CENTER FOR DRUG EVALUATION AND RESEARCH

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 I 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
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
5/19/03 11:19:13 AM
CSO

Dotti Pease
5/20/03 06:45:05 AM
CSO
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Staten
1/29/03 12:01:58 PM
CSO
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Ann Staten
1/29/03 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

<table>
<thead>
<tr>
<th>Patient Identifier</th>
<th>Capsules opened/liquid vehicle</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>POG #</td>
<td>Accession #</td>
<td></td>
</tr>
<tr>
<td>586873</td>
<td>1001</td>
<td>No</td>
</tr>
<tr>
<td>524845</td>
<td>1002</td>
<td>Yes/cherry syrup</td>
</tr>
<tr>
<td>140348</td>
<td>1003</td>
<td>No</td>
</tr>
<tr>
<td>140400</td>
<td>1004</td>
<td>No</td>
</tr>
<tr>
<td>130302</td>
<td>1005</td>
<td>No</td>
</tr>
<tr>
<td>140637</td>
<td>1006</td>
<td>No</td>
</tr>
<tr>
<td>536385</td>
<td>1007</td>
<td>No</td>
</tr>
<tr>
<td>127816</td>
<td>1008</td>
<td>No</td>
</tr>
<tr>
<td>573141</td>
<td>1009</td>
<td>No</td>
</tr>
<tr>
<td>140968</td>
<td>1010</td>
<td>No</td>
</tr>
<tr>
<td>132222</td>
<td>1011</td>
<td>No</td>
</tr>
<tr>
<td>131083</td>
<td>1012</td>
<td>No</td>
</tr>
<tr>
<td>700740</td>
<td>1013</td>
<td>No</td>
</tr>
<tr>
<td>128144</td>
<td>1014</td>
<td>No</td>
</tr>
<tr>
<td>600704</td>
<td>1015</td>
<td>Yes/unspecified liquid</td>
</tr>
<tr>
<td>600754</td>
<td>1016</td>
<td>Yes/water or apple juice</td>
</tr>
<tr>
<td>702523</td>
<td>1017</td>
<td>No</td>
</tr>
<tr>
<td>702564</td>
<td>1018</td>
<td>No</td>
</tr>
<tr>
<td>525413</td>
<td>1019</td>
<td>No</td>
</tr>
<tr>
<td>703225</td>
<td>1020</td>
<td>No</td>
</tr>
<tr>
<td>580944</td>
<td>1021</td>
<td>Yes/apple juice</td>
</tr>
<tr>
<td>704979</td>
<td>1022</td>
<td>Yes/apple juice</td>
</tr>
<tr>
<td>707888</td>
<td>1023</td>
<td>No</td>
</tr>
<tr>
<td>707344</td>
<td>1024</td>
<td>Yes/apple juice</td>
</tr>
<tr>
<td>569959</td>
<td>1025</td>
<td>No</td>
</tr>
<tr>
<td>685865</td>
<td>1026</td>
<td>No</td>
</tr>
<tr>
<td>709468</td>
<td>1027</td>
<td>No</td>
</tr>
<tr>
<td>706912</td>
<td>1028</td>
<td>No</td>
</tr>
<tr>
<td>711047</td>
<td>1029</td>
<td>No</td>
</tr>
<tr>
<td>711575</td>
<td>1030</td>
<td>No</td>
</tr>
<tr>
<td>712334</td>
<td>1031</td>
<td>No</td>
</tr>
</tbody>
</table>
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
12/4/02 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                    Peter Bross, MD
Regulatory Health Project Manager  Medical Reviewer

Attachment: FDA review questions
Redacted 4

pages of trade

secret and/or

confidential

commercial

information
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
12/4/02 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
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.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Liquid vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1002</td>
<td>Cherry syrup</td>
</tr>
<tr>
<td>1016</td>
<td>Water or Apple juice</td>
</tr>
<tr>
<td>1021</td>
<td>Apple juice</td>
</tr>
<tr>
<td>1022</td>
<td>Apple juice</td>
</tr>
</tbody>
</table>

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

/s/
Ann Staten
11/19/02  03:02:32  PM
CSO
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.................
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 management 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.
Redacted / 

pages of trade secret and/or confidential commercial information
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ann Staten
11/14/02 03:57:44 PM
CSO
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
Sent: Wednesday, November 13, 2002 12:55 PM
To: statena@cdr.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.................
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
---------------------
Ann Staten
11/14/02 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
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
12/17/02 04:05:55 PM
CSO
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....
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-----------------------
Ann Staten
11/12/02 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
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
8/19/02 04:18:07 PM
Signed for Dotti Pease
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-------------------
Ann Staten
11/7/02 03:28:25 PM
CSO
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
-------------------
Ann Staten
11/4/02 02:13:18 PM
CSO
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
To: STATENA@cdrf.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
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
10/30/02 10:28:28 AM
CSO
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
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
10/24/02 10:23:10 AM
CSO
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dotti Pease
10/21/02 01:51:35 PM
CSO
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
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
10/16/02 10:49:23 AM
CSO
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
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
10/15/02 12:36:29 PM
CSO
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>
c:
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
> 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?
>
> ----------------------------------------
----------------------------------------

2
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
10/8/02 03:15:51 PM
CSO
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?
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
10/7/02 02:44:33 PM
CSO
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

APPEARS THIS WAY ON ORIGINAL
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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

Dotti Pease
9/26/02 07:10:21 AM
CSO
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.............
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
9/19/02 10:04:09 AM
CSO
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods used</th>
</tr>
</thead>
<tbody>
<tr>
<td>3001</td>
<td>B</td>
</tr>
</tbody>
</table>

---

1
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)

-----------------------------------
-----------------------------------
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
9/9/02 02:28:42 PM
CSO
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
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
8/19/02 08:39:18 AM
CSO