CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

Chemistry Review(s)

NDA 21-923

Nexavar™
(sorafenib) tablets

Bayer HealthCare.

Chengyi Liang, Ph.D.
HFD-150 Division of Oncology Drug Products

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Chemistry Review Data Sheet

1. **NDA 21-923**

2. **REVIEW:** # 1

3. **REVIEW DATE:** Dec. 10, 2005

4. REVIEWER: Chengyi Liang

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date	
Sorafenib Tosylate	IND 60,453, 5/30/2000	Sorafenib Tosylate Tablets
EOP 2 Meeting	IND 60,453, 9/17/2003	EOP II - Assay Spec. for [ ]
EOP 2 Meeting	IND 60,453, 3/4/2005	Discuss Content & Format
CMC/Biopharm pre-NDA Follow-up Meetings	IND 60,453, 5/18/2005	Follow-up Meetings

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original	7/15/2005
Amendment (fax)	12/7/2005
Amendment (fax)	12/12/2005

7. **NAME & ADDRESS OF APPLICANT:**

Name: Bayer HealthCare Pharmaceuticals Corp.
Address: 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/#:
Internal Codes: Bay 43-9006: sorafenib
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

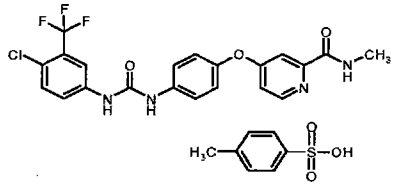
13. ROUTE OF ADMINISTRATION: Oral

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)-*N*2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate



Molecular Formula: $C_{21}H_{16}ClF_3N_4O_3$ * $C_7H_8O_3S$
Molecular Weight/Mass: 637.0 g/mole

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COM-PLETED	COM-MENTS
[redacted]	II	[redacted]	[redacted]	3	adequate	5-1-2002	Brian Rogers
[redacted]	II	[redacted]	[redacted]	3	adequate	12-13-1995	Sung Kim
[redacted]	II	[redacted]	[redacted]	3	adequate	7-27-2000	Sharon Kelly

[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:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,453	BAY 43-9006 Sorafenib

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	8/16/2005	S. Ferguson
Methods Validation	May be requested post approval		
DMETS	Acceptable	9/30/2005	K. Arnwine
EA	Acceptable	8/1/2005	J.Jee
Microbiology	N/A		N/A

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 $C_{21}H_{16}ClF_3N_4O_3$ x $C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Its chemical name is 4-(4-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}phenoxy)-*N*²-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

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

/S/

Chengyi Liang, Ph.D., Review Chemist

/S/

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 ManagerName/Date: Patricia Garvey

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

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/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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Chemistry Review Data Sheet

1. NDA 21-923

2. REVIEW: # 1

3. REVIEW DATE: 01-AUG-2005

4. REVIEWER: Josephine M. Jee

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date	
Sorafenib Tosylate	IND 60,453, 30-MAY-2000	Sorafenib Tosylate Tablets
EOP 2 Meeting	IND 60,453, 17-SEP-2003	EOP II – Assay Spec. for C J
EOP 2 Meeting	IND 60,453, 04-MAR-2005	Discuss Content & Format
CMC/Biopharm pre-NDA Follow-up Meetings	IND 60,453, 18-MAY-2005	Follow-up Meetings

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA 21-923 - (Rolling Submission - CMC)	17-JUN-2005

7. NAME & ADDRESS OF APPLICANT:

Name: Bayer HealthCare Pharmaceuticals Corp.

Address: 400 Morgan Lane, West haven, CT 06516

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: ™

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

c) Code Name/# (ONDC only):
Internal Codes: Bay 43-9006: sorafenib
Bay 54-9085: sorafenib tosylate

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)-*N*2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate

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

4-{4-[({[4-Chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]phenoxy}-Nmethylpyridine-2-carboxamide 4-methylbenzenesulfonate

4-{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

f) 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

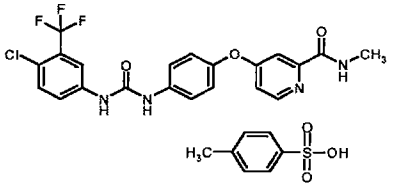
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 200 mg
13. ROUTE OF ADMINISTRATION: Oral

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)-*N*2-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:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
None reviewed							

[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)

Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,453	BAY 43-9006 Sorafenib

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable	23-NOV-2005	S. Tang, Ph.D.
EES	Acceptable	16-AUG-2005	Office of Compliance
Pharm/Tox	Acceptable	03-NOV-2005	H. Mahloogi, Ph.D.
Biopharm	Acceptable	23-NOV-2005	Gene Williams, Ph.D.
Methods Validation			
DMETS	Acceptable	30-SEP-2005	K. Arnwine
EA	Acceptable	01-AUG-2005	J.Jee
Microbiology	N/A		N/A

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 contains sorafenib tosylate, a multikinase inhibitor. Sorafenib tosylate is a white to yellowish or brownish solid with the molecular formula $C_{21}H_{16}ClF_3N_4O_3$ x $C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Its chemical name is 4-(4-{3-[4-Chloro-3-(trifluoromethyl) phenyl]ureido} phenoxy)-N^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, [ ] Polyethylene glycol), titanium dioxide and ferric oxide, red [ ] 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.

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

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/s/

Josephine Jee
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Nallaperumal Chidambaram
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CHEMIST
See Dr. Chengyi Liang's review for overall executive summary.