CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-938 (GIST)
NDA 21-968 (MRCC)

Chemistry Review(s)
NDA 21-938

SUTENT™
(Sunitinib malate) 12.5, 25 and 50 mg capsules

Pfizer Inc.

Chengyi Liang, Ph.D.
HFD-150 Division of Oncology Drug Products
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Chengyi Liang, Ph.D.
Jan. 2006
2. CHEM. REVIEW #:  1

3. REVIEW DATE: Jan. 24, 2006

4. REVIEWER: Chengyi Liang, Ph.D.

5. PREVIOUS DOCUMENTS

Previous Documents
None

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed     Document Date
Original                   08-10-2005
Amendment (BC)             10-06-2005
Amendment                  01-10-2006
Amendment                  01-23-2006

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer Inc
      10777 Science Center Dr.
      San Diego, CA 92121

Representative: NA
Telephone: NA

8. DRUG PRODUCT NAME/CODE/TYPE:

a. Proprietary: Sutent
b. Nonproprietary Name/USAN: Sunitinib Malate
   SU011248 L-malate

d. Chem. Type/Submission Priority
   Chem. Type 1
   Submission Priority P

9. LEGAL BASIS FOR SUBMISSION: Fulfilled PDUFA filing requirements

10. PHARMACOL. CATEGORY/INDICATION:

11. DOSAGE FORM: Capsules

12. STRENGTHS/POTENCY: 12.5, 25 and 50 mg

Chengyi Liang, Ph.D.
Jan. 2006
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  x  Rx  ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM) No

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

![Chemical Structure](image)

IUPAC: \((\text{Z})\cdot N\cdot [2\cdot(\text{Diethylamino})\text{ethyl}]\cdot 5\cdot [(5\cdot\text{fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene})\text{methyl}]\cdot 2,4\cdot\text{dimethyl-1H-pyrrole-3-carboxamide}(S)\cdot 2\cdot\text{hydroxysuccinate}\)

CAS: \(N\cdot [2\cdot(\text{Diethylamino})\text{ethyl}]\cdot 5\cdot [(\text{Z})\cdot(5\cdot\text{fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidene})\text{methyl}]\cdot 2,4\cdot\text{dimethyl-1H-pyrrole-3-carboxamide, compound with (S)\cdot 2\cdot\text{hydroxybutanedioic acid}}\)

USAN Chemical Name:

1. Butanedioic acid, hydroxy-, (2S)-, compound with \(N\cdot [2\cdot(\text{diethylamino})\text{ethyl}]\cdot 5\cdot [(\text{Z})\cdot(5\cdot\text{fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine})\text{methyl}]\cdot 2,4\cdot\text{dimethyl-1H-pyrrole-3-carboxamide (1:1)}\)

2. \(N\cdot [2\cdot\text{Diethylamino})\text{ethyl}]\cdot 5\cdot [(\text{Z})\cdot(5\cdot\text{fluoro-2-oxo-1,2-dihydro-3H-indol-3-ylidene})\text{methyl}]\cdot 2,4\cdot\text{dimethyl-1H-pyrrole-3-carboxamide hydrogen (2S)\cdot 2\cdot\text{hydroxybutanedioate}}\)

Molecular formula \(\text{C}_{22}\text{H}_{27}\text{FN}_{4}\text{O}_{2} \cdot \text{C}_{4}\text{H}_{6}\text{O}_{5}\)

MW 532.57
17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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<th>DMF #</th>
<th>TYPE</th>
<th>HOLDER</th>
<th>ITEM REFERENCED</th>
<th>CODE</th>
<th>STATUS</th>
<th>DATE REVIEW COMPLETED</th>
<th>COMMENTS</th>
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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")

18. STATUS:

<table>
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<tr>
<th>Consults/CMC Related Reviews</th>
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<tr>
<td>EBS</td>
<td>Acceptable</td>
<td>9-26-2005</td>
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<td>DMETS</td>
<td>Acceptable</td>
<td>12-7-2005</td>
<td>Felicia Duffy</td>
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<td>Methods Validation</td>
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<td>EA</td>
<td>Categorical exclusion is acceptable</td>
<td>6/6/2005</td>
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<td>Microbiology</td>
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The Chemistry Review for NDA 21-938

The Executive Summary

Chengyi Liang, Ph.D.
Jan. 2006
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 substance and drug product have been satisfactorily addressed. The Office of Compliance has given an overall acceptable recommendation.

   B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable
      N/A

II. Summary of Chemistry Assessments
   A. Description of the Drug Product(s) and Drug Substance(s)
      SUTENT™ (sunitinib malate), an oral multi-tyrosine kinase receptor inhibitor, is the malate salt of sunitinib. Sunitinib malate is described chemically as butanedioic acid, hydroxy-, (2S)-, compound with N-[2-(diethylamino)ethyl]-5-[(Z)-(5-fluoro-1,2-dihydro-2-oxo-3H-indol-3-ylidine)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide (1:1). The molecular formula is C₅₂H₅₀FN₄O₁₀ • C₇H₈O₈, and has the following structural formula:

      ![Chemical Structure](image)

      The DS is a fine, yellowish crystalline powder and is soluble in water and ethanol.

      SUTENT (sunitinib malate) capsules is manufactured [ ] and supplied supplied as printed hard gelatin capsules containing sunitinib malate equivalent to 12.5 mg, 25 mg and 50 mg of sunitinib respectively together with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients.

   B. Description of How the Drug Product is Intended to be Used
      Sunitinib malate is a small molecule, multi-tyrosine kinase receptor's inhibitor that selectively targets and intracellularly blocks the signaling pathways of receptor tyrosine kinases (RTKs). It is being submitted for the treatment of malignant gastrointestinal stromal tumors.

Chengyi Liang, Ph.D.
Jan. 2006
CHEMISTRY REVIEW

NDA 21-938
Pfizer Inc., Review #1

Sutent (sunitinib malate) capsules

(GIST) after failure of imatinib mesylate treatment, and for the
treatment of metastatic renal cell carcinoma (mRCC) after failure of
prior cytokine-based therapy.

The recommended daily dose of DP is orally 50 mg per day.

C. Basis for Approvability Recommendation
A number of minor deficiencies related to the drug substance and drug
product have been satisfactorily addressed by the applicant. This
application is recommended for approval from the standpoint of chemistry,
manufacturing and controls.

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: Christy Cottrell

C. CC Block
CC:
Orig. NDA 21-938
HFD-150 Division File
HFD-150/CLiang
HFD-150/NChidambaram
HFD-150/CCottrell

Chemistry Review Data Sheet

Chengyi Liang, Ph.D.
Jan. 2006
66 Page(s) Withheld

☑ § 552(b)(4) Trade Secret / Confidential

☐ § 552(b)(5) Deliberative Process

☐ § 552(b)(4) Draft Labeling
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
1/25/2006 03:13:54 PM
CHEMIST

Nallaperumal Chidambaram
1/25/2006 05:10:20 PM
CHEMIST