submitted	Critical Comments
STUDY TYPE			
Table of Contents present and sufficient to locate reports, tables, data, etc.	x		
Tabular Listing of All Human Studies	x		Module 5.2
HPK Summary	x		Module 2.7.2
Labeling	x		Module 1.14
Reference Bioanalytical and Analytical Methods	x		Report A59117 (module 4.2.2.1.1)
I. Clinical Pharmacology			
Mass balance			
Isozyme characterization			
Blood/plasma ratio			
Plasma protein binding			
Pharmacokinetics			
Healthy Volunteers -			
single dose			
multiple dose			
Patients -			
single dose			
multiple dose	x	1	Study 14935 / R-8715, GIST, phase 2
Dose proportionality -			
in-vivo effects on primary drug			
in-vivo effects of primary drug			
in-vitro			
Subpopulation studies -			
ethnicity			
gender			
pediatrics			Orphan Drug granted January 2011
geriatrics			
renal impairment			
hepatic impairment			
Pharmacodynamics			

Phase 2			
Phase 3			
PK/PD			
Phase 1 and/or 2, proof of concept	x	1	Study 14935 / R-8715, GIST
Phase 3 clinical trial	x	1	Study 14874, GIST – PK, biomarker (KIT exon 11, KIT exon 9, and / or PDGFR mutational status); PK and biomarker data are not provided in the final study report
Population Analyses			
Data rich			
Data sparse			
II. Biopharmaceutics			
Absolute bioavailability			
Relative bioavailability			
solution as reference			
alternate formulation as reference			
Bioequivalence			
traditional design; single/multi dose			
replicate design; single/multi dose			
Food-drug interaction			
Bio-waiver request			
BCS class	2		Based on drug transport in Caco-2 cells and poor solubility.
Dissolution - alcohol induced dose-dumping			
III. Other Studies			
Genotype/phenotype			None
Pediatric development plan	x		Orphan Drug
Literature references			Multiple
Total Number of Studies		2	

The applicant submitted an original NDA (NDA 203-085) for regorafenib in patients with metastatic colorectal cancer that was approved on Thursday, September 27, 2012. It is anticipated that this type 9 NDA will be converted to an efficacy supplement to NDA 203-085 upon its approval. Only two additional studies relevant to clinical pharmacology were submitted under this submission that were not reviewed under NDA 203-085. The clinical development of regorafenib for GIST has been conducted under IND 113,896 with earlier information under IND 75,642.

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	It appears that the 'to-be-marketed' drug product was administered in the clinical efficacy and safety trial. A BE study comparing an earlier clinical trial product to the 'to-be-marketed' product was reviewed under NDA 203-085.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			PMR under NDA 203-085 to assess potential pharmacokinetic interaction with cytochrome P450 probe substrates. The final study report will be submitted in November 2012.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		The applicant proposes to submit ER analyses for the clinical efficacy and safety trial as a PMC in March 2013.
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Orphan Drug
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Orphan Drug
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		The applicant proposes to submit ER analyses for the clinical efficacy and safety trial as a PMC in March 2013.
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

The application is fileable from a clinical pharmacology perspective.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No potential review issues need to be forwarded in the 74-day letter.

Stacy S. Shord, Pharm.D.

Reviewer

Date

Hong Zhao, Ph.D.

Team Lead

Date

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

/s/

STACY S SHORD
10/10/2012

HONG ZHAO
10/10/2012
I concur.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	204369
Submission Date	8/30/12 (date of last piece of rolling submission)
Product name, generic name of the active	Stivarga (regorafenib)
Dosage form and strength	Film Coated Tablet - 40 mg/tablet
Route of Administration	Oral
Applicant	Bayer Healthcare Pharmaceuticals, Inc.
Clinical Division	Division of Oncology Products
Type of Submission	Original NDA – 505(b)(1)
Biopharmaceutics Reviewer	Elsbeth Chikhale, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		Refer to NDA 203085
2.	Is the dissolution test part of the DP specifications?	x		Refer to NDA 203085
3.	Does the application contain the dissolution method development report?	x		Refer to NDA 203085
4.	Is there a validation package for the analytical method and dissolution methodology?	x		Refer to NDA 203085
5.	Does the application include a biowaiver request?		x	Not needed.
6.	Does the application include an IVIVC model?		x	
7.	Is information such as BCS classification mentioned, and supportive data provided?	x		Refer to NDA 203085
8.	Is information on mixing the product with foods or liquids included?		x	
9.	Is there any in vivo BA or BE information in the submission?	x		

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
10.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		
11.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
12.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			NA
13.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		x	

The Biopharmaceutics information submitted in this NDA is the same as that submitted in NDA 203085. NDA 203085, for Stivarga (rigorafenib) Tablets 40 mg, was approved (for a different indication) on September 27, 2012. For reference, see Biopharmaceutics review of NDA 203085 by Elsbeth Chikhale, Ph.D. dated 8/28/2012.

{See appended electronic signature page}

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

10/9/12
Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

10/9/12
Date

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

/s/

ELSBETH G CHIKHALE
10/09/2012

ANGELICA DORANTES
10/10/2012