CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-335/S-001

Correspondence

Redacted 3

pages of trade

secret and/or

confidential (b)(s)

commercial

information

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Bob Miranda	**From:** Ann Staten, Project Manager
Fax: 973-781-5217	**Fax:** 301-827-4590
Phone: 973-781-2282	**Phone:** 301-594-5770
Pages: 3	**Date:** January 8, 2002
Re: NDA 21-335 Gleevec	

■ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Dear Bob,

Please refer to your sNDA 21-335/S-001, Gleevec for patients with GIST.

The indication proposed in your sNDA is being considered for accelerated approval. Approval of applications under the accelerated approval regulations, 21 CFR314.510, require further adequate and well-controlled studies to verify and describe clinical benefit. You need to make the following accelerated approval commitments before we can take an action on this application.

A. Commitments required for accelerated approval of Gleevec™ for patients with GIST:

1. Complete follow-up of sNDA trial B2222 and submit mature data regarding duration of response and survival. Suggested timelines are as follows: last quarter of 2002 for response and response duration, and at 50% and 70% of events for survival analyses.

2. An updated report of the central pathology review for sNDA trial B2222 should be submitted when review of the 13 pending cases is complete.

3. Submit data from the two ongoing multicenter trials of imatinib that are testing 400 mg/day versus 800 mg/day in patients with GIST (EORTC and NCI sponsored trials). Response rate, duration of response, safety and survival data should be submitted when it becomes available.

4. Submit the final study report for the EORTC phase 1 study of imatinib in patients with GIST and other soft-tissue sarcomas when it is available.

5. Assure availability of a validated test kit for detection of CD117 tumor expression by immunohistochemistry.

6. Provide a plan for investigating the incidence and etiology of GI/tumor hemorrhage associated with imatinib therapy.

7. Investigate and submit data regarding :
   a) correlation of c-kit tumor mutation status with outcome
   b) tumor c-kit phosphorylation status at baseline and post-exposure to Gleevec™
   c) correlation between serum VEGF levels and tumor response

B. We also request that you agree to the following as a regular phase 4 commitment which is not a condition of accelerated approval:

1. Submit the PK/PD data from the comparison of 400 mg/day versus 800 mg/day in GIST patients in the two ongoing multicenter trials of imatinib (EORTC and NCI sponsored trials)

C. We remind you of your prior phase 4 commitments:

Prior commitments required for accelerated approval Gleevec™ for CML patients:

1. To conduct and submit the final study report for Protocol 106 entitled "A phase III study of STI571 versus Interferon-α (IFN-α) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)" with Time to Progression (TTP) as the primary surrogate endpoint. TTP is defined as any of the following: loss of complete hematologic response (CHR), loss of cytogenetic response, inability to maintain peripheral blood counts, increasing organomegaly, accelerated phase CML, blast crisis, or death from CML. Protocol 106 interim analysis (one-year hematologic response and QoL) is planned for first quarter, 2002 and the final analysis is expected in the fourth quarter, 2005.

2. To provide interval follow-up information on studies 102, 109 and 110. The safety and efficacy update will be provided in July, 2001, with a final analysis report expected in the third quarter, 2001.

Prior commitments which are not a condition of accelerated approval:

1. To conduct and submit the final study report for the pediatric study, Protocol 103 entitled "A Phase I Study in Children with Refractory/Relapsed Ph+ Leukemias". Protocol 103 is currently ongoing and being conducted by the cooperative group COG (Children's Oncology Group).

2. To conduct and submit the final study report for a phase 2 pediatric efficacy study in an appropriate pediatric population. This will be conducted by a pediatric cooperative group under the NCI.

3. To conduct an appropriate study to assess hepatotoxic drug interactions (e.g., acetaminophen) and submit final reports.

4. To conduct the appropriate study to assess the potential drug interaction between Gleevec and a substrate of CYP2D6 and to submit the final study report.

5. To conduct a pharmacokinetics study with Gleevec in subjects or patients with liver impairment and submit the final study report.

6. To conduct an *in vitro* study to assess the plasma protein binding of the N-demethylated piperazine derivative of Gleevec and submit the final study report.

7. To evaluate the etiology and treatment of the fluid retention syndrome associated with imatinib treatment

Please call me with any questions.

Sincerely,

ann

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Staten
1/8/02 04:40:26 PM
CSO

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

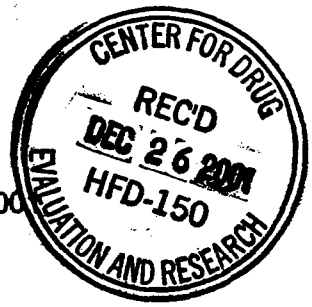
Tel 973 781 8300

NOVARTIS

DUPLICATE

NDA SUPP AMEND

SE1-001
BM



December 21, 200

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: Request for Information

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and /or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to an e-mail message dated December 19, 2001 from Ms. Ann Staten requesting information for the medical reviewer. At this time we are providing our response to this request.

The request for information in the December 19th e-mail stated:

> "Please provide patient ID numbers for the 25 patients who had PET evaluations as described in Table 6 of the ISE."

Response

The following are identification numbers for the 25 patients as requested:

050100001
050100002
050100003
050100006
050100007
050100005
050100004

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	12/21/01
TELEPHONE NO. (*Include Area Code*)	FACSIMILE (FAX) Number (*Include Area Code*)
(973) 781-2282	(973) 781-5217
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
59 Route 10 East Hanover, New Jersey 07936-1080	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (*If previously issued*) 21-335

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
imatinib mesylate	**Gleevec™**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
	STI571, CGP57148B

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsules	**50 and 100 mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:
Gastrointestinal stromal tumors (GIST)

APPLICATION INFORMATION

APPLICATION TYPE (*check one*)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (*check one*)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
MINOR AMENDMENT TO PROVIDE 25 PATIENT ID NUMBERS

PROPOSED MARKETING STATUS (*check one*) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND [redacted]

This application contains the following items: (*Check all that apply*)

	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert A Miranda	Robert A. Miranda,Director Drug Regulatory Affairs	12/21/01

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
59 Route 10 East Hanover, New Jersey 07936-1080	(973) 781-2282

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973-781-8300

NOVARTIS

DUPLICATE

NDA SUPPLEMENT
SE1-001
~~131~~
BB

December 13, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: Request for Information

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and /or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to an e-mail message dated December 3, 2001 from Ms. Ann Staten requesting information for the clinical pharmacology reviewer. At this time we are providing our response to this request.

The request for information in the December 3rd e-mail stated:

> "The clinical pharmacology reviewer cannot complete a review of the report PCS(J)2001/035.
>
> Please submit the full final study report PCS(J) 2001/23 as well as the bioanalytical data reports PCS(J)2001/21 and PCS(J)2001/022, preferably in an electronic format."

The three reports involved studies conducted at our Japanese facility and were in Japanese. These have been translated and are attached.

This submission consists of one volume.

If you have any questions or comments regarding this submission, please contact me at
(973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh
Attachments

Desk Copy (coverletter only) via fax: Ann Staten (HFD-150 at 301/827-4590)

59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

DUPLICATE

NDA SUPP AMEND

SE1-001

BM

December 10, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: CML Safety and Efficacy Update

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to two recent telephone requests (11/27/01 and 12/7/01) from Ms. Ann Staten for updated information concerning the CML studies 102, 109 and 110. This information is being provided at this time.

The enclosed safety and efficacy update report provides 9 months of additional data than was included in the original NDA submission for the CML indication and what is reflected in the current approved package insert (PI). The PI table of adverse experiences ≥10% for all three trials has been updated, as well as the response rate tables. Data on duration of response is also included.

We agree that updating the CML safety and efficacy information in the PI at this time is appropriate and provides important information to healthcare professionals. Our expectation is that during the revision of the Gleevec package insert for the new GIST indication, the CML response and adverse experience tables would be updated, and data on duration of response added.

Paper Section

The paper portion of this submission consists of the Safety/Efficacy Update report dated December 8, 2001, and case report forms for all new deaths and dropouts due to adverse experiences.

Electronic Section

As requested, the case report forms and case report tabulations (datasets) supporting the updated safety and efficacy report is contained on one CD-ROM that is located in Volume E1 of the paper submission.

The virus scanning software used for the submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

This submission consists of 17 volumes (paper volumes 1-16 and electronic volume E1).

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh

Desk Copy (coverletter only) via fax: Ann Staten (HFD-150 at 301/827-4590)

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commercial

information

East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

Post-it® Fax Note 7671	Date	# of pages ▶ 2
To Ann Staten	From Robert Miranda	
Co./Dept. FDA	Co. Novartis	
Phone #	Phone # 973-781-3282	
Fax # 301-827-4590	Fax #	

December 7, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: Requests for Information

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to an e-mail request dated December 3, 2001 from Ms. Ann Staten concerning the Bioanalytical Data Report for CSTI571 0118. A response was provided by return e-mail on December 5, 2001. At this time we are providing a formal record of this communication.

FDA Request:

On p. 21 (under 6. Sample analysis) of the Bioanalytical Data Report (Appendix 5) for CSTI571 0118 the following statement is made:

> "Samples with a concentration above the upper limit of the calibration range were re-analyzed after appropriate dilution. The value found in the re-analysis is reported".

Please provide the following:
1. identify which samples were re-analyzed with such dilution, and
2. provide us with the details of the dilution procedure and it's validation.

Novartis Answer:

The standard report template approach was used for this study. We have confirmed that due to the sample concentrations being lower than the upper limit of calibration range of both STI and Simvastatin, no sample was diluted.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh

Desk Copy (coverletter only) via fax: Ann Staten (HFD-150 at 301/827-4590)

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

DUPLICATE

NOVARTIS

NDA SUPP AMEND
SE1-001
BM

December 4, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: Case Report Forms (7 patients on Study B2222)

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to a fax dated November 28, 2001 from Ms. Ann Staten requesting case report forms (CRFs) for seven additional patients. At this time we are providing the paper copies of the CRFs for the seven patients as requested.

Attached are copies of the CRFs for the following patients who were enrolled in the pivotal GIST study B2222:

501/007
502/025
502/026
502/110
502/125
503/018
503/036

This submission consists of one volume.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh
Attachments

Desk Copy (coverletter only) via fax: Ann Staten (HFD-150 at 301/827-4590)

DUPLICATE

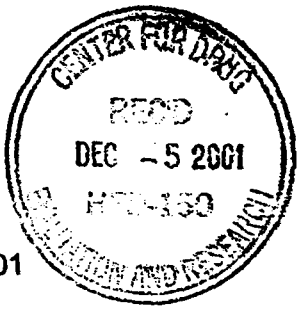
NOVARTIS

59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NEW CORRESP

SNC to
SC1-001



December 4, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: Requests for Information

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and /or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to two e-mail messages dated November 13 & 16, 2001 and one fax dated November 16, 2001 from Ms. Ann Staten. At this time we are providing copies of our e-mail responses to each of these FDA messages to our NDA, as an official record of these communications.

A summary of the topic for each of these three communications is provided as follows:

November 13, 2001 e-mail: This was a FDA information request for the patient identifications from the historical group at DFCI that were ultimately enrolled on trial B2222. On November 20, 2001 Novartis responded via e-mail with a list of the 74 patient identifications as requested. (Please see copies attached)

November 16, 2001 e-mail: This was a FDA information request for clarification regarding the randomization vs. initiation dates. On November 20, 2001 Novartis responded via e-mail with the clarification and attached a spreadsheet with the patient ID, date of randomization and date of first dose. (Please see copies attached)

November 16, 2001 fax: This fax provided the FDA reviewer's comments regarding three patients whose response assessments were in disagreement. FDA believes these three confirmed partial responses reflected stable disease in accordance with the protocol. On November 21, 2001 Novartis responded via e-mail providing specific data for each of the three patients to help clarify why it was believed that the original response of confirmed partial response was still valid. (Please see copies attached).

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh
Attachments

Desk Copy (coverletter only) via fax: Ann Staten (HFD-150 at 301/827-4590)

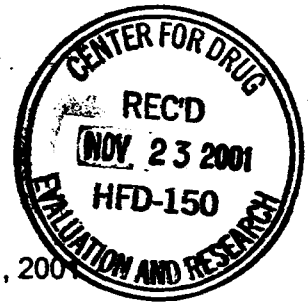
DUPLICATE

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

NDA SUPP AMEND
SE1-001
BM



November 21, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: CT Scans & Responders

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and /or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to an e-mail dated October 25, 2001 from Ms. Ann Staten requesting clarification concerning the number of responders and the CT scans originally submitted to our IND [redacted] on September 18, 2001 (Serial No 338). A clarification as requested was provided in our e-mail response of October 26, 2001.

At this time we are providing copies of the October 25th e-mail request from Ms. Staten and our October 26th e-mail response to our NDA as an official record of these communications.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh
Attachments

DUPLICATE

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

NDA SUPP AMEND
SE1-001
BM

November 7, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: CT Scans

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and /or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to our Gleevec IND [redacted] correspondence dated September 21, 2001 (Serial No. 338), which provided CT scans for all responders. At this time we are providing additional CT scans as requested by fax from Ms. Ann Staten on November 1, 2001.

The following additional scans are provided for the patients and dates requested in the November 1st fax:

Patient #	Dates
501_00085	11JAN01 and 05MAR01
501_00087	04JAN01 and 05MAR01
502_00025	08SEP00, 09OCT00 and 14DEC00
502_00042	04DEC00 and 29JAN01
502_00090	29JAN01 and 07MAR01
502_00109	13FEB01 and 13MAR01

Only one copy of the CT scans is being submitted as previously agreed. We ask that when you are completed with your review to please return these to us. This submission consists of one volume.

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh
Attachments (CT Scans=one set only)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	11/7/01
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
(973) 781-2282	(973) 781-6325
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
59 Route 10 East Hanover, New Jersey 07936-1080	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-335

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
imatinib mesylate	**Gleevec™**

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*

CODE NAME *(If any)*: **ST1571, CGP57148B**

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Capsules	**50 and 100 mg**	**Oral**

(PROPOSED) INDICATION(S) FOR USE:
Gastrointestinal stromal tumors (GIST)

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)*

☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT

☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
MINOR AMENDMENT TO S-01 TO PROVIDE CT SCANS

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND [redacted]

This application contains the following items: (*Check all that apply*)

	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i); 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
	8. Clinical data section (e.g., 21 CFR 314.50 (d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10. Statistical section (e.g., 21 CFR 314.50 (d)(6); 21 CFR 601.2)
	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1); 21 CFR 601.2)
	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert A Miranda	Robert A. Miranda,Director Drug Regulatory Affairs	11/7/01

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
59 Route 10 East Hanover, New Jersey 07936-1080	(973) 781-2282

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DUPLICATE

NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

SE1-001
BM

October 23, 2001

NDA No. 21-335

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: Electronic Reports

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of unresectable and /or metastatic malignant gastrointestinal stromal tumors (GIST). Reference is also made to a telcon on October 18, 2001 with Ms. Ann Staten, in which she requested pdf files of certain sNDA documents. At this time we are providing these sNDA documents as requested and in accordance with the electronic submission guidelines.

The following documents are provided as pdf files and are contained on one CD-ROM attached.

- Pivotal Clinical Study Report B2222 (core report only)
- Integrated Summary of Efficacy
- Integrated Summary of Safety
- Integrated Summary of Benefits and Risks

The virus scanning software used for this electronic file submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

This submission consists of one electronic volume.

If you have any questions or comments regarding this NDA, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

Attachment

Desk Copy (coverletter only) via fax: Ann Staten (HFD-150 at 301/827-4590)

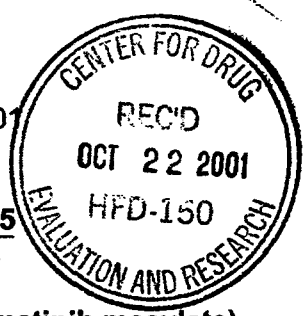
ORIGINAL

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

ARTIS

NDA SUPP AMEND
SE1-001
BH



October 19, 2001

NDA No. 21-335

MD

ology Drug Products/HFD-150
Administration
A Oncology Drug Group
Control Room #20N
Pike
ryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

SUPPLEMENT 01

GENERAL CORRESPONDENCE:
DSI Information (Preliminary)

zdur:

to our Supplemental NDA 21-335 for Gleevec™, which provides a new indication ment of unresectable and /or metastatic malignant gastrointestinal stromal tumors erence is also made to a fax from Ms. Ann Staten with a listing of information to be the Division of Scientific Investigation (DSI) at the time of sNDA submission. At e are providing the preliminary information for DSI.

ing information is provided as requested:

21-335 was approved on May 10, 2001 for the treatment of patients with chronic leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure eron-alpha therapy. A supplemental NDA (S-01) was submitted on October 15, o provide for a new indication in the treatment of GIST. A request for priority review ubmitted with this application. The expected user fee goal date is April 16, 2002. n designation is also pending FDA review.

ec is a small molecule inhibitor of Kit receptor tyrosine kinase activity, as well as the n tyrosine kinase activity of the platelet-derived growth factor (PDGF) receptor and himeric Bcr-Abl fusion protein found in chronic myeloid leukemia (CML).

copy of Volume 1 of the sNDA is attached.

his sNDA consists of one pivotal clinical trial entitled, "Open, Randomized, Phase II tudy of STI571 in Patients with Unresectable or Metastatic Malignant astrointestinal Stromal Tumors Expressing c-kit" (Protocol No. CSTI571B2222 or abbreviated as Protocol B2222). A copy of this protocol with all amendments, unsigned consent form and a blank CRF are attached.

ption of the primary efficacy endpoint and a table by study site with the various on requested (e.g. # subjects, # reportable AEs, etc.) are provided in the attached data document.

Contact: Robert A. Miranda
Drug Regulatory Affairs
973/781-2282

/

vartis conducted and is responsible for all monitoring activities under GCPs.

ubmission consists of two volumes.

have any questions or comments regarding this matter, please contact me at 781-2282.

erely,

ert A. Miranda
ctor
g Regulatory Affairs

M/vh
closures

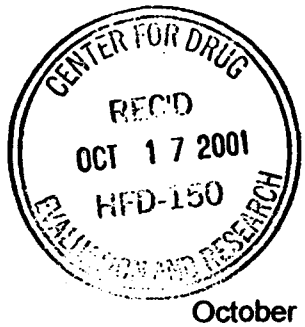
sk Copies: Khin Maung U, MD; FDA/HFD-47
Ann Staten FDA/HFD-150 (Letter only via fax at 301/827-4590)

ORIGINAL

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS



NDA NO. 21-335 REF NO. 001
NDA SUPPL FOR SE1-001

RECEIVED
OCT 16 2001
CDR/CDER

October 15, 2001

NDA No. 21-335 / S-01

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

GLEEVEC ™ (imatinib mesylate)
Capsules

EFFICACY SUPPLEMENT – CHANGES REQUIRING PRIOR APPROVAL

NEW INDICATION: GIST

Dear Sir/Madam:

Reference is made to our NDA 21-335 for Gleevec™ (imatinib mesylate, formerly STI571 and CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. At this time Novartis Pharmaceuticals Corporation submits a supplemental New Drug Application (sNDA) for the use of Gleevec in a new indication for the treatment of patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

As you know Gleevec is a small molecule inhibitor of the Bcr-Abl tryosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Gleevec is also an inhibitor of the receptor tyrosine kinases associated with the platelet-derived growth factor receptor (PDGF-R) and Kit, the product of the proto-oncogene c-kit. There is strong evidence that the Kit receptor, mutated and constitutively activated in a majority of GIST, plays a role in the growth of these tumors, providing the rationale for testing Gleevec therapy in these patients.

This sNDA consists of the results of a single phase 2, open-label, two-arm randomized, multinational study (B2222) conducted in 147 patients with unresectable or metastatic malignant GIST. Results of this study indicate unprecedented efficacy with relatively few serious safety concerns. The overall response rate in the 147 patients evaluated, based on confirmed PR at the time of the data cut-off is 40%. However, as will be described in a subsequent report (120-Day update), a significantly higher rate of responses are achievable with this therapy. Contrasted with the available historical data that shows there is no effective standard therapy, there is clearly an overwhelming benefit relative to the risks of therapy with Gleevec.

This sNDA has been prepared in a manner that is consistent with existing regulations relevant guidelines and understandings that were reached at our EOP2 and pre-sNDA meetings. A

copy of the relevant correspondence related to these meetings is located in Volume 1 of the sNDA.

The Gleevec formulation is the same as previously approved for CML. The dose and schedule are similar. Therefore, there is no new preclinical or technical information in this sNDA. The CMC section is limited to a categorical exclusion for an environmental assessment in accordance with 21 CFR Part 25.31(b). For these reasons, the PAI requirements are not applicable and no certified copy of Section 3 is being provided to our district office.

Electronic Sections
As proposed in our pre-sNDA meeting of July 17, 2001, this submission includes the following sNDA components in electronic form only, and is contained on one CD-ROM that is located in Volume 2 of the paper submission:

Item 2: Labeling
Item 11: Case Report Tabulations
Item 12: Case Report Forms

The overall size of the electronic file contained in Volume 2 is approximately 162.9 MB. The virus scanning software used for the submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

Request for Priority Review
Gleevec has demonstrated unprecedented efficacy in a serious and life-threatening disease where there is no effective standard therapy.

We believe that this application qualifies for priority review according to CDER's MAPP 6020.3 in that Gleevec offers a significant improvement in the treatment of GIST, a serious and life-threatening condition, compared to available therapies as demonstrated in comparison to historical controls.

Pediatric Waiver

A request for a waiver from pediatric labeling for Gleevec in GIST was submitted as part of the briefing document for the pre-sNDA Meeting on July 17, 2001 and was granted at that meeting. The basis of this waiver is that GIST is rare in children.

In addition, Orphan designation in GIST was requested on August 9, 2001 in accordance with 21CFR316. While formal written confirmation of orphan status has not been received, it is expected very soon. This application would thereby also qualify for pediatric waiver under the orphan designation.

User Fee
The FDA User Fee for this application (user fee ID 4219) was submitted on October 12, 2001. As you know, user fees are excluded for orphan designated drugs/indications. The user fee for this clinical supplement has been paid in advance of receiving such written confirmation of the orphan designation as discussed above, in order not to delay this application. Since orphan designation is expected, we hereby request a refund at the time of orphan designation as provided under the user fee regulations.

90-Day Conference
We would like to request a 90-day post-submission conference (or earlier, if deemed appropriate) as provided for by 21 CFR 314.102. We would like to have the opportunity to meet with you and be advised of the general status of your review of this application and to discuss the review classification and potential for an advisory committee hearing.

Novartis Pharmaceuticals Corporation considers the information contained within this application to be confidential, and its contents are not to be disclosed without express written consent.

If you have any questions or comments regarding this sNDA, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

Attachments: Form FDA 356h
Form FDA 3397
Volumes 1-14

14 Desk Copies of Volume 1: Ann Staten (HFD-150)

Coverletter: Ann Staten (HFD-150) via fax at 301/827-4590

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-335/S-001

PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
Route 10
Hanover, New Jersey 07936-1080

Attention: Robert A. Miranda, Associate Director
Drug Regulatory Affairs

Dear Mr. Miranda:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Gleevec (imatinib mesylate) 50 and 100 mg capsules.

NDA Number: 21-335

Supplement Number: S-001

Review Priority Classification: Priority (P)

Date of Supplement: October 15, 2001

Date of Receipt: October 16, 2001

This supplement proposes the following change(s): Gleevec for the treatment of patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 15, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 16, 2001.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Rockville MD 20857

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room 3036
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Division Document Room 3036
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Ann Staten, Project Manager, at (301) 594-5770.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Staten
11/7/01 04:34:56 PM
Signed for Dotti Pease