CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21-335

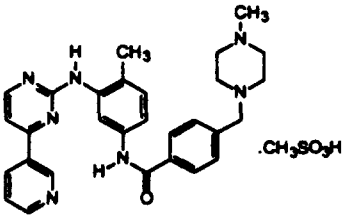
CHEMISTRY REVIEW(S)

NDA 21-335 CMC Review for 45 Day Fileability Meeting:

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

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

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



4-[4-(Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]-benzamide methanesulfonate

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 [redacted] DMFs [redacted] and [redacted]

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 571is available, please provide proof (e.g. a letter from the USAN Council).

/S/
Review Chemist, HFD-150

cc:
Original NDA # 21-335
HFD-150/Div. File
HFD-150/SKim
HFD-150/AStaten
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 (BC)	March 14, 2001	March 15, 2001	March 16, 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: Gleevec™ Capsule
Nonproprietary/USAN: 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

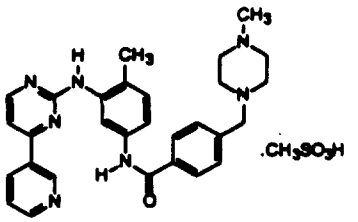
PHARMACOL. CATEGORY/INDICATION: Signal Transduction Inhibitor (Protein the Bcr-Abl Tyrosine Kinase Inhibitor)

DOSAGE FORM: Hard Gelatin Capsule
STRENGTHS: 50mg and 100mg/capsule
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _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.: $C_{29}H_{31}N_7O.\ CH_4SO_3$
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:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
				Adequate	4/16/99 8/9/99 9/20/00	HFD-510 HFD-120 HFD-510

	9/11/00	container	Adequate	9/26/00	HFD-1290
	3/3/00		Adequate	3/24/00	HFD-120
	3/3/00		Adequate	8/9/99 8/10/99	HFD-120 HFD-110
	8/30/00		Adequate	9/10/97 8/2/99 9/19/00 9/26/00	HFD-180 HFD-120 HFD-510 HFD-510
	8/7/00		Adequate*	5/16/99	HFD-510/580

* This review notes concern the last update of 2/4/99 that include the information cross-referenced in this NDA. Although this review was focussed on coni-snap size 4, hard gelatin capsules, we concur with this 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), Pharmanalytica SA (Switzerland), Novartis Pharm (New York and New Jersey), and , **Submitted to OC on 3/8/01. Acceptable recommendation on 5/4/01 by the Office of Compliance.**

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/AStaten
HFD-150/SKim
HFD-150/RWood
HFD-810/HPatel
HFD-810/JSimmons
R/D Init. by:_____

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pages of trade

secret and/or

confidential

commercial

information