CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203085Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	10 Sep 2012
From	Steven Lemery, M.D., M.H.S.
Subject	Cross-Discipline Team Leader Review
NDA #	203085
Applicant	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	27 Apr 2012
PDUFA Goal Date	27 Oct 2012
Proprietary Name / Established Name	Stivarga / regorafenib
Dosing Regimen	160 mg regorafenib (four 40 mg tablets) taken orally once daily for the first 21 days of each 28-day cycle.
Proposed Indication(s)	Regorafenib is indicated for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy
Recommended:	*Approval pending final agreement on labeling and Post-Marketing Requirements*

Table of Contents

1. Introduction....4
1.1 One versus two trials....4
1.2 Clinical-pharmacology submission....5
1.3 Food effects....6
2. Background....6
2.1 Disease and therapy related issues....6
2.2 U.S. regulatory history....9
2.3 Application history....11
3. CMC....12
3.1 Drug substance review....12
3.2 Drug product review....12
3.3 Biopharmaceutics review....13
3.4 Manufacturing inspections....13
4. Nonclinical Pharmacology/Toxicology....13
5. Clinical Pharmacology....14
5.1 General clinical pharmacology considerations....14
5.1.1 Dose selection....14
5.1.2 Pharmacokinetics....15
5.1.3 Food effects....16
5.2 Drug-drug interactions....17
5.3 Demographic interactions/special populations....17
5.4 Thorough QT study or other QT assessment....17
5.5 Biomarker assessments....17

6. Clinical Microbiology 18
7. Clinical/Statistical-Efficacy 18
7.1 Background of clinical program 18
7.2 Design of Bay 73-4506/14387 18
7.2.1 Primary endpoint 18
7.2.2 Secondary endpoints 18
7.2.3 Eligibility criteria 19
7.2.4 General study design/treatment plan 19
7.2.5 Statistical design and analysis issues 20
7.3 Summary results 22
7.3.1 Demographics 22
7.3.2 Disposition 23
7.3.3 OS analyses 23
7.3.4 Secondary endpoints 26
8. Safety 27
8.1 Adequacy of database 27
8.2 Deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests 28
8.2.1 Deaths 28
8.2.2 SAEs 28
8.2.3 Drop-outs and discontinuations due to adverse events 29
8.2.4 Common adverse events 29
8.2.5 Laboratory tests 30
8.3 Special safety concerns 31
8.3.1 Drug-demographic interactions 31
8.3.2 Additional in-depth analyses of specific events 32
8.4 Discussion of primary reviewer's findings and conclusions 32
9. Advisory Committee Meeting 33
10. Pediatrics 33
11. Other Relevant Regulatory Issues 34
11.1 Application Integrity Policy (AIP) 34
11.2 Financial disclosures 34
11.3 GCP issues 34
11.4 OSI audits 35
11.5 Other discipline consults 35
11.5.1 DRISK 35
11.5.2 DMEPA 35
11.5.3 Pediatric and Maternal Health Staff review 35
11.5.4 Predictive Safety consult 35
11.6 Drug name review 36
12. Labeling 36
13. Recommendations/Risk Benefit Assessment 38
13.1 Recommended regulatory action 38
13.2 Risk-benefit assessment 39
13.3 Recommendation for postmarketing Risk Evaluation and Management Strategies 40
13.4 Recommendation for other postmarketing requirements and commitments 40

Table of Figures

Figure 1 K-M curves for OS, Bay 73-4506/14387 24
Figure 2 K-M curves for PFS, Bay 73-4506/14387 27

Table of Tables

Table 1 Summary of efficacy results 4
Table 2 FDA approved drugs for the treatment of patients with CRC 7
Table 3 Regimens used to treat mCRC 8
Table 4 Amendments to NDA 203085 (as of the date of the completion of this review) 11
Table 5 Amendments to Bay 73-4506/14387 21
Table 6 Demographics, Bay 73-4506/14387 22
Table 7 Disease characteristics at baseline, Bay 73-4506/14387 22
Table 8 Patient disposition, Bay 73-4506/14387 23
Table 9 OS analyses (ITT), Bay 73-4506/14387 24
Table 10 Subgroup analyses for OS, Bay 73-4506/14387 25
Table 11 PFS analyses (ITT), Bay 73-4506/14387 26
Table 12 Response rate (ITT), Bay 73-4506/14387 27
Table 13 SAEs, Bay 73-4506/14387 28
Table 14 AEs leading to permanent discontinuation (≥ 1%), Bay 73-4506/14387 29
Table 15 Common AEs, Bay 73-4506/14387 30
Table 16 Hematologic findings, Bay 73-4506/14387 31
Table 17 Liver function tests, Bay 73-4506/14387 31

1. Introduction

FDA received NDA 203085 from Bayer on 27 Apr 2012 requesting marketing authorization (regular approval) for regorafenib (proposed trade-name Stivarga) for the treatment of patients with metastatic colorectal cancer (CRC) who have been previously treated with, (b) (4) fluoropyrimidine-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

Disclaimer: Any data or information described below that Bayer does not own (for example, summary data from other drugs used to treat patients with mCRC or other cancers) is included for descriptive purposes only. This information was not relied upon or necessary to make a decision regarding this application.

The following section describes the primary issues identified during the review of this application:

1.1 One versus two trials

The primary issue considered during the review of this application was whether the results of a single adequate and well-controlled trial were sufficient to support approval. FDA Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf) identified characteristics that can contribute to the conclusion that results from a single study can support an efficacy claim. The characteristics identified were (a) large multicenter study; (b) consistency across study subsets; (c) multiple studies in a single study; (d) multiple endpoints involving different events; and (e) statistically very persuasive findings. Results of the Bay73-4506/11650 trial submitted in support of this NDA satisfied all of these characteristics except (c).

Bay 73-4506/11650 was a large, randomized (2:1), multi-national trial that randomized 760 patients with previously treated mCRC. Patients in Bay 73-4506/11650 received regorafenib plus best supportive care or placebo plus best supportive care. Table 1 (data obtained from the statistical review) summarizes the efficacy results from Bay 73-4506/11650. The results (demonstrating that regorafenib prolonged overall survival in patients with previously treated mCRC) were statistically robust and supported by consistent results in subgroup analyses.

Table 1 Summary of efficacy results

	Regorafenib N = 505	**Placebo N = 255**
Overall survival		
# of events	275	157
Median (in mos.)	6.4	5.0
Stratified HR (95% CI)	0.77 (0.64, 0.94)	
p-value (two-sided)	0.01	
Progression free survival (FDA analysis)		
# of events	417	231
Median (in mos.)	2	1.7

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