CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-588

Chemistry Review(s)

NDA 21-588

Gleevec (imatinib mesylate) Tablets, 100 mg and 400 mg

Novartis Pharmaceuticals Corporation

Yung-Ao Hsieh, Ph.D.

Division of Oncology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-588

2. REVIEW No.: 1

3. REVIEW DATE: 14-Mar-03

4. REVIEWER: Yung-Ao Hsieh, Ph.D.

5. PREVIOUS DOCUMENTS: None

6. SUBMISSIONS BEING REVIEWED:

Submissions Reviewed	Document date
NDA 21-588	13-Dec-02
NDA 21-588 BC	13-Mar-03

7. NAME & ADDRESS OF APPLICANT:

Name: Novartis Pharmaceuticals Corporation

Address: One health Plaza, East Hanover, NJ 07936-1080

Representative: Robert A. Miranda, Director, Drug Regulatory Affairs

Telephone: 973-781-2282

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Gleevec
b) Non- Proprietary Name (USAN): imatinib mesylate
c) Chem. Type/Submission Priority:
   - Chem. Type: a purine derivative
   - Submission Priority: 1P

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: protein-tyrosine kinase inhibitor

11. DOSAGE FORM: film-coated tablets

12. STRENGTH/POTENCT: 100 mg (divisible) and 400 mg (not divisible)

13. ROUTE OF ADMINISTRATION: oral

14.Rx/OTC DISPENSED: _x_ Rx ___ OTC

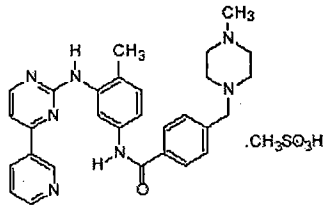
15.SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

___SPOTS products – Form Completed

_x_ Not a SPOTS product

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

IUPAC Name: 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] aminophenyl]benzamide methanesulfonate salt
INN: Imatinib mesylate
CAS Number: 220127-57-1 (for the free base: 152459-95-5)
MOLECULAR FORMULA: $C_5H_{10}N_2O_7P_2 \bullet H\ O$
MOLECULAR WEIGHT: 290.11
M.F.: $C_{29}H_{31}N_7O.\ CH_4SO_3$
STRUCTURAL FORMULA:



Molecular Weight: 589.7

17.RELATED SUPPORTING DOCUMENTS: N/A

DMF No.	Type	Holder	Item Referenced	Code	Status	Date Review Completed	Comments
	IV	[redacted]		4	Adequate	N/A	USP/NF grade
	IV			4	Adequate	N/A	USP/NF grade
	III			3	Adequate	20-Sep-00	
	III			3	Adequate	26-Sep-00	
	III			3	Adequate	20-Mar-01	
	III			3	Adequate	10-Aug-99	
	III			3	Adequate	7-Oct-02	

		[	]				

18.CONSULT STATUS:

Consults	Recommendation	Date	Reviewer
Biometrics	Acceptable	24-Mar-03	Dr. Mark Rothman
EES	Acceptable	22-Jan-03	
Method Validation	Not required at this time		

The Chemistry Review for NDA 21-588

The Executive Summary

I. Recommendations:

The application is recommended for approval from a chemistry point of view.

II. Summary of Chemistry Assessments:

A. Description of the Drug Product and Drug Substance:

The drug product is a film-coated, immediate release tablet, containing imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base. The 100 mg strength is a very dark yellow to brownish orange, round film-coated tablet and debossed with "NVR" on one side and "SA" with score on the other side. The tablet is divisible. The Gleevec 400 mg strength is also colored dark yellow to brownish orange and ovaloid in shape and biconvex with bevelled edges. The tablet is debossed with "NVR" on one side and "SL" on the other side. The 100 mg strength is available in bottles of 100-count and the 400 mg strength, in bottles of 30-count. The drug product tablets can be stored at 25°C/60% RH. An expiration dating of eighteen months under the recommended storage conditions has been granted.

The drug substance, imatinib mesylate is obtained by chemical synthesis. It is a white to off-white powder with good water solubility. Complete information on the drug substance were provided in the approved Gleevec Capsule NDA (NDA 21-335, approved 10-May-01).

B. Description of How the Drug Product is Intended to be Used

For the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failing interferon-alpha therapy. Gleevec is approved for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST) as well. The recommended dosage is 400 mg/day for patients in chronic phase CML and 600 mg/day for patients in accelerated phase or blast crisis. The prescribed dose should be administered orally, once daily with a meal and a large glass of water.

C. Basis for Approvability Recommendation

NDA 21-588 provides for a tablet dosage form (100 mg and 400 mg) which may replace the existing approved Gleevec capsule dosage of NDA 21-335. No clinical studies have been performed with the tablet dosage form. This

application relies on results from a bioequivalence study comparing the capsule and tablet formulations. Complete CMC section for the new tablet dosage forms and a bioequivalency study comparing the tablets with the capsules were presented. Since there have been no changes in the drug substance and the daily recommended doses remain unchanged, the applicant refers to the original NDA 21-335 for other pertinent clinical and pre-clinical data and information. It is concluded that satisfactory CMC information has been provided to support this NDA. Additionally, the CGMP compliance status of the manufacturing and testing facilities for the drug product is acceptable. Approval is recommended.

Administrative

A. Reviewer's Signature

_____

Review Chemist, HFD-150
Yung-Ao Hsieh, Ph.D.

B. Endorsement Block

Y. A. Hsieh, Review Chemist:
R. H. Wood, Chemistry Team Leader:
A. Staten, Project Manager:

C. CC Block

Original NDA 21-588
HFD-150 Div. File
HFD-150/YAHsieh
HFD-150/RHWood
HFD-150/AStaten

19 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/

Yung-Ao Hsieh
3/31/03 09:05:01 AM
CHEMIST

Rebecca Wood
3/31/03 10:13:42 AM
CHEMIST