CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204369Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	204-369
Supporting document/s:	NDA 203-085, IND 75,642, and IND 113,896
Applicant's letter date:	August 30, 2012 (last date to complete rolling submission)
CDER stamp date:	August 30, 2012
Product:	Stivarga Tablets (regorafenib)
Indication:	Gastrointestinal stromal tumor (GIST)
Applicant:	Bayer Healthcare Pharmaceuticals, Inc. 340 Changebridge Road Pine Brook, NJ 07058
Review Division:	Division of Hematology Oncology Toxicology (Division of Oncology Products 2)
Reviewer:	M. Anwar Goheer, Ph.D.
Supervisor/Team Leader:	Whitney S. Helms, Ph.D.
Division Director:	John Leighton, Ph.D., D.A.B.T. (Patricia Keegan, M.D.)
Project Manager:	Monica L. Hughes

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204-369are owned by Bayer Healthcare Pharmaceuticals Inc. or are data for which Bayer has obtained a written right of reference.Any information or data necessary for approval of NDA 204-369 that Bayer does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204-369.

1Executive Summary

Bayer Healthcare Pharmaceuticals Inc. has submitted a 505(b)(1) New Drug Application for regorafenib (Stivarga™) for the treatment of patients with [redacted] (b) (4) The current NDA 204-369 is a type 9 NDA, which by definition will be converted to an efficacy supplement under NDA 203-085 upon approval of NDA 204-369. Under NDA 203-085, also submitted by Bayer, Stivarga was approved in September of 2012 for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatinum- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

The nonclinical pharmacology/toxicology data previously submitted under NDA 203-085 to support the colorectal cancer indication is also sufficient to support the treatment of patients with gastrointestinal stromal tumors; thus, no new nonclinical were required in the current submission. For further reference, see the Pharmacology/Toxicology NDA/BLA Review and Evaluation by Drs. Anwar Goheer and Andrew McDougal.

Recommendations: There are no non-clinical findings or outstanding issues that would preclude the approval of regorafenib in the proposed indication. No changes to sections of the previously approved Stivarga label regarding pharmacology/ toxicology data are recommended at this time.

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/s/

M A GOHEER
12/19/2012

WHITNEY S HELMS
12/20/2012

I concur with Dr. Goheer's conclusion that the studies previously submitted under NDA 203085 to support the approval of Stivarga for the treatment of patients with metastatic colorectal cancer are also sufficient to support the use of Stivarga for the treatment of patients with GIST and that no further nonclinical studies are warranted at the current time to support the approval of Stivarga for the treatment of patients with GIST.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA

NDA Number: 204-369 **Applicant:** Bayer Healthcare **Stamp Date:** August 30, 2012

Drug Name: Regorafenib (Stivarga®) **NDA Type:** new molecular entity (NME)

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

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	√		CTD format
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	√		Electronic submission
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	√		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	√		Carcinogenicity – not done/not required Mutagenicity – done Teratogenicity – done Fertility – not required Juvenile studies – not done/not required Acute and repeat dose toxicity – done (6-month in rats and 52-week in dogs) ADME – done Safety pharmacology – done (cardio, neuro, renal, gastrointestinal, pulmonary, local tolerance)
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	√		Similar formulations were used in pivotal preclinical and clinical studies
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	√		Same route of administration
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	√		

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	√		
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	√		
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	√		Sufficient for filing.
11	Has the applicant addressed any abuse potential issues in the submission?		√	N/A; Does not constitute a filing issue
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? _YES__

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

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. **None**

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/s/

M A GOHEER
10/16/2012

WHITNEY S HELMS
10/17/2012