CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-335/S-001

Administrative Documents

Time Sensitive Patent Information

Pursuant to 21 C.F.R. 314.53

for

NDA # 21-335

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Gleevec^{tm}
- Active Ingredient(s): imatinib mesylate
- Strength(s): 50 mg, 100 mg
- Dosage Form: Capsule
- Approval Date: Pending

A. This section should be completed for each individual patent

U.S. Patent Number: 5,521,184

Expiration Date: May 28, 2013

Type of Patent—Indicate all that apply:

1.	Drug substance (Active Ingredient)	✓Y	N
2.	Drug Product (Composition/Formulation	✓Y	N
3.	Method of Use	Y	✓N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent:

Name of Patent Owner: Novartis Corporation

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US):

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,521,184 covers the composition, formulation and/or method of use of imatinib mesylate (STI571). This product is:

- Currently approved under section 505 of the Federal Food, Drug,

___ and Cosmetic Act)

or

• ✓ the subject of this application for which approval is being sought.)

Signed: George L Dohmann

George Dohmann

Title: Patent Attorney

Date: October 4, 2001

Telephone Number: (908) 522-6922

Time Sensitive Patent Information

Pursuant to 21 C.F.R. 314.53

for

NDA # 21-335

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or

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Signed: George L Dohmann

George Dohmann

Title: Patent Attorney

Date: October 4, 2001

Telephone Number: (908) 522-6922

EXCLUSIVITY SUMMARY for NDA # 21-335 SUPPL # 001
Trade Name Gleevec Generic Name imatinib mesylate
Applicant Name Novartis HFD-150
Approval Date February 1, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_x__/

   b) Is it an effectiveness supplement? YES /_x__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_x__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   d) Did the applicant request exclusivity?

      YES /___/ NO /_x__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_x__/

If yes, NDA # ____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__x_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-335 Gleevec

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__x_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__x/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_x__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__x_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # B2222

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /_x_/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 21-335_____ Study # B2222
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_x_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /_x_/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /__x/

If yes, explain: _____

_____

_____

Ann Staten
Signature of Preparer Date
Title: Regulatory Project Manager

Richard Pazdur, M.D.
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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
1/31/02 04:11:47 PM

Richard Pazdur
1/31/02 04:51:12 PM

Printable Pediatric Page

Welcome to the Pediatric Page Printed Page. To produce your pediatric page, simply print this page (this paragraph will not print). However, most versions of Internet Explorer will print a header on each page (i.e., the name of the web site, etc.) To eliminate these when printing the Pediatric Page, go to 'File', then 'Page Setup', and clear the 'Header' and 'Footer' Boxes. (Cut and paste to a document [or write down] the contents of these boxes first if you want to restore the headers and footers afterwards.)

PEDIATRIC PAGE

NDA Number:	021335	**Trade Name:**	GLEEVEC (IMATINIB MESYLATE) 50/100 MG CA
Supplement Number:	001	**Generic Name:**	IMATINIB MESYLATE
Stamp date:	10/16/01	**Action Date:**	10/16/01
Supplement Type:	SE1		
COMIS Indication:	TREATMENT OF CHRONIC MYELOID LEUKEMIA		

Indication #1: Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES : Gastrointestinal Stromal Tumors) The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates in CML and objective response rates in GIST (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival. - Date Entered: 12/17/01

Status: A full waiver was granted for this Indication.

Reason for This Waiver: Too few children with the disease to study

Comments: Also, Orphan Drug Designation. Sponsor is conducting pediatric studies as a phase 4 commitment for the CML indication.

This page was printed on 12/17/01

12/17/01

Signature

Date

Gleevec™ (imatinib mesylate) Capsules
NDA 21-335 / S-01

(GIST Indication)

NOVARTIS CERTIFICATION IN COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

10/11/01
Date

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Redacted 5

pages of trade

secret and/or

confidential

commercial

information

(b)(5)

Team Leader Review
NDA 21-335/S-01
Drug: **Imatinib mesylate**
Date of Submission: **October 16, 2001**
Date of Review: **January 27, 2002**

Imatinib mesylate (Gleevec ™) was approved under Subpart H accelerated approval regulations in the United States on May 10, 2001 for treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. In the current supplemental application the applicant has proposed extending the indication for imatinib mesylate (Gleevec ™) to treatment of malignant gastrointestinal stromal tumors (GIST) as follows:

Gleevec™ (imatinib mesylate) is indicated 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. **Gleevec is also indicated for the treatment of patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).**

The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates in CML and **objective response rates in GIST** (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Imatinib mesylate, an orally administered tyrosine kinase inhibitor, inhibits not only the Bcr-Abl kinase produced in CML by the Philadelphia chromosome, but also the c-kit receptor, platelet-derived growth factor receptor and VEGF (vascular endothelial growth factor) tyrosine kinases. There are data that show c-kit receptor is expressed by the tumor cells of over 95% of patients with malignant GIST, making this tumor an excellent candidate for study of a molecularly targeted therapy like imatinib mesylate. Conventional chemotherapy is ineffective in the treatment of malignant GIST - tumor responses are reported in <10% of patients. Radiotherapy is reported to be of little palliative benefit, and tumors frequently recur after resection.

The foundation for this supplemental application for an indication in GIST is a single randomized phase 2, open-label study (B2222) in which 147 patients with metastatic and/or recurrent malignant GIST were randomized between two doses of imatinib mesylate - 400 mg vs. 600 mg daily. Four centers enrolled patients. Three of those were U.S. centers. The primary endpoint of this study was tumor response rate, and the responses observed early in the conduct of this trial led to the design of two large multicenter studies that are currently underway in Europe and North America, sponsored individually by the EORTC and the NCI. These trials, which randomize again between two dose levels of imatinib mesylate – this time 400 mg vs. 800 mg, are ongoing and were not submitted as part of this NDA. The phase 2 study that was the basis for this supplemental NDA, B2222, prospectively stated that efficacy would be proven if the lower limit of the 95% confidence interval of response rate was at least 10%.

In their review of the efficacy in this NDA, the FDA reviewers evaluated the radiographs submitted by the sponsor on patients that were considered to have achieved at least a partial response by SWOG response criteria, confirmed or unconfirmed, at a subsequent tumor evaluation. If the FDA reviewers did not concur with the sponsor's response evaluation, the

radiographs were reviewed by a radiologist consultant to the FDA, Dr. Ronnelle Dubrow from M.D Anderson Cancer Center, and her evaluation was accepted as final by both the FDA and applicant. The final assessment of response rate by the FDA in each treatment arm of Study B2222 was 33% (95% CI: 22%, 45%) in the 400 mg treatment group (N=73) and 43% (95% CI: 32%, 55%) in the 600 mg treatment group (N=74). The response rate only changed in the 400 mg treatment arm and was only slightly lower than that claimed by the sponsor in the application, – 37%. There were no CRs observed in this study by either the FDA or sponsor's assessment. The 10% lower limit of the confidence interval was excluded in both treatment groups, and the confidence intervals overlapped between the two groups, making it impossible to conclude that the higher dose level reliably yields a higher response rate than 400 mg. In addition, none of the patients randomized to 400 mg whose dose was escalated to 600mg for PD achieved a PR/CR when crossed over to 600 mg (N=12).

Follow-up on the study at the time of NDA submission was limited – the vast majority had been followed on study for less than one year, and median duration of response could not yet be evaluated. Response duration ranged from 7 to 38 weeks, and at the time of data cutoff all but one confirmed PR was maintained. There were additional patients who had what appeared to be a radiographically documented PR, but who had not yet had a confirmatory evaluation. The clinical relevance of this relatively high response rate without the added perspective of associated survival or other clinical benefit data, e.g. symptom improvement, is uncertain. Without mature response duration data the relevance of the response rate observed in this study is even more uncertain since the median survival of patients with metastatic or recurrent GIST tumors treated with conventional therapy is reported in the literature in the range of 19 –31 months[i ii iii].

The safety data base was limited by the relatively short follow-up on study. If the duration of treatment was evaluated by the study cut-off date, the majority of patients had ≤ 12 months of drug exposure, and over half of those had ≤6 months' exposure. Only 7% of the entire study population had been treated over 12 months, and none of those over 18 months. If the duration of treatment exposure was evaluated by the last date a patient was documented to be taking study medication (actual study evaluation date), the majority of patient had ≤6 months of treatment, approximately 75%, and no patient had an exposure that exceeded one year.

The imatinib mesylate toxicity profile in GIST was very similar to that observed in the CML data submitted for review in the original NDA application. The higher rate of grade ¾ cytopenias observed in the CML trials probably reflected the underlying hematological disease. Hemorrhage occurred in a higher percentage of patients with blast crisis and accelerated phase CML than in GIST, as might be expected in a patient population with leukemia, but the overall rate of hemorrhage was similar in the GIST and chronic phase CML studies, 19% vs. 22%, and the rate of grade ¾ hemorrhages was actually higher in the GIST study 7% vs. 2% in the CML study. Gastrointestinal hemorrhages occurred in 5% of GIST patients, similar to the blast crisis and accelerated phase CML studies, but higher than the 2% seen in the chronic phase CML study, and these hemorrhages were grade ¾ in 3% of GIST patients, compared to 0.4% of chronic phase CML study patients. GIST patients had an additional category of hemorrhage that was not observed in the CML trials, tumor hemorrhage, which occurred in 3%, all grade ¾. The gastrointestinal bleeds may have reflected hemorrhage from tumor sites, a phenomenon reportedly associated with GIST tumors. Query of the electronic dataset of medical history using "bleed" "hem" "melen" and "anemia" yielded 14 patients (7 in each dose level) who were reported to have a medical history of gastrointestinal bleeding at the time of entering this study (two specifically stated to be related to GIST tumor and one related to GIST tumor surgery), in addition to one patient with a history of "hemorrhage" not otherwise specified. Twenty-one of

the patients reported a history of anemia at baseline – 8 in the 400 mg arm and 13 in the 600 mg arm. There was no definite dose relationship to the hemorrhages observed in the GIST study.

The gastrointestinal bleeds and tumor bleeds could not be correlated with tumor response. The table below compares the time to response and the time to event in patients reported to have had a gastrointestinal bleed, tumor bleed, hemorrhage (NOS) and hemorrhage related to a biopsy procedure.

Patient No.	Dose	Adverse Event	Time to AE	Tumor Response
001-012	400 mg	**Hemorrhage** Grade 1	3 mo. 4 mo.	PR 1 mo. PR 3 mo.
501-001	400 mg	**GI bleed** (hematochezia) Grade 1	8.5 mo.	PR 3 mo. PR 8 mo.
501-049	400 mg	**GI Bleed** Grade 3 **Tumor Bleed** Grade 3	1 mo. 7 mo.	PD 1 mo., SD 3 mo., PD 5 mo.
502-034	400 mg	**GI Bleed** Grade 3	1 week	?
502-121	400 mg	**GI Bleed** Grade 3	3 mo.	PD 3 mo.
501-002	600 mg	**Hematoma Pleural Bx** Grade 3	1 mo.	SD 2 mo. PR 3 mo.
501-003	600 mg	**Hepatic Capsular Bleed Post-Bx** Grade3	1.5 mo.	SD 1.5 mo. PD 6 mo.
501-008	600 mg	**GI Bleed** Grade 3	1 week 1 mo. 2 mo.	SD
501-011	600 mg	**Tumor Bleed** Grade 3	4.5 mo.	SD 4 mo. PR 8 mo.
501-074	600 mg	**Tumor Bleed** Grade 4	3.5 mo.	SD
501-089	600 mg	**Tumor Bleed** Grade 3	2 weeks	SD 2 weeks PR 3 mo.

Although no deaths on study were attributed to gastrointestinal or tumor bleeds, the sponsor reported in the ISS of the application that eight such hemorrhages had occurred in the other ongoing GIST studies, and 3 of those had a fatal outcome.

Superficial edema was the most common adverse event observed in the GIST study and was similar in incidence to that observed in the CML studies – 74% in GIST vs. a range of 64-71% across the three CML populations studied. Grade ¾ edema events occurred in 4% of the GIST patients compared to a range of 3 – 12% across the CML populations. There was no definite relationship of dose level to fluid retention in the GIST study. Investigation of the etiology of the fluid retention associated with this drug was a phase 4 commitment for the accelerated approval of imatinib mesylate for the treatment of CML. The mechanism has yet to be defined.

Ten patients who entered the GIST study had died within 30 days of taking study drug by the time of study cutoff for filing the NDA. Of those, the investigators and sponsor attributed six to disease progression. Patient narratives were submitted to the NDA on six of the patients. (The Agency had made a pre-NDA agreement to allow the sponsor to submit narratives and CRFs on only patients whose serious adverse events on study were considered potentially drug related.) Three of the patients had narratives submitted because of death on study, and three had their narrative submitted for another adverse event that occurred on study (a distinction made on the basis of the issue of attribution: Pt. 502-034, Pt. 502-121 and Pt. 501-126). Narratives and CRFs were reviewed and the FDA review team did not disagree with the sponsor/investigator assessment of cause of deaths on study. There were two sudden deaths on study and a brief narrative for those two patients is provided below:

Pt. 502-064 (400 mg) was found unresponsive and died despite efforts at resuscitation approximately a month after hospitalization for exacerbation of COPD, and 5 months after starting study drug. She took 400 mg imatinib up until the time of her death, but her death was not attributed to study medication. Her concomitant medications included **flecainide**, digoxin, levofloxacin, steroids.

Reviewer Comment: Imatinib mesylate is a competitive inhibitor of CYP2D6 in in vitro studies, and blood levels of drugs that are substrates might be elevated by concomitant administration of imatinib. This patient was taking the antiarrhythmic flecainide, which is metabolized by CYP2D6. The risk of proarrhythmic effect of flecainide may increase with increased blood levels. The cause of this patient's sudden death is unknown based on the available narrative data.

Pt. 503-124 (400 mg) died suddenly from a presumed cardiac arrest approximately 3.5 months after starting study drug. Autopsy revealed 99% stenosis of his right coronary artery. His concomitant medications included Viagra, which is metabolized by CYP3A4.

Reviewer Comment: Viagra is metabolized by CYP3A4. Imatinib is a competitive inhibitor of CYP 3A4. The reviewer found no data in the literature correlating Viagra blood levels with cardiac events.

In addition, review of the SAE described in the following patient's narrative raises a potential role for a drug interaction between imatinib and metoprolol in the adverse event of bradyarrhythmia:

Pt. 502-025 (400 mg) This patient had seizures and a bradyarrhythmia on the same day, April 22, 2001. The bradyarrhythmia continued x 4 days, while she was hospitalized. She had a history of atrial fibrillation and ischemic heart disease, and her concomitant medications at study entry included metoprolol and digoxin. Entered study in August 2000.

Reviewer Comment: Metoprolol is a beta blocker that is metabolized by CYP 2D6 , and the role of a drug interaction with imatinib in this adverse event cannot be completely ruled out.

The sudden death of Pt 502-064 and the bradyarrhythmia observed in Pt. 502-025 could have been related to CYP2D inhibition and elevated drug levels of flecainide and metoprolol in these two patients, but there is no proof that this is in fact what occurred. The phase 4 commitments for the approval of the NDA for CML in May 2001 included a commitment to educate patients and physicians on the potential drug interactions associated with imatinib. The sponsor fulfilled that commitment and those materials were re-examined during the review of this supplemental NDA.

The physician teaching included a "Dear Healthcare Provider" letter that provided a list of potential medications that might be impacted by imatinib's interaction with CYP 3A4, CYP2D6 and CYP2C9. The patient materials were specifically designed for patients with CML and included information on the potential for serious drug interactions, stressing the need to review concomitant medications with the treating physician. Because the patient materials were CML specific and the prescribing physician population for GIST could be different than those who treat CML, the FDA once again included patient and physician education regarding potential drug interactions in the phase 4 commitments for approval of this supplemental NDA for GIST.

The safety review of this application revealed only relatively small differences in the safety profiles of the two imatinib doses evaluated, 400 mg and 600 mg. Overall (all grades) fluid retention, diarrhea, nausea, and fatigue were only slightly higher in the 600 mg arm. The most dramatic differences between arms were in overall (all grades) muscle cramps, rash and taste disturbance, and 600 mg was associated with an approximate 12% higher incidence in those AE's. Incidence of grade ¾ AE's was very similar between dose levels, although there was a slightly higher incidence of grade ¾ hemorrhage in the 600 mg arm. These data did not clearly establish either dose level as superior in terms of patient risk, but suggested that the higher dose level may be associated with more frequent low grade toxicities.

Conclusions

The review team has recommended accelerated approval of imatinib mesylate for the treatment of Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors. Subpart H of the NDA regulations provides for accelerated approval based on a surrogate endpoint that is reasonably likely to predict clinical benefit for drugs that appear to provide benefit over available therapy in treatment of serious or life-threatening diseases. No effective therapy exists for unresectable and/or metastatic malignant GIST, and the response rates observed with imatinib doses 400 mg and 600 mg, 33% and 43% respectively, in the study reviewed in this NDA are dramatically higher than those associated with conventional chemotherapy (<10%). Because there was no statistically significant difference detected between the response rates of the two dose levels evaluated in the study and the small differences in toxicities observed with these two doses did not establish that one dose was superior to the other in its risk/benefit ratio, both doses were approved for this indication. The limited duration of follow-up in the study does not allow reliable assessment of duration of response associated with imatinib in this disease. The final labeled indication reads:

Gleevec™ (imatinib mesylate) is indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. **Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors(GIST). (See CLINICAL STUDIES: Gastrointestinal Stromal Tumors).**

The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates in CML and **objective response rate in GIST (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.**

The phase 4 commitments required for conversion of accelerated approval to full approval include submission of mature response rate, response duration, survival and safety data from sNDA trial B2222 and the two ongoing multicenter trials of 400mg vs. 800mg/day in GIST

(EORTC and NCI sponsored trials). In addition, because imatinib's activity in GIST is believed to be mediated through c-Kit, the applicant has agreed to assure availability of a validated test kit for detection of CD117 tumor expression by immunohistochemistry. The sponsor has agreed to develop a plan for investigating the incidence and etiology of GI/tumor hemorrhage associated with imatinib therapy in GIST, and the label's Precautions section was amended to provide information about these specific hemorrhagic events that were observed in the GIST study B2222. The sponsor has also agreed to pursue a program to educate both patients and physicians on the potential drug interactions associated with imatinib therapy. They have a previous phase 4 commitment from the original NDA accelerated approval for CML to conduct an appropriate *in vivo* study to definitively describe any imatinib interaction with drugs metabolized through CYP2D6, and were reminded of this commitment in the approval letter for this supplemental NDA in GIST.

---

[i] Pidhorecky I, Cheney RT, et al. Gastrointestinal stromal tumors: current diagnosis, biologic behaviour, and management. Ann Surg Oncol 705-712, 2000

[ii] Casper ES. Gastrointestinal Stromal Tumors. Curr Treat Options Onc 1:267-273, 2000.

[iii] Goss, GA et al. Clinical features and lack of response to conventional therapies of metastatic and advanced gastrointestinal stromal tumors (GIST) defined by the KIT receptor tyrosine kinase (CD117). In preparation

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

/s/

Donna Griebel
2/1/02 08:08:53 PM
MEDICAL OFFICER

PROJECT MANAGER REVIEW OF LABELING

NDA 21-335/S-001

Drug:	**Gleevec™ (imatinib mesylate) Capsules, 100 mg**	
Applicant:	**Novartis Pharmaceuticals Corporation**	
Submission Dates:	**October 15, 2001 sNDA**	**May 16, 2001 FA**
Receipt Dates:	**October 16, 2001**	**May 17, 2001**

BACKGROUND:

On May 10, 2001, NDA 21-335 was approved, which provided for Gleevec (imatinib mesylate) 50 and 100 mg 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. The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates (see Clinical Studies section). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival."

On October 16, 2001, an efficacy supplement was received which provides for Gleevec for the treatment of patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

DOCUMENTS REVIEWED:

I compared the approved May 16, 2001 label against the proposed draft labeling provided in the October 15, 2001 supplement.

REVIEW:

I found that all of the proposed changes to the package insert were identified by the underline and strikethrough feature.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

In this supplement, the sponsor has correctly identified all of the proposed changes to the package insert using the underline and strikethrough feature.

JS

Ann Staten, Regulatory Health Project Manager

JS

Dotti Pease, Chief, Project Manager Staff

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
11/21/01 10:49:17 AM
CSO

Dotti Pease
11/21/01 11:03:40 AM
CSO

20 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Novartis Pharmaceuticals Corp.
59 Route 10
East Hanover, NJ 07936

2. TELEPHONE NUMBER *(Include Area Code)*

(973) 781-6869 - Robert Kowalski

3. PRODUCT NAME

Gleevec™ (imatinib mesylate) Capsules

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

4219

6. LICENSE NUMBER / NDA NUMBER

NDA 21-335 / S-01

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Robert W. Kowalski, PharmD.	Director, DRA Planning & Administration	10/19/01

FORM FDA 3397 (5/98)

Continued on Electronic Document Submission

Staten, Ann M

From: Dagher, Ramzi
Sent: Monday, October 29, 2001 4:05 PM
To: Staten, Ann M
Griebel, Donna J
Subject: GIST (what else)

Ann,

Regarding the GIST supplement:

1. There will be no need for an inspection by DSI
2. Please make sure the following advisory committee memebers are cleared for Novartis as we may want to consult each of them separately by phone regarding the submission at some point : Bruce Redman, David Kelson, Stacey Nerenstone

Thanks,
ramzi

59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS

SAVER™ FAX MEMO 01616	Date 30 Jan 02	# of pages ▶ 2
To ANN STATEN	From Robert Miranda	
Co./Dept. FDA / HFD150	Co. Novartis	
Phone # 301 594-5770	Phone # 973 781 2282	
Fax # 301 827-4696	Fax # 2-5217	

January 30, 2002

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: Phase 4 Commitments

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

Reference is also made to a fax dated January 8, 2002 and an e-mail dated January 25, 2002 from Ms. Ann Staten, which contained the Phase 4 commitments regarding the GIST indication. On January 29, 2002 we provided our agreement to comply with all of these commitments. On January 30, 2002 a fax from Ms. Staten requested agreement to one additional phase 4 commitment which is the subject of this letter.

At this time we would like to provide our agreement to comply with the additional phase 4 commitment as follows below, with our estimated timelines for completion.

B. Other phase 4 commitments which are not a condition of accelerated approval:

4. Implement a physician and patient education program for GIST regarding the use of concomitant medications with Gleevec within two months of the date of this letter.

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

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

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:	1	**Date:**	January 30, 2002
Re:	NDA 21-335 Gleevec		

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

Dear Bob,

Please refer to the sNDA for Gleevec in GIST.

We have an additional phase 4 commitment for which we would like your response.

> *To implement a physician and patient education program for GIST regarding the use of concomitant medications with Gleevec within 2 months of the date of this letter.*

If you agree to this agreement and plan to implement a Dear Dr. Letter, the Division would like your feedback on adding flecainide and encainide to the CYP2D6 table.

Please call me with any questions.

Sincerely,

ann

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
1/30/02 11:33:00 AM
CSO

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

Tel 973 781 8300

NOVARTIS

Post-it® Fax Note 7671	Date 29-Jan	# of pages ▶ 4
To Ann Staten	From ROBERT Miranda	
Co./Dept. FDA / HFD-150	Co. NOVARTIS Pharma.	
Phone # 301 594-5776	Phone # 973 781-2282	
Fax # 301 827-4690	Fax # 973 781-5217	

January 29, 2002

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

NDA No. 21-335

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-01)

OTHER: Phase 4 Commitments

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-01 for Gleevec™, which provides a new indication in the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

Reference is also made to a fax dated January 8, 2002 and an e-mail dated January 25, 2002 from Ms. Ann Staten, which contained the Phase 4 commitments regarding the GIST indication. At this time we would like to provide our agreement to comply with all of these commitments. Each of the commitments mentioned in the fax and revised by the e-mail is repeated below followed by our estimated timelines where appropriate.

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

1. Complete the follow-up of sNDA trial B2222 and submit mature response rate, response duration and survival data. The suggested timelines for these submissions are December 31, 2002 for response and response duration, and after either when 70% of events have occurred or at the 5 year follow-up for survival analysis (March 31, 2007).

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 (June 2002).

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. The data should be submitted in a timeline consistent with the statistical analysis plan of each respective protocol (est. June 2003).

4. Submit clinical and PK data for the EORTC phase 1 study of imatinib in patients with GIST and other soft-tissue sarcomas when it is available.
   (Submission: July 31, 2002)

5. Assure availability of a validated test kit for detection of CD117 tumor expression by immunohistochemistry. → Pre-Market Application
   Timelines: - PMA filing by 3rd party planned by December 31, 2002

B. Other phase 4 commitments which are 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) (Submission: June 30, 2003)

2. Provide a plan for investigating the incidence and etiology of GI/tumor hemorrhage associated with imatinib therapy. (Submission: July 31, 2002)

3. Investigate and submit data regarding :
   a) correlation of c-kit tumor 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
   (Submission: December 31, 2002)

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

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

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	**1/29/02**
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
Agreement to Phase 4 commitments

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)

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 knowledge 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	1/29/02

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.

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

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

Staten, Ann M

From: Staten, Ann M
Sent: Friday, January 25, 2002 10:37 AM
To: 'robert.miranda@pharma.novartis.com '
Subject: Phase 4 commitments

Importance: High


commitments[2].doc

Dear Bob,

Please find attached a copy of the phase 4 commitments with our comments in italics.

PLease call me with any questions.

Sincerely,

ann
301-874-1098

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/s/

Ann Staten
1/28/02 09:57:31 AM
CSO

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

1. Complete the follow-up of sNDA trial B2222 and submit mature response rate, response duration and survival data. The suggested timelines for these submissions are last quarter of 2002 for response and response duration, and after either 70% of events have occurred or 5 years follow-up for survival analysis.

   In addition to data on response and response duration, survival data would also be required to meet this commitment.

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. The data should be submitted in a timeline consistent with the statistical analysis plan of each respective protocol.

   One-year data may represent an insufficient followup period.

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

   The Lancet report represents a brief presentation which does not allow a comprehensive assessment of the data. Since a final study report is not planned, you may submit clinical and PK data for assessment by FDA.

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

   This testing is a vital component of defining the disease population.

B. Other phase 4 commitments which are 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)

   Since an assessment would not be available, we request that you submit the raw data for an assessment by FDA.

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

This commitment has been moved to section B per your request.

3. Investigate and submit data regarding :
   a) correlation of c-kit tumor 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

This commitment has been moved to section B per your request.

C. Prior phase 4 commitments

Please refer to previous correspondence.

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/s/

Ann Staten
1/28/02 10:02:51 AM
CSO

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Tuesday, January 29, 2002 4:03 PM
To: statena@cder.fda.gov
Cc: griebeld@cder.fda.gov; dagherr@cder.fda.gov
Subject: Hemorrhages Numbers in Table 5


Hemorrhage.doc


wssinfo.txt

Dear Ann,

The changes in the "any hemorrhage" category involved two patients in the hemorrhage sub-groups of this table that were not included in the "any hemorrhage" group.

One 400 mg patient (502_ 098) was listed in the cerebral hemorrhage but was left out of the "any hemorrhage" group. This is the reason we changed 16% to 18% for any hemorrhage. This patient was also a grade 3 /4 so it changed the grade 3/4 any hemorrhage from 4% to 5%.

One 600 mg patient (502_073) was listed in the GI tract hemorrhage but was left out of the "any hemorrhage" group. This is the reason we changed 18% to 19% for any hemorrhage.

Attached are the patient numbers for each of the hemorrhages.

I hope this provides the clarity you needed. Sorry for any confusion.

Best regards,
Bob.....

Appendix 7.1: Listing 10.1- 3 (pages 18 - 22 of 97)
Adverse events by AE grouping
Treatment group : 400 mg

Haemorrhage

001/ 012 79/ F/ Cau HEMORRHAGE Haemorrhage NOS
001/ 037 68/ F/ Cau BRUISING Contusion
001/ 159 56/ M/ Cau BRUISING Contusion PETECCHIAL Petechiae
501/ 001 64/ F/ Cau HEMATOCHEZIA Rectal haemorrhage
501/ 007 63/ M/ Cau INTERMITTENT EPISTAXIS Epistaxis
501/ 049 63/ F/ Cau BRUISING Contusion GI BLEED Gastrointestinal haemorrhage NOS INTRA- ABDOMINAL TUMOR BLEED Tumour haemorrhage INTRA- ABDOMINAL TUMOR BLEEDING Tumour haemorrhage INTRATUMORAL BLEED Tumour haemorrhage POSSIBLE INTRA- TUMORAL BLEED Tumour haemorrhage
501/ 076 54/ F/ Cau HEMATURIA Haematuria INTERMITTENT BURSTING OF BLOOD Eye haemorrhage NEC VESSELS IN EYES INTERMITTENT BURSTING OF BLOOD Haemorrhage NOS VESSELS IN FACE
501/ 104 70/ F/ Cau NOSE BLEEDS Epistaxis
502/ 034 38/ F/ Cau GI BLEED Gastrointestinal haemorrhage NOS

502/ 121 75/ M/ Cau GI BLEED Gastrointestinal haemorrhage NOS
503/ 036 48/ M/ Cau EPISTAXIS INTERMITANT Epistaxis
503/ 058 57/ M/ Cau SINGLE EPISODE BLOOD CLOT IN STOOL Blood in stool

Tumour Haemorrhage

501/ 049 63/ F/ Cau INTRA- ABDOMINAL TUMOR BLEED Tumour haemorrhage INTRA- ABDOMINAL TUMOR BLEEDING Tumour haemorrhage INTRATUMORAL BLEED Tumour haemorrhage POSSIBLE INTRA- TUMORAL BLEED Tumour haemorrhage

Cerebral

502/ 098 66/ M/ Cau LEFT HEMISPHERIC CVA Cerebrovascular accident NOS haemorrhage/ subdural haematoma*

Upper G- I tract

501/ 049 63/ F/ Cau GI BLEED Gastrointestinal haemorrhage NOS bleeding/ perforation
502/ 034 38/ F/ Cau GI BLEED Gastrointestinal haemorrhage NOS
502/ 121 75/ M/ Cau GI BLEED Gastrointestinal haemorrhage NOS
503/ 058 57/ M/ Cau SINGLE EPISODE BLOOD CLOT IN STOOL Blood in stool

Appendix 7.1: Listing 10.1- 3 (pages 66 through 68 of 97)
Adverse events by AE grouping
Treatment group : 600 mg

Hemorrhage
001/ 129 53/ F/ Cau BRUISING Contusion
501/ 002 57/ M/ Cau INTERMITTENT NOSE BLEEDS Epistaxis PLEURAL HEMATOMA POST BIOPSY Post- operative haematoma
501/ 003 52/ M/ Cau HEPATIC CAPSULAR BLEED POST BIOPSY Post- operative haemorrhage
501/ 008 25/ M/ Cau GASTROINTESTINAL BLEED Gastrointestinal haemorrhage NOS
501/ 011 54/ M/ Cau INTRAHEPATIC TUMOR BLEED Tumour haemorrhage
501/ 054 63/ F/ Cau SUBCONJUNCTIVAL HEMORRAGE Conjunctival haemorrhage
501/ 056 54/ M/ Cau SUBCONJUNCTIVAL HEMORRHAGE Conjunctival haemorrhage
501/ 074 41/ F/ Cau INTRATUMORAL BLEED Tumour haemorrhage
501/ 086 50/ F/ Cau CHRONIC MENORRHAGIA Menorrhagia
501/ 089 59/ F/ Cau INTRA- TUMORAL BLEED Tumour haemorrhage
501/ 111 53/ F/ Cau INTERMITTENT BLOOD VESSEL BURSTING Eye haemorrhage NEC IN EYE
502/ 033 50/ F/ Cau BLOODY BOWEL MOVEMENT Melaena
503/ 031 49/ M/ Cau GUIAC POSITIVE STOOLS Blood in stool

Tumour Haemorrhage
501/ 011 54/ M/ Cau INTRAHEPATIC TUMOR BLEED Tumour haemorrhage
501/ 074 41/ F/ Cau INTRATUMORAL BLEED Tumour haemorrhage
501/ 089 59/ F/ Cau INTRA- TUMORAL BLEED Tumour haemorrhage

Upper G- I tract
501/ 008 25/ M/ Cau GASTROINTESTINAL BLEED Gastrointestinal haemorrhage NOS bleeding/ perforation
502/ 033 50/ F/ Cau BLOODY BOWEL MOVEMENT Melaena
502/ 073 51/ F/ Cau DUODENAL ULCER Duodenal ulcer*
503/ 031 49/ M/ Cau GUIAC POSITIVE STOOLS Blood in stool

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/s/

Ann Staten
1/30/02 10:54:03 AM
CSO

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 16, 2002
Re:	NDA 21-335 Gleevec		

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

Dear Bob,

Please refer to the sNDA for Gleevec in GIST.

We are sending you two sections, lines 183-209 and 547-567, of the PI for your review and comment at this time.

Please call me with any questions.

Sincerely,

ani /S/

21 pages redacted from this section of the approval package consisted of draft labeling

Staten, Ann M

From: Staten, Ann M
Sent: Tuesday, January 22, 2002 12:58 PM
To: 'robert.miranda@pharma.novartis.com'
Subject: RE: Comments to FDA Review of Updated Efficacy Responses (Study 110)

Novartis 0110 questions 1-22-0...

Dear Bob,

Here is our response. Please let me know if there are any questions.

thanks,
ann

-----Original Message-----
From: robert.miranda@pharma.novartis.com
[mailto:robert.miranda@pharma.novartis.com]
Sent: Friday, January 18, 2002 12:50 PM
To: statena@cder.fda.gov
Subject: Comments to FDA Review of Updated Efficacy Responses (Study 110
)

Hi Ann,

We have completed our review of the 110 data and would like to share our

comments in the hopes that our numbers can agree. The largest discrepancy is
in the major cytogenetic response in which we have a 60% MCR with 42% complete
response. The FDA data assessment seems to show a 58% MCR with a 31% complete
response.

Could you clarify if the complete response of 31% we calculated from the FDA
data is actually confirmed response?

Study 110 (chronic phase CML)

Hematologic response

We accept the numbers.

Cytogenetic response

57 patients were assigned as partial response (>0%-35% Ph+) by the FDA, but had
0% Ph+ (complete cytogenetic response) at least at one assessment:

Patient	days
001_0003	338

002_0021	350
003_0003	169
004_0009	512
005_0011	414
005_0030	85
006_0002	378
006_0003	497
007_0012	539
008_0003	549
008_0006	253
009_0002	506
009_0010	338
012_0004	85, 169, 253
014_0004	379
015_0003	93, 175, 261
016_0001	260, 344, 512
016_0003	253, 505
020_0001	176
501_0002	170
501_0007	170
501_0013	169
501_0014	338
501_0022	337
501_0040	337
502_0003	421, 589
502_0004	85, 337, 503
502_0011	430
502_0015	344, 524
502_0024	337, 419
503_0005	336
503_0006	253, 327, 508
503_0012	84
503_0037	266
503_0042	343
503_0058	542
503_0063	168, 336, 510
503_0068	175, 259, 357
503_0074	346
503_0082	86
503_0083	518
503_0084	264, 336, 392
503_0096	554
503_0118	254, 461, 545
503_0126	365
503_0128	167
503_0145	251, 337
504_0003	337, 547
504_0014	363
505_0024	254
509_0002	171, 424
509_0005	247
509_0006	74, 336
510_0004	272, 370, 464
511_0008	336
512_0007	254, 431
512_0010	429

The following additional 16 patients are in major cytogenetic response, but