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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-923

Bayer Pharmaceuticals Corporation
Attention: Aileen Ryan, M.Sc.
Director, Global Regulatory Affairs Therapeutic Area Oncology
400 Morgan Lane
West Haven, CT 06516

Dear Ms. Ryan:

Please refer to your new drug application (NDA) dated July 6, 2005, received July 8, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nexavar (sorafenib) 200 mg tablets.

We acknowledge receipt of your submissions dated April 28, June 1 and 17, August 8, 19, 23, and 25, September 13, 16, and 23, October 7, 13, 18, 24, and 31, November 4 (2 submissions) and 8, and December 2, 5, 6, 15 and 19, 2005.

This new drug application provides for the use of Nexavar (sorafenib) tablets 200 mg for the treatment of patients with advanced renal cell carcinoma.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-923**." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your post-marketing study commitments as agreed upon on December 19, 2005. These commitments, along with any completion dates agreed upon, are listed below.

Clinical

Regarding Study 11213, "A phase 3 randomized study of BAY43-9006 in patients with unresectable and/or metastatic renal cell cancer":

1. Provide the results of the second interim analysis of overall survival (cutoff date of November 30, 2005).

   Protocol Submission: October 16, 2003 (IND 60,453, serial number 317)
   Study start: November 15, 2003
   Report submission on second interim analysis: February 2006

2. Provide the complete study report and datasets with the definitive statistical analysis of overall survival (after approximately 540 events).

   Protocol Submission: October 16, 2003 (IND 60,453, serial number 317)
   Study start: November 15, 2003
   Final report submission: March 2007

Clinical Pharmacology and Biopharmaceutics

3. Provide a full report for the dose-ranging Phase 1 study in Japan (Study 11497) and additional data in Asian patients from ongoing studies. The evaluation and submission of data from this Phase 1 study and other ongoing studies will be completed by December 2006. If the FDA concludes that further trials are warranted, you will conduct modeling and simulation analyses to devise a dosing regimen designed to achieve similar exposures between Asians and Caucasians. After agreement with the FDA on the proposed dosing regimen and study design, you will perform a clinical pharmacokinetic study to confirm that the proposed regimen achieves similar exposures between these two populations.

   The modeling and simulation analysis to determine a dosing regimen will be completed in March 2007. If a PK study to evaluate an alternative dosing regimen in Asian patients is warranted, the study will be reported by June 2008.

   Protocol submission: March 2007
   Study start: July 2007
   Final report submission: June 2008

4. Complete the ongoing study of the effect of sorafenib on paclitaxel (a CYP 2C8 substrate) pharmacokinetics: Study 100375.

   Protocol submission: November 29, 2001 (IND 60,453, serial number 038)
   Study start: July 15, 2002
   Final report submission: June 2006

5. Complete the ongoing investigation of biomarkers to identify patients who respond to sorafenib. This request will be fulfilled based on data from studies 100391 and 11213.

   Study 100391
   Protocol Submission: April 12, 2002 (IND 60,453, serial number 67)
   Study start: September 25, 2002
   Final report submission: September 2006

   Study 11213
   Protocol Submission: October 16, 2003 (IND 60,453, serial number 317)
   Study start: November 15, 2003
   Final report submission: September 2006

6. Complete the ongoing study examining rifampin's effects on sorafenib pharmacokinetics.

   Protocol submission: October 3, 2005 (IND 60,453, serial number 1109)
   Study start: October 27, 2005
   Final report submission: June 2006

7. Complete the ongoing study examining sorafenib pharmacokinetics in patients with renal impairment.

   Protocol submission: April 4, 2005 (IND 60,453, serial number 798)
   Study start: June 3, 2005
   Final report submission: September 2006

The FDA acknowledges your commitment to make appropriate changes as recommended by the USAN Council if the Council does not accept your proposed nonproprietary name.

In addition, although not considered post-marketing commitments, we have the following suggestions and comments.

1. Hemorrhage has been reported in association with sorafenib. Consider performing a study of platelet function [(b) (4)] or similar assay) in patients before and during sorafenib therapy,

2. Hypophosphatemia occurs commonly during treatment with sorafenib and is an unusual adverse event of anti-neoplastic therapy. Consider further study to elucidate the mechanism of sorafenib-associated hypophosphatemia.

3. Thyroid changes and hypothyroidism were observed in nonclinical sorafenib studies. Although only two sorafenib-treated patients were diagnosed with clinical hypothyroidism in the phase 3 study, this adverse event was not prospectively assessed. We recommend close monitoring of post-marketing adverse event reports for hypothyroidism. Further study to assess changes in thyroid function may be warranted based on post-marketing reports.

4. Sorafenib may act as a VEGF-R inhibitor. Another approved VEGF inhibitor has been associated with thrombosis, hemorrhage, and delayed surgical wound healing. We recommend careful post-marketing monitoring of these adverse events.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Drug Oncology Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Patty Garvey, Regulatory Project Manager, at (301) 796-1356.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Richard Pazdur
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