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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-335/S-003

Administrative/Correspondence

PROJECT MANAGER REVIEW OF LABELING

NDA 21-335/S-003 (AZ)

NDA 21-588/S-001

Drug: Gleevec (imatinib mesylate), 50 mg and 100 mg Capsules
Gleevec (imatinib mesylate), 100 mg and 400 mg Tablets

Applicant: Novartis Pharmaceutical Corporation

Submission Date: February 27, 2003; April 23, 2003

Receipt Date: February 28, 2003; April 24, 2003

BACKGROUND:

The following is the approved indication section from the approval of NDA 21-588 dated April 18, 2003 which provided for Gleevec (imatinib) Tablets:

Gleevec™ (imatinib mesylate) is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in chronic phase. Follow-up is limited.

Gleevec is also 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. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival in patients with CML blast crisis, accelerated phase or chronic phase after failure of alpha interferon.

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 in GIST is based on objective response rate (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

NDA 21-335/S-003, submission dated February 27, 2003 (AZ) (also submitted on April 23, 2003 as NDA 21-588/S-001 following the approval of a Tablet formulation) provides a response to the NDA 21-335/S-003 approvable letter dated December 20, 2002. The original supplement NDA 21-335/003 provided the results from a dose-escalation, phase 1 study in children with Ph+ CML and acute leukemias. The data included an evaluation of pharmacokinetics with maximum tolerated doses determined for all appropriate age groups, safety and efficacy. The supplement proposed the addition of the subsection **Pediatric** under **Special Populations** in the CLINICAL PHARMACOLOGY section and the addition of **Pediatric Use** section. Additionally, the supplement proposed pediatric

dosing information by adding the subsection **Pediatric Patients** under the **DOSAGE AND ADMINISTRATION** section.

The NDA 21-335/S-003 approvable letter dated December 20, 2002 provided draft text for the package insert to include an indication in pediatrics CML. The supplement received an approvable action due to the lack of a suitable formulation for children (Tablet formulation would remedy the deficiency), the need to reach agreement on an accelerated approval phase 4 commitment and the need to make major labeling revisions.

Additionally, the submission is a partial response to a written request. The sponsor is not requesting exclusivity at this time as the phase 2 study detailed in the September 12, 2000 written request is ongoing at this time and has become the accelerated approval phase 4 commitment.

DOCUMENTS REVIEWED:

A comparison of the proposed labeling submitted on February 27, 2003 was not necessary because the labeling from NDA 21-588 Gleevec Tablets (approved April 18, 2003) was used as the base labeling for this action. I transferred the proposed changes from the February 27, 2003 submission to the approved Tablet package insert and then the document was reviewed by the reviewers.

REVIEW:

Additional changes to the package insert were made following the Division and Office level reviews, thus not matching the proposed labeling text in the December 20, 2003 approvable letter.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

This supplement may be approved with the concurrence of the medical and clinical pharmacology reviewers.

____ *{See appended electronic signature page}*
Ann Staten, Regulatory Health Project Manager

____ *{See appended electronic signature page}*
Dotti Pease, Chief, Project Manager Staff

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/s/

Ann Staten
5/19/03 11:19:13 AM
CSO

Dotti Pease
5/20/03 06:45:05 AM
CSO

Staten, Ann M

From: Staten, Ann M
Sent: Wednesday, January 29, 2003 11:54 AM
To: Robert Miranda (E-mail)
Subject: NDA 21-335/S-003 Gleevec - pediatrics supplement

Importance: High

Dear Bob,

Please refer to the approvable letter for this supplement and the need for an accelerated approval post-marketing study commitment. After further discussion, we are willing to accept either the Gleevec 260 mg/m² or 340 mg/m² dose for the Phase 4 study in children with CML.

Please let me know if there are any questions.

Sincerely,

Ann

APPEARS THIS
ON ORIGINAL

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/s/

Ann Staten
1/29/03 12:01:58 PM
CSO

Staten, Ann M

From: Johnson, John R
Sent: Wednesday, January 29, 2003 11:05 AM
To: Staten, Ann M
Cc: Pazdur, Richard; Shapiro, Alla
Subject: Gleevec P2 Ped CML Protocol

Ann

Rick says to tell Novartis that FDA is willing to accept either the Gleevec 260 mg/m² or 340 mg/m² dose for the Phase 4 study in children with CML.

Thanks
John

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/s/

Ann Staten
1/29/03 12:08:36 PM
CSO

From: kevin.carl@pharma.novartis.com
Sent: Friday, November 22, 2002 11:22 AM
To: STATENA@cder.fda.gov
Subject: Gleevec in Liquid-Final Response

Re: Gleevec NDA 21-335/s-003

Dear Ann,

To complete our response to your October 15, 2002 query regarding which pediatric patients in Study 0103 received Gleevec dispersed in liquid on PK study days, we are providing the following table (attached) which now includes information for all patients in the study.

Since our last update (November 13 e-mail), one additional patient was identified as receiving Gleevec in liquid (Patient No. 707344 (1024)). Therefore, a total of 6 of the 31 patients in Study 103 received Gleevec in liquid.

As the information was not initially captured during the study, the Pediatric Oncology Group (POG) was able to retrospectively obtain the data describing which patients received Gleevec dispersed in liquid during the study.

While the response we received from POG did not explicitly say that the Gleevec was administered dispersed in liquid on PK study days, it is our assumption that the patients received Gleevec in liquid throughout the study.

(See attached file: 112202_Final_Gleevec in Liquid.doc)

Again, thank you for your patience as we conducted this retrospective review. Please let me know if you need anything further on this request. Also, please advise if this response will require formal filing to the sNDA.

Sincerely,

Kevin for Bob

Study 103**Determination of Which Patients Received Gleevec Dispersed in Liquid**

Patient Identifier		Capsules opened/liquid vehicle	Age
POG #	Accession #		
586873	1001	No	16
524845	1002	Yes/cherry syrup	3
140348	1003	No	7
140400	1004	No	17
130302	1005	No	15
140637	1006	No	18
536385	1007	No	14
127816	1008	No	19
573141	1009	No	18
140968	1010	No	15
132222	1011	No	11
131083	1012	No	15
700740	1013	No	10
128144	1014	No	18
600704	1015	Yes/unspecified liquid	12
600754	1016	Yes/water or apple juice	3
702523	1017	No	14
702564	1018	No	4
525413	1019	No	15
703225	1020	No	20
580944	1021	Yes /apple juice	3
704979	1022	Yes/apple juice	3
707888	1023	No	8
707344	1024	Yes/apple juice	8
569959	1025	No	7
685865	1026	No	17
709468	1027	No	17
706912	1028	No	12
711047	1029	No	15
711575	1030	No	15
712334	1031	No	11

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/s/

Ann Staten
12/4/02 09:04:58 AM
CSO

**MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS**

DATE: November 7, 2002 (1pm-1:30pm)

SUBJECT: NDA 21-335/S-003, Gleevec (imatinib mesylate)

Discussion:

⌈

⌋

Dr. Przepiorka was also consulted regarding pediatric CML. Since the disease is similar to adult CML, the adult data can be used to support an indication in children.

Ann Staten, RD
Regulatory Health Project Manager

Peter Bross, MD
Medical Reviewer

Attachment: FDA review questions

Redacted

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/s/

Ann Staten
12/4/02 09:39:48 AM
CSO

Peter Bross
12/4/02 09:48:38 AM
MEDICAL OFFICER

**MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS**

DATE: November 19, 2002 (10am-11am)
SUBJECT: NDA 21-335/S-003, : (imatinib mesylate)

Discussion:

The Division called Novartis to inform Novartis that the Division was

Additionally, the Division informed Novartis that the pediatric supplement (S-003) would not be approved at this time due to the small number of patients at each of the doses tested in the Phase 1 study and lack of sufficient information to determine the recommended dose. Data from the planned Phase 2 study will hopefully provide the needed information.

The FDA clinical pharmacology reviewer shared the concern that the proposed pediatric dose of 260mg/m² and the recommended adult dose of 400mg did not have the same AUCs. Further discussion would take place via written correspondence.

/S/
Ann Staten, RD
Regulatory Health Project Manager

/S/
Peter Bross, MD/ Alla Shapiro, MD
Medical Reviewers

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/s/

Ann Staten
11/26/02 09:06:48 AM
CSO

Peter Bross
12/4/02 11:06:38 AM
MEDICAL OFFICER

Alla Shapiro
12/20/02 02:23:44 PM
MEDICAL OFFICER

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Tuesday, November 05, 2002 4:18 PM
To: statena@cder.fda.gov
Subject: Pediatric Submission

Importance: High

Dear Ann,

In response to your October 15, 2002 query regarding which pediatric patients in Study 0103 received capsules dispersed in liquid on PK study days, we are providing the following response.

As the information was not initially captured during the study, the Pediatric Oncology Group (POG) was able to retrospectively obtain the following data describing which patients received drug dispersed in liquid during the study.

While the response we received from POG did not explicitly say that the drug was administered dispersed in liquid on PK study days, it is our assumption that the patients did receive drug dispersed in liquid throughout the study.

Patient No.	Liquid vehicle
1002	Cherry syrup
1016	Water or Apple juice
1021	Apple juice
1022	Apple juice

Patients 1018 (age 4) and 1025 (age 7) took capsules whole (not dispersed in liquid) despite their young age.

Thank you for your patience as we conducted this retrospective review.

Please let me know if you need anything further on this request. Also, please advise if this response will require formal filing to the SNDA.

Sincerely,

Bob

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/s/

Ann Staten
11/19/02 03:02:32 PM
CSO

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Wednesday, November 13, 2002 12:55 PM
To: statena@cdcr.fda.gov
Subject: S-003 - 50 mg dose

Importance: High



111302 Rationale for
100mg rou...



111302 table1.doc

Hi Ann,

As further follow-up to our teleconference yesterday and regarding the potential concern expressed over the lack of a 50 mg dose, we would like to provide the following information.

We believe the existing data supports a rounding of the pediatric dose to the nearest 100mg and we recommend revising the current draft pediatric dosing information in the PI to reflect this. The rationale for this is provided in the attached document and table.

(See attached file: 111302 Rationale for 100mg rounding.doc) (See attached file: 111302 table1.doc)

Please let me know if the unavailability of a 50 mg dose for pediatric dosing remains a concern. If it does maybe we can have a teleconference to discuss further.

Also let me know if you want me to formally submit this to the SNDA.

Thanks for all your help,
Bob.....

November 13, 2002

Rationale for recommending a rounding of the pediatric dose to the nearest 100 mg:

In the attached Table 1, the following informations are provided :

- the actual body surface area (BSA) for the pediatric patients (age under 18 years) treated on Study 103
- the dose cohort assigned for each pediatric patient in this Phase I study
- the actual dose received during the study
- the dose that would be recommended according to the submitted guidelines for the stage of the disease (240 mg/m² for chronic phase patients, and 360 mg/m² for accelerated phase and blast crisis patients, with a cap in the total dose of 400 mg for chronic phase patients and 600 mg for accelerated phase and blast crisis patients),
- the dose that would have been given with rounding to the nearest 100 mg capsule size
- the absolute difference in milligrams between the recommended dose and rounded dose.

As illustrated by the Table, the difference in milligrams between the calculated, recommended dose for the CML disease stage, and the dose to be delivered, rounding to nearest 100 mg or applying the cap for the total dose, ranges from 1.6 to 48.8 mg imatinib. The difference exceeds 25 mg in only six patients. These data serve to illustrate the degree of variability in the dose, rounding to the nearest 100 mg capsule size, that could be expected in the general pediatric use of imatinib for chronic phase CML and for accelerated phase and blast crisis CML.

In the Phase I study, Study 103, the frequency of side effects was greater among patients in the dose cohorts of 570 mg/m² and above, particularly among accelerated and blast crisis patients. The episodes of dose-limiting toxicity at the 570mg/m² dose were typical of the complication encountered during the mangement of patients with acute leukemias, and thus it was felt that unequivocal evidence for a maximally tolerated dose was not obtained.

Recognizing the potential concern that rounding to the nearest 100 mg capsule size may increase the risk of side effects, we wish to point out that even the children with the largest increase in dose from the calculated dose due to rounding, i.e. 45.8 mg of imatinib, the actual dose given with rounding to the nearest 100 mg capsule size, in mg/m², would still only be 368 mg/m², instead of the recommended 340 mg/m². Such an increase in imatinib by mg/m² leaves the actual dose delivered well within the range of safety, and well below 570mg/m². For large children, the recommendation that the dose be capped at the total dose that is recommended for adults (400 mg for chronic phase, and 600 mg for accelerated phase and blast crisis) provides additional reassurance that pediatric patients will not present a higher risk of side effects due to rounding of the dose to the nearest 100 mg capsule size.

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/s/

Ann Staten
11/14/02 03:57:44 PM
CSO

Staten, Ann M

From: Staten, Ann M
Sent: Thursday, November 14, 2002 9:30 AM
To: Robert Miranda (E-mail)
Subject: FW: S-003 - 50 mg dose

Importance: High

Dear Bob,

Thank you for the information. Data is provided for 26 of the 31 patients enrolled in study 0103. Could you please provide the data for the remaining 5 patients in Table 1.

thanks,
Ann

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

From: robert.miranda@pharma.novartis.com
[mailto:robert.miranda@pharma.novartis.com]
Sent: Wednesday, November 13, 2002 12:55 PM
To: statena@cder.fda.gov
Subject: S-003 - 50 mg dose
Importance: High

Hi Ann,

As further follow-up to our teleconference yesterday and regarding the potential concern expressed over the lack of a 50 mg dose, we would like to provide the following information.

We believe the existing data supports a rounding of the pediatric dose to the nearest 100mg and we recommend revising the current draft pediatric dosing information in the PI to reflect this. The rationale for this is provided in the attached document and table.

(See attached file: 111302 Rationale for 100mg rounding.doc) (See attached file: 111302 table1.doc)

Please let me know if the unavailability of a 50 mg dose for pediatric dosing remains a concern. If it does maybe we can have a teleconference to discuss further.

Also let me know if you want me to formally submit this to the SNDA.

Thanks for all your help,
Bob.....

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/s/

Ann Staten
11/14/02 09:47:41 AM
CSO

**MEMORANDUM OF TELEPHONE CONVERSATION
DIVISION OF ONCOLOGY DRUG PRODUCTS**

DATE: December 12, 2002 (10am)
SUBJECT: NDA 21-335/S-003 Gleevec (imatinib mesylate)

Discussion:

The Division called Novartis to inform Novartis that the Division was planning on an accelerated approval (subpart H) for the pediatric CML supplement (S-003). However, the 50 mg dose capsules is not marketed and Novartis has informed the Agency that they will not market the 50 mg capsule. The 100 mg scored Tablet NDA is to be submitted to the Agency for review on December 13, 2002. The Division informed Novartis that an approvable action would be taken. Deficiencies include: Lack of the 50 mg dosage form and pediatric labeling.

The accelerated approval phase 4 post-marketing commitment would include phase 2 data for the recommended 260mg/m² dose.

Ann Staten, RD
Regulatory Health Project Manager

Alla Shapiro, MD
Medical Reviewers

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/s/

Ann Staten
12/17/02 04:05:55 PM
CSO

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Monday, November 11, 2002 11:54 AM
To: Statena@cder.fda.gov
Subject: Response to Reviewer Questions (Fax 11/6/02)

Importance: High

Dear Ann,

This is a response to your fax of 11/6/02 concerning S-003.

1) Laboratory data (only hemoglobin, WBC and platelets) are listed in Post-text supplement 3 in Listing 10.3-1. No further laboratory data is electronically available.

2) Available bone marrow aspirate differentials (%blasts and %lymphs) are listed in Post-text supplement 3 in Listing 9.2-1.

3) There are no current plans for marketing the 50 mg capsules. A new NDA (21-588) is planned to be filed next month (est. 12/13/02) to provide for 100mg and 400mg tablets, which is intended to replace the 100 mg capsule dosage form. The 100 mg tablet is scored to allow for 50 mg dosing.

4) The system organ class term "investigations" is a general term from our coding dictionary and is defined with preferred terms in Post-text supplement 3 in Listing 10.1-2 (Adverse Events - system organ class preferred terms).

Above table 10-1 of the clinical study report the text reads: During this study, abnormal laboratory values were routinely recorded as AEs as a result of which "investigations" and "blood and lymphatic system disorder" comprised the most frequently reported body systems.

In Post-text supplement 3 in Listing 10.1-1 all belonging preferred terms are listed, e.g. 'Haemoglobin decreased' is in the 'Investigations' category and was seen in >70% of patients.

I hope this response provide the clarification sought.

Please let me know if you need anything further on this.

Thanks
Bob....

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/s/

Ann Staten
11/12/02 11:01:33 AM
CSO



NDA 21-335/S-003

PRIOR APPROVAL SUPPLEMENT

Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Attention: Robert Miranda, Director
Drug Regulatory Affairs

Dear Mr. Miranda:

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

Name of Drug Product: Gleevec™ (imatinib mesylate) Capsules

NDA Number: 21-335

Supplement Number: S-003

Review Priority Classification: Priority (P)

Date of Supplement: June 28, 2002

Date of Receipt: June 28, 2002

This supplement proposes the following change: proposes to update the labeling under the CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION sections based on the results of a phase 1 study in children with Ph+ CML and acute leukemias.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 28, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 28, 2002.

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

Please cite the application number listed above at the top of the first page of any communications

concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-
150
Attention: Division Document Room #3067
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-
150
Attention: Division Document Room #3067
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Ann Staten, Project Manager, at (301) 594-0490.

Sincerely,

{See appended electronic signature page}

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

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/s/

Ann Staten
8/19/02 04:18:07 PM
Signed for Dotti Pease

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, Novartis/cc: Kevin Carl **From:** Ann Staten, Project Manager

Fax: 973-781-5217 **Fax:** 301-827-4590

Phone: 973-781-3758 **Phone:** 301-594-5770

Pages: 1 **Date:** November 6, 2002

Re: NDA 21-335/001 Gleevec/S-003

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

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Dear Bob/Kevin:

We have the following questions:

1. Please explain the absence of hematological data for the pediatric patients with Ph+ CML, ALL and AML, including CBC with differential and platelets count, that should have been obtained prior to the bone marrow aspiration. Can these missing data be retrieved from the patient's medical records?
2. Please explain the absence of differential counts for the bone marrow for the same patient population. Can these missing data be retrieved from the patient's medical records?
3. Please provide your plans for making the 50 mg capsules dose available (i.e., will it be available prior to the availability of the scored 100mg tablets)?
4. Please clarify the category "investigations", listed as adverse events in Table 10-1, Clinical Study Report, v. 7, p.49.

Sincerely,

Ann

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/s/

Ann Staten
11/7/02 03:28:25 PM
CSO

Staten, Ann M

From: kevin.carl@pharma.novartis.com
Sent: Thursday, October 31, 2002 11:47 AM
To: STATENA@cder.fda.gov
Cc: robert.miranda@pharma.novartis.com
Subject: Gleevec NDA 21-335/s-003: Response to FDA Request of October 28, 2002

Dear Ann,

Here is our response to your request of October 28, 2002:

1. Were all patient samples —
— ? If not, do you have stability data for later
times?

An internal audit of the collection vs analysis dates for protocol 103
is
in progress and expected to be completed by Nov 12, 2002. Available
results to date — revealed a longest
interval
from collection to analysis of —

2. —

The samples were stable and the results are given in report
DMPK(US)99-170,
Section 3.7 and Tables 5 and 6 (Study report located in original Gleevec
NDA Volume 35, page 5-92).

3. Please explain your table. What is NR? What is "-"? Did you make two
separate QC samples at each concentration, or are — the
same QC sample?

In the assay, the LOQ was — ng/mL for STI571 and — ng/mL for the
metabolite. The symbol "-" means "not applicable". NR indicates a
failed
injection yielding no result.
The results represent two analyses of the same QC sample. —

—
Please let me know if you need anything further on this request. We
will
provide the results of the internal audit as detailed in the response to
question number 1 as soon as it is available. Also, please advise if
any
of these responses require formal filing to the sNDA.

Thank you,

Kevin for Bob

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/s/

Ann Staten
11/4/02 02:13:18 PM
CSO

Staten, Ann M

From: Staten, Ann M
Sent: Monday, October 28, 2002 3:38 PM
To: 'kevin.carl@pharma.novartis.com'; Staten, Ann M
Cc: robert.miranda@pharma.novartis.com
Subject: RE: Gleevec s-003 : Response to October 15, 2002 Query

Importance: High

Dear Kevin/Bob,

Thank you for the information below. Additionally, we have the following questions.

1. Were all patient samples _____
_____ If not, do you have stability data for later times?
2. _____
3. Please explain your table. What is NR? What is "-"? Did you make two separate QC samples at each concentration, or are _____ the same QC sample?

Thank you,

Ann

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

From: kevin.carl@pharma.novartis.com
[mailto:kevin.carl@pharma.novartis.com]
Sent: Friday, October 25, 2002 10:12 AM
To: STATENA@cder.fda.gov
Cc: robert.miranda@pharma.novartis.com
Subject: Gleevec s-003 : Response to October 15, 2002 Query

Dear Ann,

Here is our response to your questions of October 15th:

The following data are provided regarding stability studies for STI571 and CGP74588 and support the statement that the compounds are

_____ contained in the initial

NDA

volume 35, page 5-122.

(Embedded image moved to file: pic10178.pcx)

2. No pediatric patients in study 03 001 received Gleevec dispersed in liquid.
We are awaiting information regarding patients receiving Gleevec

dispersed in liquid on PK study days for study 0103 from our
colleagues

at the Pediatric Oncology Group (POG). Please note that this
information may not have been initially captured, however we are
attempting to obtain this information retrospectively for all
patients

in study 0103. We expect to have an answer to this request by next
week and apologize for the delay on this response.

Please let me know if you need anything further on this request. Also,
please advise if any of these responses require formal filing to the
sNDA.

Thanks,
Kevin for Bob

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/s/

Ann Staten
10/30/02 10:28:28 AM
CSO

Staten, Ann M

From: kevin.carl@pharma.novartis.com
Sent: Wednesday, October 23, 2002 8:28 AM
To: STATENA@cder.fda.gov
Cc: robert.miranda@pharma.novartis.com
Subject: Response to October 21, 2002 FDA Request: Gleevec 21-335/s-003

Dear Ann,

Re: Gleevec 21-335/s-003

Here is our response to the FDA statistics request of October 21, 2002 received from Dotti Pease. A copy of this e-mail was also sent to Dotti's attention via fax on October 23, 2002 as you requested be done in your absence.

The requested information which was used to calculate survival (i.e. start of treatment, last date of treatment, last date of contact, death cause and date, as well as the censoring indicator) is included in Post-text Listing 7.1-4 which was submitted with the CSR for Study 103 in Post-text supplement 3 of the sNDA. This is located in Volume 8 of the sNDA submission, pages 8-121 through 8-128.

Please let me know if you need anything further on this request. Also, please advise if any of this response will require formal filing to the sNDA.

Thanks,

Kevin Carl for Bob Miranda

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/s/

Ann Staten
10/24/02 10:23:10 AM
CSO

FOOD AND DRUG ADMINISTRATION OFFICE OF DRUG EVALUATION I



DIVISION OF ONCOLOGY DRUG PRODUCTS

HFD-150, 5600 Fishers Lane
Rockville, Maryland 20857

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PHONE: (301)594-5742 FAX: (301) 594-0498

TO: Judith Fast
Fax: 973 781-7177

FROM: Dotti Pease, Project Manager
Phone: (301) 594-5742

Total number of pages, including cover sheet 1

Date: 10-21-02

COMMENTS: Re: your pending sNDA 20-Gleevec 21-335/S003 the 6-28-02 submission, we have the following request from statistics:

For the pediatric study 0103, we were not able to fully replicate your survival results. Please provide for each patient (31 patients in all) the beginning and ending dates for survival, and an indicator for whether the survival was censored.

Thanks

Dotti for Ann

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/s/

Dotti Pease
10/21/02 01:51:35 PM
CSO

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Kevin Carl for Bob Miranda, Novartis **From:** Ann Staten, Project Manager

Fax: 973-781-5217 **Fax:** 301-827-4590

Phone: 973-781-3758 **Phone:** 301-594-0490

Pages: 1 **Date:** October 16, 2002

Re: NDA 21-335/001 Gleevec/S-003

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

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Dear Kevin,

The Medical Reviewer has the following request:

For study 103, please provide the CRF for the following patients (paper or electronically, which ever is easier):

1. patient identified as 1021
2. The electronic database identifies only one patient (1028) as going off study due to the reason "other". However, the final study report (page 61) refers to 2 patients going off study due to the reason "other". Please provide the CRFs for these two patients.
3. Patients with SAEs (approximately 12 patients)

Sincerely,

Ann

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/s/

Ann Staten
10/16/02 10:49:23 AM
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Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Kevin Carl for Bob Miranda, Novartis **From:** Ann Staten, Project Manager

Fax: 973-781-5217 **Fax:** 301-827-4590

Phone: 973-781-3758 **Phone:** 301-594-0490

Pages: 1 **Date:** October 15, 2002

Re: NDA 21-335/001 Gleevec/S-003

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

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Thank you.

Dear Kevin,

The clinical pharmacology reviewer has the following request:

Please provide details regarding:

1. The initial assay validation, in particular about stability studies of STI571 and CGP74588. In the initial NDA volume 35, page 5-122 it is stated that the compounds are ' _____ but no data are provided.
2. Which pediatric patients in study 0103 and 03001 received the Gleevec in liquid on PK study days, and which liquid (water, apple juice).

Sincerely,

Ann

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/s/

Ann Staten
10/15/02 12:36:29 PM
CSO

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Tuesday, October 08, 2002 3:11 PM
To: STATENA@cder.fda.gov
Cc: kevin.carl@pharma.novartis.com
Subject: Re: Gleevec assay questions for s-003

Dear Ann,

Here is our response to your questions of Oct 4th:

_____ is the code used during development for the Test method:
_____ This method
is
described under the code _____ in the Testing Monographs, dated
22-Dec-2000: DP-127_R_1 (in the original NDA, Volume 5, page 4-74)
and
DP-128_R_1 (original NDA, Volume 5, page 4-103). The
corresponding Method Validation Report for this method is provided in
the original NDA, _____ dated 20-Dec-2000 (original NDA,
Volume 5, page 4-128).

Yes, you are correct, _____ do correspond to 20-Mar-00,
26-Apr-00, and 23-May-00, on pages 6-79 to 6-84.

Please let me know if you need anything further on this request. Also,
please advise if any of these responses require formal filing to the
SNDA.

Thanks,
Bob.....

"Staten, Ann M" <STATENA@cder.fda.gov> on 10/04/2002 11:12:32 AM

To: "'robert.miranda@pharma.novartis.com'"
<robert.miranda@pharma.novartis.com>
cc:
Subject: Gleevec assay questions for s-003

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 additional questions.

Thanks,
Ann

> 1. In the "Report of compatibility tests with beverages", the —
assay
> used to measure imatinib is Test method — Does this
correspond
to
> — and if so,
> which one?
> If not, could the sponsor please supply the method and validation
report
> for this assay.
>
> 2. Volume 5 of 21-335 sNDA 003, Appendix 8, presents assay validation
for
> assays DMPK . — (method B from previous correspondence) and
—
> (method C from previous correspondence). On page 6-77, it is stated
that
> — [according to method B]..." Do
> — correspond to 20-Mar-00, 26-Apr-00, and 23-May-00, on
pages
> 6-79-84?
>
>

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/s/

Ann Staten
10/8/02 03:15:51 PM
CSO

Staten, Ann M

From: Staten, Ann M
Sent: Friday, October 04, 2002 11:13 AM
To: 'robert.miranda@pharma.novartis.com'
Subject: Gleevec assay questions for s-003

Importance: High

Dear Bob,

We have the following additional questions.

Thanks,
Ann

1. In the "Report of compatibility tests with beverages", the _____ assay used to measure imatinib is Test method _____ Does this correspond to one of the three imatinib assays used for patient samples, and if so, which one? If not, could the sponsor please supply the method and validation report for this assay.
2. Volume 5 of 21-335 sNDA 003. Appendix 8, presents assay validation for assays DMPK _____ (method B from previous correspondence) and _____ (method C from previous correspondence). On page 6-77, it is stated that "_____ [according to method B]..." _____ correspond to 20-Mar-00, 26-Apr-00, and 23-May-00, on pages 6-79-84?

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/s/

Ann Staten

10/7/02 02:44:33 PM

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PROJECT MANAGER REVIEW OF LABELING

NDA 21-335/S-003

Drug: Gleevec (imatinib mesylate), 50 and 100 mg

Applicant: Novartis Pharmaceutical Corporation

Submission Date: June 28, 2002

Receipt Date: June 28, 2002

BACKGROUND:

Gleevec is approved for the treatment of patients with Philadelphia positive (Ph+) chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also approved for the treatment of patients with kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST).

The current supplement S-003 provides the results from a dose-escalation, phase 1 study in children with Ph+ CML and acute leukemias. The data includes an evaluation of pharmacokinetics with maximum tolerated doses determined for all appropriate age groups, safety and efficacy. This supplement proposes the addition of the subsection **Pediatric** under **Special Populations** in the CLINICAL PHARMACOLOGY section and the addition of **Pediatric Use** section. Additionally, this supplement proposes pediatric dosing information by adding the subsection **Pediatric Patients** under the DOSAGE AND ADMINISTRATION section.

This supplement is a partial response to a written request. The sponsor is not requesting exclusivity at this time as the phase 2 study detailed in the September 12, 2000 written request is ongoing at this time.

DOCUMENTS REVIEWED:

I compared the approved FPL dated March 6, 2002 to the proposed labeling in S-003 dated June 28, 2002.

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. This supplement may be approved with the concurrence of the medical and clinical pharmacology reviewers.

___ *{See appended electronic signature page}* ___
Ann Staten, Regulatory Health Project Manager

___ *{See appended electronic signature page}* ___
Dotti Pease, Chief, Project Manager Staff

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/s/

Ann Staten
9/25/02 04:32:21 PM
CSO

Dotti Pease
9/26/02 07:10:21 AM
CSO

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Wednesday, September 18, 2002 3:21 PM
To: STATENA@cder.fda.gov
Subject: RE: Pk Assays - clin. pharm. information request

Importance: High

Hi Ann,

Sorry for the delay, but several of our Clin Pharm people were away.
Here
is the identification for the three patients requested by the Clin Pharm
Reviewer where method B was used in Study 103:

pog# 140348
pog# 140400
pog# 130302

Thanks,
Bob.....

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/s/

Ann Staten
9/19/02 10:04:09 AM
CSO

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Friday, September 06, 2002 12:39 PM
To: STATENA@cder.fda.gov
Subject: Re: Pk Assays - clin. pharm. information request

Importance: High

Dear Ann,

Here is our response to the Clinical Pharmacology requests in your e-mail of 8/28/02. Sorry for the delay but it had to be reviewed by our Clinical Pharm staff in Basle and US.

Item 1
The method validation reports are available as listed in table 2. The method dated 7/21/00 is a typographical error and should be listed as 7/25/00 (method B)

Item 2:
Table 1 lists the methods used for each of the three studies. Table 2 provides additional details on the method references.

Table 1

Study	Methods used
3 001	B
103 B was used)	C (with the exception of 3 patients where method

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

dated
7/25/00.

2. It is unclear from the study reports which assay(s) was/were used in which study. Please provide a table that lists each clinical PK study and the assay(s) used in each study.

0103:
03 001:

3. If more than one assay was used per study, please provide the cross-validation report.

Thank you.

Ann M. Staten, RD
LCDR, U.S. Public Health Service
Senior Regulatory Project Manager
FDA/Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
5600 Fischers Lane
Rockville, MD 20857
301.594.0490 (phone)
301.827.4590 (fax)

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/s/

Ann Staten
9/9/02 02:28:42 PM
CSO

Staten, Ann M

From: Staten, Ann M
Sent: Friday, August 16, 2002 3:11 PM
To: 'robert.miranda@pharma.novartis.com'
Subject: sNDA 21-335/003 . PK assay for Studies 103

Importance: High

Dear Bob,

We have the following request from the Clinical Pharmacology Reviewer:

Please submit the following information:

Study number, pt ID, date of sample analysis, analytical method used, analytical method validation

If this data is available in the electronic data sets, could you let me know where to find them ?

Please let me know if there are any questions.

Thanks,
Ann

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/s/

Ann Staten
8/19/02 08:39:18 AM
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