

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-588/S-002

Administrative

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: GleevecSM
- Active Ingredient(s): imatinib mesylate
- Strength(s): 100mg, 400mg
- Dosage Form: tablets (PDA) 12/10/2
- 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) | <u>√Y</u> | <u>N</u> |
| 2. Drug Product (Composition/Formulation) | <u>√Y</u> | <u>N</u> |
| 3. Method of Use | <u>Y</u> | <u>√N</u> |

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.

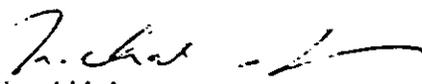
The undersigned declares that the above stated United States Patent Number 5,521,184 covers the composition, formulation and/or method of use of imatinib mesylate (STI571). This product is:

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

or

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

Signed:


Michael U. Lee

Title: Patent Attorney

Date: January 11, 2001

Telephone Number: 908) 522-6794

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within 30 days of the date of issuance of the patent.

To expedite publication in the *The Orange Book*,* a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
HFD-93
5600 Fishers Lane
Rockville, MD 20857

OR

Location address: (for FedEx deliveries)

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Information Services Team
Building A
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane
Kensington, MD 20895

OR faxed to: (301)-594-6463

* - Please note that patents for unapproved compositions, formulations, or uses will NOT be published in the *The Orange Book*.

EXCLUSIVITY SUMMARY for NDA # 21-588 SUPPL # S-002
Trade Name Gleevec Tablets Generic Name imatinib mesylate

Applicant Name Novartis Pharmaceuticals Corporation HFD- 150

Approval Date: December 8, 2003

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.)? SE7

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 /_X_/ NO /___/

If yes, NDA # 21-335 Drug Name Gleevec (imatinib mesylate) Capsules

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 /___/

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 /___/ NO /___/

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

NDA #

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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 /___/ 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 /___/ 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 /___/

- (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 /___/

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 #

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 /___/ 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 # ___ Study #
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 /___/

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 /___/ ! 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 /___/

If yes, explain: _____

Signature of Preparer
Title:

Date

Signature of Office or Division Director

Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/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
12/8/03 10:53:38 AM

Richard Pazdur
12/8/03 11:44:39 AM



Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

NDA debarment (tablets) 100203.doc

Gleevec® (imatinib mesylate) Tablets
NDA 21-588 / S-002

**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.

10/02/03
Date


Robert A. Miranda
Director
Drug Regulatory Affairs

12/9/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-588 / SE7 - 002

Drug Gleevec (imatinib mesylate) Tablets Applicant Novartis

RPM Ann Staten Phone 301-594-0490

505(b)(1)
 505(b)(2) Reference listed drug •

Fast Track Rolling Review Review priority: S P

Pivotal IND(s) 55,666

Application classifications:	PDUFA Goal Dates:
Chem Class (conversion from accelerated to full approval)	Primary <u>June 28, 2004</u>
Other (e.g., orphan, OTC) <input checked="" type="checkbox"/> V Orphan designation	Secondary <u> </u>

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- ◆ User Fee Information: User Fee Paid
 User Fee Waiver (attach waiver notification letter)
 User Fee Exemption
- ◆ Action Letter..... AP AE NA
- ◆ Labeling & Labels
 - FDA revised labeling and reviews..... X
 - Original proposed labeling (package insert, patient package insert) X
 - Other labeling in class (most recent 3) or class labeling..... N/a
 - Has DDMAC reviewed the labeling? No need for Yes (include review) No
 - DDMAC to review se Medical TL e-mail..
 - Immediate container and carton labels N/a
 - Nomenclature review N/a
- ◆ Application Integrity Policy (AIP) Applicant is on the AIP. This application is is not on the AIP.
 - Exception for review (Center Director's memo)..... N/a

- OC Clearance for approval..... N/a
- ◆ Status of advertising (if AP action) Reviewed (for Subpart H – attach review) ■ Materials requested in AP letter
- ◆ Post-marketing Commitments
- Agency request for Phase 4 Commitments..... N/a
- Copy of Applicant's commitments N/a
- ◆ Was Press Office notified of action (for approval action only)?..... ■ Yes No
- Copy of Press Release or Talk Paper..... X -draft
- ◆ Patent
- Information [505(b)(1)] X
- Patent Certification [505(b)(2)]..... X
- Copy of notification to patent holder [21 CFR 314.50 (i)(4)]..... N/a
- ◆ Exclusivity Summary X
- ◆ Debarment Statement X
- ◆ Financial Disclosure
- No disclosable information X
- Disclosable information – indicate where review is located Page 9 of review dated 11-5-03
- ◆ Correspondence/Memoranda/Faxes X
- ◆ Minutes of Meetings N/a
- Date of EOP2 Meeting N/a
- Date of pre NDA Meeting N/a
- Date of pre-AP Safety Conference N/a
- ◆ Advisory Committee Meeting N/a
- Date of Meeting N/a
- Questions considered by the committee N/a
- Minutes or 48-hour alert or pertinent section of transcript N/a
- ◆ Federal Register Notices, DESI documents N/a

CLINICAL INFORMATION:

Indicate N/A (not applicable),
X (completed), or add a
comment.

- ◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) N/a

- ◆ Clinical review(s) and memoranda X dated 11-5-03 and 12-4-03
- ◆ Safety Update review(s) N/a
- ◆ Pediatric Information:
 - Waiver/partial waiver (Indicate location of rationale for waiver) Deferred Pediatric Page..... Orphan drug designation
 - Pediatric Exclusivity requested? Denied Granted Not Applicable
- ◆ Statistical review(s) and memoranda N/a
- ◆ Biopharmaceutical review(s) and memoranda..... N/a
- ◆ Abuse Liability review(s) N/a
 Recommendation for scheduling N/a
- ◆ Microbiology (efficacy) review(s) and memoranda N/a
- ◆ DSI Audits N/a
 Clinical studies bioequivalence studies

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ CMC review(s) and memoranda N/a
- ◆ Statistics review(s) and memoranda regarding dissolution and/or stability N/a
- ◆ DMF review(s) N/a
- ◆ Environmental Assessment review/FONSI/Categorical exemption N/a
- ◆ Micro (validation of sterilization) review(s) and memoranda N/a
- ◆ Facilities Inspection (include EES report)
 Date completed N/a Acceptable Not Acceptable
- ◆ Methods Validation Completed Not Completed

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- ◆ Pharm/Tox review(s) and memoranda N/a

- ◆ Memo from DSI regarding GLP inspection (if any) N/a
- ◆ Statistical review(s) of carcinogenicity studies N/a
- ◆ CAC/ECAC report N/a

**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

12/9/03 10:19:58 AM

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

NDA 21-588/S-002
Gleevec®
(imatinib mesylate) Tablets

SUBPART H POSTMARKETING COMMITMENTS
(Completion And Conversion to Full Approval for 2nd Line CML Indication)

Table of Contents

Item.	Description	Paper archive copy volume #	Electronic archive copy - folder.
1.	Table of Contents (Index)	N/A	N/A
2.	Labeling	N/A	Labeling
3.	Summary	N/A	N/A
4.	Chemistry, Manufacturing and Controls	N/A	N/A
5.	Nonclinical Pharmacology and Toxicology Section	N/A	N/A
6.	Human Pharmacokinetics and Bioavailability Section	N/A	N/A
7.	Clinical Microbiology	N/A	N/A
8.	Clinical Data	N/A	N/A
9.	Safety Update	N/A	N/A
10.	Statistical Section	N/A	N/A
11.	Case Report Tabulations	N/A	N/A
12.	Case Report Forms	N/A	N/A
13.	Patent Information	N/A	N/A
14.	Patent Certification	N/A	N/A
15.	Establishment Description	N/A	N/A
16.	Debarment Certification	N/A	N/A
17.	Field Copy Certification	N/A	N/A
18.	User Fee Cover Sheet (Form FDA 3397)	N/A	N/A
19.	Financial Disclosure Certification	N/A	N/A
20.	Other information	N/A	N/A

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

Completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fees can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS Novartis Pharmaceuticals Corporation One Health Plaza East Hanover, New Jersey 07936		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 21-588/S-002
2. TELEPHONE NUMBER (Include Area Code) (862) 778-2282		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO 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: <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: <u>21-588 & 21-335</u> (APPLICATION NO. CONTAINING THE DATA)
3. PRODUCT NAME Gleevec® (imatinib mesylate) Tablet		6. USER FEE I.D. NUMBER
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input checked="" type="checkbox"/> 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.) <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) <input type="checkbox"/> 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.)		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input type="checkbox"/> NO (See Item 8, reverse side if answered YES)		
Public reporting burden for this collection of information is estimated to average 30 minutes 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 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. Food and Drug Administration CDER, HFD-94 CBER, HFM-99 and 12420 Parklawn Drive, Room 3046 1401 Rockville Pike Rockville, MD 20852 Rockville, MD 20852-1448 Rockville, MD 20852		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE <i>for</i> Robert A. Miranda, Director Drug Regulatory Affairs DATE 10/07/03

12/1/03

PROJECT MANAGER REVIEW OF LABELING

NDA 21-588/S-000, 001 and 002

Drug: Gleevec (imatinib mesylate) Tablets, 100mg and 400 mg
Applicant: Novartis Pharmaceuticals Corporation
Submission Date: August 14, 2003 (FA for 000 and S-001) and August 26, 2003 (S-002)
Receipt Date: August 15, 2003 and August 28, 2003

BACKGROUND:

NDA 21-588 and S-001

On April 18, 2003, NDA 21-588 (which provided for a change in formulation of Gleevec from Capsules to Tablets) was approved. On May 20, 2003, NDA 21-588/S-001 which provided for the pediatric CML indication was approved. On August 14, 2003, the sponsor submitted FPL for both supplements.

NDA 21-335/S-006

On October 31, 2003, the sponsor submission dated April 30, 2003 containing FPL for the Changes Being Effected (CBE) sNDA 21-335/006 Gleevec Capsules was approved. This supplement provided for additions to the **Post Marketing Experiences** subsection of the **ADVERSE REACTIONS** section of the package insert. The sponsor agreed to make the FDA requested modifications, as stated in the approval letter, to the package insert text within the next 6 months or at the next printing, whichever comes first. Note: The CBE was submitted to the Capsules NDA because the Tablet formulation wasn't planned to be implemented until July 2003.

NDA 21-588/S-002

The medical reviewer and medical team leader of NDA 21-588/S-002 have concurred with the package insert proposal contained in S-002.

DOCUMENTS REVIEWED:

I compared the proposed draft package insert text submitted August 26, 2003 (NDA 21-588/S-002) and against the approved draft labeling text attached to the approval letters dated April 18, 2003 (NDA 21-588) and May 20, 2003 (sNDA 21-588/001).

I also compared the proposed draft package insert text submitted August 26, 2003 (NDA 21-588/S-002) against the approved sNDA 21-335/006 FPL dated April 30, 2003 and to the approval letter dated October 31, 2003.

REVIEW:

August 14, 2003 (FA for 000 and S-001)

The FPL submitted August 14, 2003 is superseded by sNDA 21-588/002 and should be acknowledged and retained.

August 26, 2003 (S-002)

The sponsor has included the CBE changes from sNDA 21-335/S-006 (dated April 30, 2003) into this sNDA 21-588/002. The changes do not include the agreed upon changes detailed in the recent October 31, 2003 approval letter for sNDA 21-335/006. The FDA edited the August 26, 2003 package insert text to include the previously agreed upon CBE changes (as stated in the approval letter 10-31-03) and sent the revised version to Novartis on November 18, 2003 for review and concurrence. On November 24, 2003, Novartis concurred with this FDA version of the package insert for S-002.

The following changes from the CBE approval letter dated October 31, 2003 are as follows:

1. Under **PRECAUTIONS, General** subsection, the following paragraph should be added as the first paragraph:

Dermatologic Toxicities:

Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, have been reported with use of Gleevec. In some cases reported during post-marketing surveillance, a recurrent dermatologic reaction was observed upon rechallenge. Several foreign post-marketing reports have described cases in which patients tolerated the reintroduction of Gleevec therapy after resolution or improvement of the bullous reaction. In these instances, Gleevec was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

2. Under **ADVERSE REACTIONS**, following the **Gastrointestinal Stromal Tumors** subsection, the following one subsection read as follows:

Additional Data From Multiple Clinical Trials

The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare (estimated less than 0.1%) adverse events have been reported during clinical trials of Gleevec. These events are included based on clinical relevance.

Cardiovascular: *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness

Clinical Laboratory Tests: *Infrequent:* blood CPK increased, blood LDH increased

Dermatologic: *Less common:* dry skin, alopecia *Infrequent:* exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction,

purpura *Rare*: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis

Digestive: *Less common*: abdominal distension, gastroesophageal reflux, mouth ulceration *Infrequent*: gastric ulcer, gastroenteritis, gastritis *Rare*: colitis

Hematologic: *Infrequent*: pancytopenia *Rare*: aplastic anemia

Hypersensitivity: *Rare*: angioedema

Infections: *Infrequent*: sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: *Infrequent*: hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased *Rare*: hyperkalemia, hyponatremia

Musculoskeletal: *Less common*: joint swelling *Infrequent*: sciatica, joint and muscle stiffness

Nervous System/Psychiatric: *Less common*: paresthesia *Infrequent*: depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare*: increased intracranial pressure, cerebral edema (including fatalities)

Renal: *Infrequent*: renal failure, urinary frequency, hematuria

Reproductive: *Infrequent*: breast enlargement, menorrhagia, sexual dysfunction

Respiratory: *Rare*: interstitial pneumonitis, pulmonary fibrosis

Special Senses: *Less common*: conjunctivitis, vision blurred *Infrequent*: conjunctival hemorrhage, dry eye, vertigo, tinnitus *Rare*: macular edema, papilledema, retinal hemorrhage

CONCLUSION - RECOMMENDED REGULATORY ACTION:

The submission to NDA 21-588/000 and 001 dated August 14, 2003 is superseded by the planned approval of sNDA 21-588/002 and should be acknowledged and retained after S-002 is approved.

The proposed draft package insert text submitted on August 26, 2003 to NDA 21-588/S-002 should be approved, as amended and agreed upon by Novartis on November 24, 2003 (Reference: November 18, 2003 emailed version of the package insert).

{See appended electronic signature page}

Ann Staten, Regulatory Health Project Manager

{See appended electronic signature page}

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
12/1/03 11:11:40 AM
CSO

Dotti Pease
12/1/03 02:08:44 PM
CSO

Staten, Ann M

From: Johnson, John R
Sent: Monday, November 24, 2003 12:49 PM
To: Cohen, Martin H; Staten, Ann M
Subject: RE: Gleevc label for current NDA 21-588/S-002

I agree.

John

-----Original Message-----

From: Cohen, Martin H
Sent: Monday, November 24, 2003 11:36 AM
To: Staten, Ann M; Johnson, John R
Subject: RE: Gleevc label for current NDA 21-588/S-002

Ann

I found the proposed PI to be acceptable as submitted.

Marty

-----Original Message-----

From: Staten, Ann M
Sent: Monday, November 24, 2003 9:27 AM
To: Cohen, Martin H; Johnson, John R
Subject: Gleevc label for current NDA 21-588/S-002

Marty and John,

I was looking for documentation that you both concurred with the PI as proposed in this supplement but didn't see it in the MO review. As you recall, we did not have a team meeting on labeling so we need something to show our agreement.

Could you please reply to this e-mail for the record that you found the proposal acceptable as it was submitted?

Thanks!
Ann

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-588/S-002

Correspondence



N-000-4M

REPORT

December 20, 2002

ORIGINAL

NDA No. 21-335

RECEIVED
DEC 27 2002
HFD-150 / CDER

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #3067
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC™ (imatinib mesylate)
Capsules

SUBPART H POSTMARKETING
COMMITMENTS

Dear Dr. Pazdur:

Please refer to our original NDA 21-335 for Gleevec™, and the approval letter dated May 10, 2001 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. This approval letter contained several postmarketing commitments. Accelerated approval postmarketing commitment #2 required that Novartis submit interval follow-up information for pivotal studies 102, 109, and 110. We provided the 120-day safety and efficacy update on June 27, 2001. At this time, we would like to provide the final analysis reports for these studies to complete this particular Subpart H commitment.

The attached three documents provide the final clinical study reports (CSRs) for pivotal studies 102, 109 and 110 without post-text supplements and appendices. The post-text supplements and appendices are available upon request.

If you have any questions or comments regarding this matter, please contact me at (862) 778-2282.

Sincerely,

for Robert A. Miranda
Director
Drug Regulatory Affairs

Attachments

Desk Copy via fax (coverletter only): Ann Staten (HFD-150 at 301/594-0498)

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Monday, November 24, 2003 3:46 PM
To: statena@cder.fda.gov
Subject: Gleevec PI

Dear Ann,

This is to confirm that the PI version in the your e-mail of 11/18/03 incorporated all of the CBE changes as agreed and is acceptable.

Thanks
Bob.....

Robert A. Miranda
Drug Regulatory Affairs
Novartis Oncology

phone: +862-778-2282
fax: +973-781-5217

11/24/2003



SUPPLEMENT CORRESP

SE7-002-SNC

October 7, 2003

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #3067
1451 Rockville Pike
Rockville, Maryland 20852-1448

NDA No. 21-588/S-002

GLEEVEC® (imatinib mesylate) Tablet

Amendment to Pending Application:
Efficacy Supplement RECEIVED

OCT 8 2003

DDR-150/ODER

Dear Dr. Pazdur:

Please refer to NDA 21-588/S-002 for Gleevec® Tablet and our previous submission dated August 26, 2003 requesting the conversion of the second line CML indication to full approval status:

As requested on October 2, 2003, by Ann Staten, Project Manager, this efficacy supplement is being amended to provide the following additional documents:

- Patent Information (unchanged from previous original submission for Gleevec under NDA 21-335)
- Debarment Certification
- User Fee Cover Sheet
- Financial Information (from previous original submission under NDA 21-335)

Please note that all relevant information (such as patent information and financial disclosure information) pertaining to NDA 21-588 are unchanged from what was previously submitted for these studies under the original capsule NDA 21-335.

If you have any questions or comments regarding this matter, please contact me at (862) 778-2282.

Sincerely,


for Robert A. Miranda
Director
Drug Regulatory Affairs

Attachments

Desk Copy via fax (coverletter only): Ann Staten (HFD-150 at 301/594-0498)

 **NOVARTIS**
ONCOLOGY

SE7-002

DUPLICATE

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza, Bldg. 105/Rm. 2W200
East Hanover, NJ 07936-1080

Tel (862) 778-2282
Fax (973) 781-5217

RECEIVED

AUG 28 2003

CDR/CDER

RECEIVED

AUG 28 2003

DDR-150/CDER

August 26, 2003

Richard Pazdur, MD
Director
Division of Oncology Drug Products/HFD-150
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #3067
1451 Rockville Pike
Rockville, Maryland 20852-1448

NDA No. 21-588

GLEEVEC® (imatinib mesylate) Tablet

SUBPART H POSTMARKETING
COMMITMENTS

(Completion and Conversion to Full
Approval for 2nd Line CML Indication)

Dear Dr. Pazdur:

Please refer to our original NDA 21-335 for Gleevec® capsule, and the approval letter dated May 10, 2001 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. This accelerated approval letter contained two postmarketing commitments for the accelerated approval of Gleevec capsule for CML patients under NDA 21-335. Please note that these commitments were later transferred to NDA 21-588 (tablet) and renumbered according to FDA letter received on May 15, 2003.

The first postmarketing commitment (#1) was completed with the submission of *final study report for protocol 106* on June 28, 2002. The second postmarketing commitment (#2) was completed with the submission of *safety and efficacy update* on June 27, 2001 and *final analysis report* on December 20, 2002 for studies 102, 109, and 110.

With the full completion of the postmarketing commitments #1 & #2 and according to FDA request, we are submitting the proposed revised Gleevec package insert with updated data for the conversion of 2nd line CML indication to full approval status. All supporting data for the proposed package insert will be cross referenced to previously submitted reports and supplemental NDAs with the exception of three attached appendices for your reference. The changes are annotated with references listed at the end of the proposed package insert.

This submission is being provided in accordance with the guidance for industry titled, *Providing Regulatory Submissions in Electronic Format – NDAs* (January 1999). This includes the three appendices (*PI_Appendix1.pdf*, *PI_Appendix2.pdf*, & *PI_Appendix3.pdf*), the marked-up versions of the PI in Microsoft Word format (*proposed.doc*) and archivable PDF format (*proposed.pdf*), the current and approved labeling for Gleevec in PDF format (*current.pdf*, *approved.pdf*), and the labeling history for Gleevec in PDF format (*history.pdf*)

- **Submission size:** approximately 2.31MB
- **Electronic media:** 1 compact disc
- **Virus scan:** Network Associates Incorporated VirusScan[®] version 4.5.0 (formerly known as the McAfee VirusScan). The submission is virus free.

If you have any questions or comments regarding this matter, please contact me at (862) 778-2282.

Sincerely,



RAM
Robert A. Miranda
Director
Drug Regulatory Affairs

Attachments

Desk Copy via fax (coverletter only): Ann Staten (HFD-150 at 301/594-0498)