CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

Chemistry Review(s)
NDA 21-923

Nexavar\textsuperscript{TM} (sorafenib) tablets

Bayer HealthCare.

Chengyi Liang, Ph.D.
HFD-150 Division of Oncology Drug Products
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1. NDA 21-923

2. REVIEW: # 1

3. REVIEW DATE: Dec. 10, 2005

4. REVIEWER: Chengyi Liang

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7. NAME & ADDRESS OF APPLICANT:

| Name:                    | Bayer HealthCare Pharmaceuticals Corp. |
|                         | 400 Morgan Lane, West haven, CT 06516 |

8. DRUG PRODUCT NAME/CODE/TYPE:

| Proprietary Name:        | Nexavar™                             |
| Non-Proprietary Name (USAN): | Sorafenib (proposed) |
|                          | Sorafenib Tosylate (proposed)        |
| c) Code Name/#:          | Bay 43-9006: sorafenib                |
| Internal Codes:          | Bay 54-9085: sorafenib tosylate      |
| d) CAS Registry Number:  | sorafenib: 284461-73-0                |
|                          | Sorafenib tosylate: 475207-59-1      |
e) Chem. Type/Submission Priority (ONDC only):

Chem. Type:
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Advanced Renal Carcinoma

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): N/A

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate

Molecular Formula: C_{23}H_{15}ClF_3N_4O_5 * C_7H_8O_3S
Molecular Weight/Mass: 637.0 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

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1 Action codes for DMF Table:
1 - DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 - Type 1 DMF
3 - Reviewed previously and no revision since last review
4 - Sufficient information in application
5 - Authority to reference not granted
6 - DMF not available
7 - Other (explain under "Comments")

B. Other Documents:

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18. STATUS:

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Appears This Way On Original
The Chemistry Review for NDA 21-938

The Executive Summary

I. Recommendations
A. Recommendation and Conclusion on Approvability
This NDA is recommended for approval from the standpoint of CMC. A number of deficiencies related to the drug product have been satisfactorily addressed by the applicant. The Office of Compliance has provided an overall acceptable recommendation.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
Bayer has provided a phase 4 commitment to the effect that in the event USAN does not accept its proposal, Bayer will commit to making appropriate changes as recommended by USAN.

II. Summary of Chemistry Assessments
A. Description of the Drug Product (s) and Drug Substance (s):

NEXAVAR® (sorafenib) tablets, a multikinase inhibitor, contains sorafenib as the active moiety. The drug substance is synthesized as a tosylate salt. Sorafenib tosylate is a white to yellowish or brownish solid with the molecular formula C₉H₇ClF₅N₄O₆ x C₇H₇O₃S and a molecular weight of 637.0 g/mole. Its chemical name is 4-(3-[4-chloro-3-(trifluormethyl)phenyl]ureido)phenoxy)-N'-methylpyridine-2-carboxamide 4-methylbenzenesulfonate.

Sorafenib tosylate is practically insoluble in water, but slightly soluble in ethanol and soluble in PEG 400.

NEXAVAR® tablets are round, biconvex, red-film coated tablet, debossed with the "Bayer cross" on one side and "200" on the other side. Each tablet contains 274 mg of sorafenib tosylate equivalent to 200 mg of sorafenib and the following inactive ingredients: cellulose microcrystalline, croscarmellose sodium, hypromellose, magnesium stearate, and sodium lauryl sulfate. The coating material consists of hypromellose, Polyethylene glycol), titanium dioxide and ferric oxide, red. The drug product is manufactured

NEXAVAR® Tablets are supplied in white opaque HDPE bottles of 120 tablets with white opaque screw cap closures and child proof seal (NDC 0026-8488-58). The bottles should be stored 25°C (77°F); excursion permitted to 15 - 30°C (59 - 86°F) in the original package and stored in a dry place.

B. Description of How the Drug Product is Intended to be Used
NEXAVAR® is intended to be used for the treatment of patients with advanced renal carcinoma. NEXAVAR® (sorafenib tosylate) tablets will

Chengyi Liang, Ph.D.
Dec. 2005
be administered orally. The recommended NEXAVAR dose is 400 mg administered orally (2 x 200 mg tablets) twice daily.

C. Basis for Approvability Recommendation
Several deficiencies related to the drug substance and drug product have been noted and forwarded to the applicant and they have been satisfactorily addressed in amendment. This application is recommended for approval from CMC standpoint.

III. Administrative
A. Reviewer’s Signature

Chengyi Liang, Ph.D., Review Chemist

Nallaperumal Chidambaram, Ph.D.
Chemistry Team Leader

B. Endorsement Block
Chemist Name/Date: Chengyi Liang, Ph.D.
Chemistry Team Leader Name/Date: Nallaperumal Chidambaram, Ph.D.
Project Manager Name/Date: Patricia Garvey

C. CC Block
CC:
Orig. NDA 21-923
HFD-150 Division File
HFD-150/CLiang
HFD-150/NChidambaram
HFD-150/PGarvey

Chengyi Liang, Ph.D.
Dec. 2005
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chengyi Liang
12/13/2005 04:00:51 PM
CHEMIST

Nallaperumal Chidambaram
12/13/2005 05:15:45 PM
CHEMIST
NDA 21-923

REVIEW # 1

NEXAVAR® (sorafenib tosylate)
200 mg Film-Coated Tablets

JOSEPHINE M. JEE
REVIEW CHEMIST

DIVISION OF ONCOLOGY
DRUG PRODUCTS
HFD-150

CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW
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1. NDA 21-923
2. REVIEW: #1
3. REVIEW DATE: 01-AUG-2005
4. REVIEWER: Josephine M. Jee
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7. NAME & ADDRESS OF APPLICANT:

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<th>Name:</th>
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8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ™

b) Non-Proprietary Name (USAN): Sorafenib Tosylate

c) Code Name/# (ONDC only):

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d) CAS Registry Number:

| Sorafenib: 28844-1-73-01 |
| Sorafenib tosylate: 475207-59-1 |

e) Chemical Name (IUPAC):
4-(4-[[3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido]phenoxy]-N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate

Alternative names:
4-(4-[[3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido]phenoxy]-N2-methylpyridine-2-carboxamide mono (4-methylbenzenesulfonate)


4-[[3-[4-Chloro-3-trifluoromethyl-phenyl]ureido]phenoxy] pyridine-2-carboxylic acid methylamide 4-methylbenzenesulfonate

Nomenclature:
INN, USAN, JAN
INN, USAN, JAN for the free base: sorafenib
INN, USAN for the tosylate salt: sorafenib tosylate
JAN for the tosylate salt: sorafenib tosilate

Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A
10. PHARMACOL. CATEGORY: Advanced Renal Carcinoma

11. DOSAGE FORM:
12. STRENGTH/POTENCY: Tablets 200 mg
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ___X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): N/A

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
4-(4-[[3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido]phenoxy]-N2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate

Molecular Formula: C21H16ClF3N4O3 * C7H8O3S
Molecular Weight/Mass: 637.0 g/mole

Calculation factors
sorafenib tosylate
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

2 Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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The Chemistry Review for NDA 21-923

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   From a Chemistry, Manufacturing and Controls (CMC) perspective, approval of the application is recommended.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
   Bayer will be submitting USAN name.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)
   NEXAVAR® (sorafenib tosylate) Tablets contain sorafenib tosylate, a multikinase inhibitor. Sorafenib tosylate is a white to yellowish or brownish solid with the molecular formula C_{21}H_{10}ClF_{3}N_{4}O_{5} x C_{3}H_{8}O_{2}S and a molecular weight of 637.0 g/mole. Its chemical name is 4-(4-4-Chloro-3-(trifluoromethyl) phenylureido) phenoxy)-N\^\text{2}-methylpyridine-2-carboxamide 4-methylbenzenesulfonate.
   Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.
   NEXAVAR® tablets are round, biconvex, red-film coated tablet, debossed with the “Bayer cross” on one side and “200” on the other side. Each tablet contains 274 mg of sorafenib tosylate equivalent to 200 mg of sorafenib; and the following inactive ingredients: cellulose microcrystalline, croscarmellose sodium, hypromellose of magnesium stearate, of sodium lauryl sulfate. The coating material consists of hypromellose, \( \text{PEG 400} \), polyethylene glycol, titanium dioxide and ferric oxide, red. NEXAVAR® Tablets are supplied in \( \text{HDPE bottles of 120 tablets with white opaque screw cap closures and child proof seal (NDC 0026-8488-58). The bottles should be stored 25°C (77°F); excursion permitted to 15 – 30°C (59 - 86°F ) in the original package and stored in a dry place.}

Sorafenib drug product section is reviewed by Cheng Yi Liang, Ph.D.

B. Description of How the Drug Product is Intended to be Used
   The product is intended to be used for the treatment of Advanced Renal Carcinoma. NEXAVAR® (sorafenib tosylate) Tablets will be administered orally. The recommended NEXAVAR dose is 200 mg administered orally

Sorafenib tosylate drug product is reviewed by Cheng Yi Liang, Ph.D.
C. **Basis for Approvability or Not-Approval Recommendation**

Approval (Drug Substance) is recommended from a CMC perspective.

III. Administrative

   A. **Reviewer’s Signature**
      See electronic signatures in Division File System (DFS).

   B. **Endorsement Block**
      See electronic signatures in DFS

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

/s/
Josephine Jee
12/9/2005 11:12:05 AM
CHEMIST

Nallaperumal Chidambaram
12/13/2005 05:08:26 PM
CHEMIST
See Dr. Chengyi Liang’s review for overall executive summary.