

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**NDA 21-588**

**Administrative/Correspondence**

Patent Submission

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<sup>™</sup>
- Active Ingredient(s): imatinib mesylate
- Strength(s): 100mg, 400mg
- Dosage Form: tablets (724M) 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):

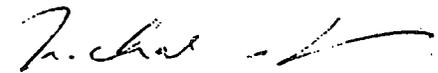
B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

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,

— and Cosmetic Act)  
or  
•  the subject of this application for which approval is being sought.)

Signed:

  
Michael U. LeeTitle: Patent Attorney

Date: January 11, 2001

Telephone Number: 908) 522-6794

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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 # \_\_\_\_\_

Trade Name Gleevec Tablets Generic Name imatinib mesylate

Applicant Name Novartis HFD- 150

Approval Date \_\_\_\_\_

**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 /  /

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

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

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 /  / 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 /  / NO /  /

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

NDA # 21-335 Gleevec Capsules

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 /\_x\_/

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 \_\_\_\_\_  
 !  
 !  
 !  
 !



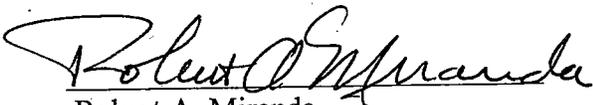
**Gleevec™ (imatinib mesylate) Tablets  
NDA 21-588**

**(New Dosage Form)**

**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.

12/13/02  
Date

  
Robert A. Miranda  
Director  
Drug Regulatory Affairs

## PROJECT MANAGER REVIEW OF LABELING

NDA 21-588

**Drug:** Gleevec (imatinib mesylate) Tablets, 100 and 400 mg

**Applicant:** Novartis Pharmaceutical Corporation

**Submission Date:** December 13, 2002; April 2, 2003

**Receipt Date:** December 16, 2002; April 9, 2003

### BACKGROUND:

This new NDA provides for a Tablet formulation for Gleevec™ (imatinib mesylate).

### DOCUMENTS REVIEWED:

I compared the approved FPL dated January 27, 2003 (submitted to NDA 21-335/S-004 Gleevec Capsules) to the proposed labeling in this new NDA dated December 13, 2002.

I then compared the FPL dated January 27, 2003 (submitted to NDA 21-335/S-004 Gleevec Capsules) to the proposed updated labeling dated April 2, 2003.

### REVIEW:

I found errors in the proposed labeling submitted December 16, 2002 and requested that the sponsor submit a new proposal for labeling to include the most recent FPL in use.

I found that all of the proposed changes to the package insert were correctly identified by the underline and strikethrough feature in the April 2, 2003 submission.

### CONCLUSION - RECOMMENDED REGULATORY ACTION:

In this new NDA, the sponsor has correctly identified all of the proposed changes to the package insert using the underline and strikethrough feature. This NDA should be approved pending Chemistry and Clinical Pharmacology reviews.

          {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.**  
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/s/

-----  
Ann Staten  
4/10/03 07:54:50 AM  
CSO

Dotti Pease  
4/10/03 10:32:43 AM  
CSO

Robert A. Miranda  
Director  
Drug Regulatory Affairs

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936

Tel (862) 778 2282  
Fax (862) 778 5217



# Fax

Attention	<b>Ann Staten Project Manager Division of Oncology Drug Products (HFD-150) Food and Drug Administration</b>
Fax Number	<b>(301) 827-4590</b>
Number of pages	<b>1</b>
Date	<b>April 10, 2003</b>
Concerning	<b>Gleevec NDA No. 21-588 PI edits per e-mail dated 4/3/03</b>

Dear Ann,

This is to confirm that we accept the PI edits provided in your e-mail of April 3, 2003.

Sincerely,

  
Robert A. Miranda

**Staten, Ann M**

---

**From:** Johnson, John R  
**Sent:** Tuesday, April 08, 2003 9:31 AM  
**To:** Staten, Ann M  
**Subject:** Gleevec Tablet Labeling NDA 21588

Ann

As we agreed at the Gleevec team meeting last week, both the Clinical Studies section and the Indications section should be revised to indicate that Gleevec is indicated for treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myelogenous leukemia in chronic phase. Due to an oversight in rushing the accelerated approval out just prior to the Christmas Holidays, the present labeling lacks the phrase "in chronic phase".

Study 106 was the sole basis for accelerated approval of this indication under subpart H. The protocol for study 106 specifically excluded patients not in chronic phase.

Actually Gleevec already has accelerated approval for patients not in chronic phase and this is in the process of being converted to regular approval. Because indications that do not have regular approval bear the caveat that clinical benefit has not been demonstrated or some other appropriate caveat, it is necessary to keep the indications separate.

Appears This Way  
On Original

**Staten, Ann M**

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**From:** Staten, Ann M  
**Sent:** - Thursday, April 03, 2003 3:23 PM  
**To:** Robert Miranda (E-mail)  
**Subject:** NDA 21-588 Gleevec PI edits attached and faxed

**Importance:** High

Hi Bob,

I will fax you the few pages containing the changes and attached is the entire PI with our edits.



NDA PI  
ests) T2002-97 FI

Sincerely,

Ann

*Appears This Way  
On Original*

44 Page(s) Withheld

       § 552(b)(4) Trade Secret / Confidential

       § 552(b)(5) Deliberative Process

✓ § 552(b)(4) Draft Labeling

DUPLICATE

N-000.102



RECEIVED  
APR 09 2003  
CDR/CDER

April 2, 2003

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

NDA No. 21-588

GLEEVEC™ (imatinib mesylate) Tablets

MINOR AMENDMENT TO A PENDING APPLICATION

Dear Dr. Pazdur:

Please refer to our NDA 21-588 for Gleevec™, which provides for a new 100 and 400 mg tablet dosage form. At this time, we would like to provide the original draft labeling revisions using the most currently approved PI (T2002-97, December 2002) for Gleevec capsules (NDA No. 21-335) as the base copy.

The proposed draft PI is provided electronically via compact disk (CD). 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 revision mode versions of the PI in WORD format (proposed.doc) and archivable PDF format (proposed.pdf), the current (current.pdf) and approved (approved.pdf) labeling for Gleevec capsules in PDF format, and the general labeling history for Gleevec in PDF format (history.pdf). The relevant technical details of the electronic portions of this submission are as follows:

- **Submission size:** approximately 976 KB
- **Electronic media:** one 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 submission, please contact me at (862) 778-2282.

Sincerely,

for Robert A. Miranda  
Director  
Drug Regulatory Affairs

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

RECEIVED  
APR 10 2003  
CDR/CDER

**Staten, Ann M**

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**From:** Staten, Ann M  
**Sent:** Tuesday, April 01, 2003 3:19 PM  
**To:** 'robert.miranda@pharma.novartis.com'  
**Subject:** RE: Gleevec Tablet NDA

**Importance:** High

Hi Bob,

The review of the bottle label is complete and we have the follow suggestion for your consideration:

USP General Chapter <1091> Labeling of Inactive Ingredients recommends that all dosage forms should be labeled to cite all the excipients present in the drug product formulation. In accordance with good pharmaceutical practice, we encourage the inclusion of all inactive ingredients in the Gleevec vial labels.

Also, please refer to my comment provided by telephone today that an expiration dating of eighteen months under the recommended storage conditions has been granted, based on available stability data (instead of the requested [ ]).

We will have a few minor edits to convey on the package insert following our internal labeling meeting.

Sincerely,

Ann

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

**From:** robert.miranda@pharma.novartis.com  
[mailto:robert.miranda@pharma.novartis.com]  
**Sent:** Friday, March 14, 2003 12:58 PM  
**To:** statena@cdcr.fda.gov  
**Subject:** Gleevec Tablet NDA  
**Importance:** High

Hi Ann,

Quick Question: Production would like to order the bottle labels in order to facilitate a timely launch after approval, and I was wondering if the review of the labels have been done and if there were any comments.

Thanks,  
Bob.....



N 000720  
DUPLICATE

Novartis Pharmaceuticals Corporation  
Global Regulatory CMC  
One Health Plaza  
East Hanover, NJ 07936-1080

Tel 862 778 8300  
Fax 973 781 6325

March 17, 2003

NDA 21-588  
Gleevec™ (imatinib mesylate) Tablets

Amendment to a Pending Application: Response to FDA Request - Chemistry, Manufacturing and Controls

Richard Pazdur, MD  
Director  
Center for Drug Evaluation and Research  
Division of Oncology Products/HFD-150  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

RECEIVED

MAR 18 2003

HFD-150/ODER

Dear Dr. Pazdur:

Please refer to the above cited application which was submitted to the FDA on 13-Dec-2002. The application provides for a new dosage form (tablets) for our currently approved drug product (Gleevec Capsules, NDA # 21-335). Please also refer to the 05-Mar-2003 e-mail sent by the FDA project manager (Ms. Ann Staten) which requested updated stability data on the proposed tablet dosage form. Please also refer to an additional question concerning tablet branding, which was sent to Novartis (by Ms. Staten) via e-mail on 11-Mar-2003.

Responses to the above cited questions were sent to Ms. Ann Staten via e-mail on Thursday 13-Mar-2003. Novartis is now following up the 13-Mar-2003 e-mail with an official submission to the file, by sending the identical information, which was sent via e-mail on 13-Mar-2003.

Please contact the undersigned at (862) 778-7921 with any questions or comments, which you may have concerning the CMC section of the above cited application. For all other questions, please contact Mr. Robert Miranda at (862) 778-2282 the Drug Regulatory Affairs, Therapeutic Area representative.

Sincerely,

*Robert Clark for John Shramko*

John Shramko  
Manager  
Global Regulatory CMC

Attachments  
Submitted in Duplicate

**Staten, Ann M**

---

**From:** Staten, Ann M  
**Sent:** Tuesday, March 11, 2003 9:51 AM  
**To:** Robert Miranda (E-mail)  
**Subject:** NDA 21-588

**Importance:** High

Dear Bob,

We have the following additional chemistry review request for information:

In the HOW SUPPLIED section of the proposed package insert, the 100 mg tablet is described as debossed with NVR on one side and SA with score on the other side and the 400 mg tablet, with NVR on one side and SL on the other side. However, the 100 mg and 400 mg tablets executed batch records indicated that the tablets of both strengths were debossed with NVR on one side and A on the other side. Please explain.

Thanks,  
Ann

Appears This Way  
On Original

**Staten, Ann M**

---

**From:** Staten, Ann M  
**Sent:** Wednesday, March 05, 2003 10:07 AM  
**To:** Robert Miranda (E-mail)  
**Subject:** Urgent request for N21-588

**Importance:** High

Dear Bob,

We have the following urgent Chemistry review information request. Additional requests will be forthcoming but we would appreciate a response to this important request be expedited.

Please refer to your pending NDA 21-588 providing for Gleevec 100 mg and 400 mg tablets. You have included 9-month long term storage stability data for the drug product tablets in the application. The stability study report was prepared in November, 2002. The data for the 12-month time point should have become available. Please submit the stability data at 12-month for both 100 mg and 400 mg tablets for review. Your timely response will be appreciated.

Sincerely,

Ann

**Staten, Ann M**

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**From:** Staten, Ann M  
**Sent:** - Wednesday, January 29, 2003 11:48 AM  
**To:** Robert Miranda (E-mail)  
**Subject:** NDA 21-588 Gleevec Tablets

**Importance:** High

Dear Bob,

Please refer to your submission dated December 13, 2002 for NDA 21-588 Gleevec scored Tablets, 100 mg and 400 mg. We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 14, 2003 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Please let me know if you have any questions.

Sincerely,

Ann

Staten, Ann M

From: robert.miranda@pharma.novartis.com  
Sent: Wednesday, January 08, 2003 9:35 AM  
To: Staten, Ann M  
Subject: Re: NDA 21-588 Gleevec tablets

Importance: High

Dear Ann,

We can confirm that the correct CFN for the Novartis facility at Lichtstrasse 35, CH-4056 Basel, Switzerland is 9611204 and not [ We appologize for this confusion. Apparently two closely located sites in Basel (each with the different referenced CFNs) were combined recently under CFN 9611204. ]

Thank you,  
Bob.....

"Staten, Ann M" <STATENA@cder.fda.gov> on 01/07/2003 04:04:14 PM

To: "Robert Miranda (E-mail)" <robert.miranda@pharma.novartis.com>  
cc:  
Subject: NDA 21-588 Gleevec tablets

-----  
This part of the message was ENCRYPTED

-----  
This part of the message was SIGNED by Email=statena@cder.fda.gov, ou="This certificate represents a secure server, not an individual.", o=FDA/CDER, cn=FDA/CDER Secure Server (proxy), who is certified by Email=secure-server@CDER.FDA.GOV, ou="This certificate represents a secure server, not an individual.", o=FDA/CDER, cn=FDA/CDER Secure Server

Dear Bob,

We have the following request from our Chemistry Reviewer:

> Our record indicated that the CFN for the Novartis facility at  
> Lichtstrasse 35, CH-4056 Basel, Switzerland is 9611204, not [ ] as  
> specified in your NDA application (page 4-46, vol. 1.2). Please  
> verify.

>  
Thanks!

Ann  
-----  
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# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-588	Efficacy Supplement Type	Supplement Number
Drug: Gleevec (imatinib mesylate)		Applicant: Novartis
RPM: Ann Staten	HFD-150	Phone # 4-0490
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		v <i>Orphan</i>
❖ User Fee Goal Dates		
		8-28-03
❖ Special programs (indicate all that apply)		
Capsules are under accelerated approval regulations. Studies on-going		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input checked="" type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input checked="" type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified
❖ Exclusivity Summary (approvals only)		
		X
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
		X

<b>General Information</b>	
<b>Actions</b>	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
<b>❖ Public communications</b>	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
<b>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings ( <i>indicate dates of reviews and meetings</i> )	X
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
<b>Labels (immediate container &amp; carton labels)</b>	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	X
• Reviews	See CMC review
<b>❖ Post-marketing commitments</b>	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
<b>❖ Outgoing correspondence (i.e., letters, E-mails, faxes)</b>	X
<b>❖ Memoranda and Telecons</b>	N/A
<b>❖ Minutes of Meetings</b>	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	
<b>❖ Advisory Committee Meeting</b>	
• Date of Meeting	N/A
• 48-hour alert	N/A
<b>❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)</b>	N/A

Clinical and Summary Information	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	N/A (Email J)Johnson)
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	N/A
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	N/A – orphan drug designation
❖ Statistical review(s) <i>(indicate date for each review)</i>	Stability review - MRothmann 3/26/03
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	X Anne Zigarek ( <del>Smith</del> )
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) <i>(indicate date for each review)</i>	X 3/31
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	X 3/31
• Review & FONSI <i>(indicate date of review)</i>	N/A
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
Micro (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	N/A
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested copies requested 4/9/03 TBD
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	N/A
❖ CAC/ECAC report	N/A

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

Form Approved: OMB No. 0910-0297  
Expiration Date: February 29, 2004.

# USER FEE COVER SHEET

## See Instructions on Reverse Side Before Completing This Form

A 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 fee rates 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 Net Plaza East Hanover, New Jersey 07936	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER <b>21-588</b>
2. TELEPHONE NUMBER (Include Area Code)  ( 973 ) 781-6940 - Vera Wolsch	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input type="checkbox"/> YES <input checked="" 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 type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:  _____ (APPLICATION NO. CONTAINING THE DATA).
3. PRODUCT NAME  Gleevec™ (imatinib mesylate) Tablets	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.

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 COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?  YES  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  
CDER, HFM-99  
1401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFD-94  
and 12420 Parklawn Drive, Room 3046  
Rockville, MD 20852

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.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Director, Drug Regulatory Affairs,  
Planning & Administration

DATE

12/10/02