CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-335

CHEMISTRY REVIEW(S)
NDA 21-335 CMC Review for 45 Day Fileability Meeting:

REVIEWER: Sung K. Kim, Ph.D.
DOCUMENT DATE: February 27, 2001

REVIEW DATE: March 27, 2001
CDER DATE: February 27, 2001

NAME AND ADDRESS OF APPLICANT:
Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME:
Proprietary: Imatinib Mesylate
Nonproprietary/USAN: STI 571 (CGP 57148B)
Code Name and Number: STI
Chemical Name/Structure:

DOSAGE FORM: Capsules
STRENGTH: 50mg and 100mg/capsule
ROUTE OF ADMINISTRATION: Oral

PHARMACOL. CATEGORY/INDICATION:
Signal Transduction Inhibitor (Protein the Bcr-Abl Tyrosine Kinase Inhibitor)
Treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated
phase, or in chronic phase after failure of interferon-alpha therapy.

RELATED IND/DMFs: IND_DMFs and

COMMENTS:
US Patent # 5,521,184 (expiration date — 5/28/2013) see Review Notes

CONCLUSION & RECOMMENDATIONS:
The initial preliminary review has been completed. With respect to CMC, the submission is fileable.

Please forward the following to the applicant at this time:
It is noted that imatinib mesylate is listed under INN (international non-proprietary name) on page 4-40,
v1.3. Please provide a status on the United States Adopted Names (USAN) for STI 571. If the USAN for
STI 571 is available, please provide proof (e.g. a letter from the USAN Council).

Review Chemist, HFD-150

cc:
Original NDA # 21-335
HFD-150/Div. File
HFD-150/SKim
HFD-150/ASStaten
HFD-150/RWood
R/D Init. by:
DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 21-335  CHEMISTRY REVIEW #: 1  REVIEW DATE: May 7, 2001

SUBMISSION TYPE  DOC. DATE  CDER DATE  ASSIGNED DATE
Original  February 27, 2001  February 27, 2001  March 2, 2001
Amendment (NC)  March 30, 2001  April 4, 2001  April 5, 2001
Amendment (BC)  April 4, 2001  April 5, 2001  April 9, 2001
Amendment (BC)  April 13, 2001  April 16, 2001  April 17, 2001
Amendment (BC)  April 19, 2001  April 23, 2001  April 24, 2001
Amendment (BC)  April 24, 2001  April 26, 2001  April 26, 2001
Amendment (Fax)  May 4, 2001  May 4, 2001  May 4, 2001

NAME & ADDRESS OF APPLICANT:
Novartis Pharmaceuticals Co.
59 Route 10
East Hanover, NJ 07936-1080

DRUG PRODUCT NAME:
Proprietary:
Imatinib Mesylate (This name was adopted by the USAN Council, a statement on 1/31/01 is attached.)

Code Name/Number:
STI 571 (CGP 57148B)

Chem. Type/Ther. Class:
1P

PHARMACOL. CATEGORY/INDICATION:
Signal Transduction Inhibitor (Protein the Bcr-Abl Tyrosine Kinase Inhibitor)
Hard Gelatin Capsule
50mg and 100mg/capsule
Oral

x  Rx  ____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA (M.F.), MOLECULAR WEIGHT (M.W.):

CAS 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)
Code Number: STI 571 (CGP 57148B)
M.F.: C26H31N8O3 CH3SO3
Salt/base ratio: 1.195 on anhydrous basis
M.W.: 493.6+96.1=589.7

SUPPORTING DOCUMENTS:
INDs: IND
Patent: US 5,521,184 (Expiration date : 5/28/2013)

DMFs:

<table>
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<th>DMF No.</th>
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<th>Subject</th>
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Adequate 4/16/99  HFD-510
8/9/99  HFD-120
9/20/00  HFD-510
This review notes concern the last update of 2/4/99 that include the information cross-referenced in this NDA. Although this review was focused on coni-snap size 4, hard gelatin capsules, we concur with these reviews since manufacturing/controls have been reviewed and adequate information is provided concerning specifications, components/composition and imprinting edible inks.

**RELATED DOCUMENTS (if applicable):** N/A

**CONSULTS:**

EER for Novartis Ringaskiddy (Ireland), Norvatis Pharma Stein (Switzerland), Novartis Grimsby (Great Britain), Novartis International Pharmaceutical Ltd. (Ireland), Novartis Pharma Basel (Switzerland), Pharmaanalytica SA (Switzerland), Novartis Pharm (New York and New Jersey), and.


Trademark consultation, Submitted to OPDRA on 3/5/01 by CSO. was not accepted (OPDRA review of 3/27/01). Gleevec™ was approved for the trade name (telecon of 4/17/01).

Micro consultation, Not Applicable due to the Oral Capsule Dosage Form.

Environmental assessment, Exemption is requested. Granted.

Stability data consultation, Not initiated due to the observation of no significant degradation.

Method validation will be initiated after the approval of this NDA.

**REMARKS/COMMENTS:**

See Review Notes.

**CONCLUSIONS & RECOMMENDATIONS:**

Adequate CMC information is provided regarding the manufacture and controls of the drug substance and the drug product. Approval of this NDA is recommended from the CMC viewpoints.

Sung K. Kim, Ph.D.,
Review Chemist, HFD-150

cc: Orig. NDA 21-335
HFD-150/Division File
HFD-150/ASExternal
HFD-150/SKim
HFD-150/RWood
HFD-810/HPatel
HFD-810/JSimmons
R/D Init. by:
Redacted 60

pages of trade secret and/or confidential commercial information