CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-335/S-004

Correspondence

973 781 5217 P.01
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS
ONCOLOGY

NATURE SAVER™ FAX MEMO 01616	Date 19 DEC 02	No. of pages ▶ 4
To ANN STATEN	From ROBERT MIRANDA	
Co./Dept. FDA HFD-150	Co. NOVARTIS	
Phone #	Phone # 862 778 2282	
Fax # 301-594-0498	Fax # 862 778-5217	

~~301-827-4590~~ TEMP. NOT WORKING

December 19, 2002

NDA No. 21-335 / S-004

GLEEVEC ™ (Imatinib mesylate) Capsules

Draft Promotional Materials: Accelerated NDA Review

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

Dear Dr. Pazdur:

Please refer to our supplemental NDA 21-335 / S-004 dated June 28, 2002, which provides a new indication for Gleevec™ in the treatment of patients with newly diagnosed Philadelphia positive chronic myeloid leukemia (CML). We understand that this sNDA is being reviewed under the accelerated approval regulations. Therefore, at this time we would like to provide copies of draft promotional materials to be used during the first 120-day postapproval period, in accordance to 21 CFR 314.550. The only promotional piece not being submitted at this time is the which DDAMC agreed in a telcon on November 19, 2002 to accept in January 2002, due to the recent notification of the accelerated review status.

This submission was prepared in accordance with the FDA guidance to industry entitled "Accelerated Approval Products – Submission of Promotional Materials". One copy of each promotional material described below is provided with this letter and two copies are being sent directly to DDMAC. For your convenience, we have also enclosed a copy of the draft package insert as agreed with the Division on December 13, 2001 (Ref 24). As you know, this version of the PI is more mature than submitted in our original sNDA, but it is still draft and under review. We recognize that these materials will need to be updated to reflect the final package insert for this new indication.

To facilitate your review, all promotional pieces are referenced as appropriate. All references are provided in a single collection and specific text in the references is highlighted.

The following is a brief description of the three draft promotional pieces enclosed in order of preference from a review timing perspective. In all cases a color copy and an annotated copy is enclosed for review.

1.

2.

3.

This submission consists of one volume.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

RAM:vh
enclosures

Desk Copy (2): Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
Room 8B-45 (HFD-42)
5600 Fishers Lane
Rockville, Maryland 20857
Attention: Joseph A. Grillo

Desk Copy (letter only): A. Staten, HFD-150 (via fax 301/827-4590)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date March 31, 2003
See OMB Statement on page 2

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICATION INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
NOVARTIS PHARMACEUTICALS CORPORATION	12/19/02
TELEPHONE NO. (*Include Area Code*)	FACSIMILE (FAX) Number (*Include Area Code*)
(973) 781-2282	(973) 781-5217
APPLICANT ADDRESS (*Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued*)	AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
59 Route 10 East Hanover, New Jersey 07936-1080	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (*if previously issued*) 21-335

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
imatinib mesylate	Gleevec™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)

CODE NAME (*If any*) STI571, CGP57148B

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION
Capsules	50 and 100 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Chronic myeloid leukemia (CML)

APPLICATION INFORMATION

APPLICATION TYPE
(*check one*)

☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (*check one*)
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
DRAFT PROMOTIONAL MATERIALS (ACCELERATED NDA REVIEW)

PROPOSED MARKETING STATUS (*check one*) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

This application contains the following items: (*Check all that apply*)	
	1. Index
	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g , 21 CFR 314 50 (d)(1); 21 CFR 601.2)
	B. Samples (21 CFR 314 50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e g., 21 CFR 314.50 (e)(2)(i), 21 CFR 601.2)
	5 Nonclinical pharmacology and toxicology section (e g., 21 CFR 314.50 (d)(2); 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3); 21 CFR 601 2)
	7 Clinical Microbiology (e.g , 21 CFR 314.50 (d)(4))
	8 Clinical data section (e g., 21 CFR 314.50 (d)(5), 21 CFR 601.2)
	9 Safety update report (e g., 21 CFR 314.50 (d)(5)(vi)(b); 21 CFR 601.2)
	10 Statistical section (e.g., 21 CFR 314.50 (d)(6), 21 CFR 601.2)
	11. Case report tabulations (e g., 21 CFR 314.50 (f)(1), 21 CFR 601.2)
	12 Case report forms (e g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C 355 (b) or (c))
	14 A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. Financial Information (21 CFR Part 54)
x	20. OTHER *(Specify)* DRAFT PROMOTIONAL MATERIALS (ACCELERATED NDA REVIEW)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314 97, 314.99, and 601.12
6. Regulations on Reports in 21 CFR 314.80, 314 81, 600 80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowlegde are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert A. Miranda	Robert A. Miranda,Director Drug Regulatory Affairs	12/19/02

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
59 Route 10 East Hanover, New Jersey 07936-1080	(973) 781-2282

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

epartment of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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

Tel 973 781 8300

NOVARTIS
ONCOLOGY

ORIGINAL

SUPPL NEW CORRESP

SB1-004 (C)

RECEIVED
NOV 2 2 2002
HFD-150 / CDER

November 20, 2002

NDA No. 21-335/S-004

GLEEVEC ™ (imatinib mesylate) Capsules

Draft Promotional Materials (Accelerated NDA Review)

RE: '

Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications (HFD-42)
Food and Drug Administration
5600 Fishers Lane, Room 8B-45
Rockville, Maryland 20857

Dear Dr. Grillo:

Reference is made to our NDA 21-335/S-004, dated June 28, 2002 for Gleevec™ (imatinib mesylate) capsules, which provides a supplement to add a new indication for the treatment of patients with newly diagnosed Philadelphia positive chronic myeloid leukemia (CML). As you know, this SNDA is being reviewed under the accelerated approval regulations of subpart H. At this time and in accordance with 21 CFR 314.640, we would like to

The referenced SNDA currently under review by the Division of Oncologic Drug Products has an action date of December 28, 2002. The attached draft
are intended to be displayed at the ASH Convention on December 6, 2002. Both panels are identical except the one with the non-US tradename spelling of "Glivec®" will be displayed at the Novartis International booth. At the bottom of this panel we indicate that "Glivec" is marketed in the US as "Gleevec™".

Additional promotional materials are pending and will be submitted to you by once we get a mutually agreed PI (expected early December).

We believe we meet your requirements for in that Gleevec is not a "black box" product and we do not mention what the new indication is.

Since we just learned yesterday, that this SNDA was being reviewed under the accelerated provisions of subpart H, we would appreciate your assistance in reviewing this before December 5th, so that we can use it at the ASH Convention.

This submission consists of one volume.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Thank you in advance for your consideration to review this as soon as possible under the given circumstances.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

RAM:vh
enclosures

Desk Copy: 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

Coverletter with enclosures via fax: Dr. Joseph Grillo (HFD-42 at 301/594-6771)

One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS
ONCOLOGY

DUPLICATE

SE1-004 (C)

NOV 2 2002

November 21, 2002

NDA No. 21-335 / S-004

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

GLEEVEC ™ (imatinib mesylate) Capsules

GENERAL CORRESPONDENCE

OTHER: PI Dose Adjustment Clarification (Table 7)

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-004 for Gleevec™ (imatinib mesylate), which provides data for the treatment of patients with newly diagnosed Philadelphia positive CML. At this time we would like to provide a clarification to Table 7 of the current package insert (Dose Adjustments for Neutropenia and Thrombocytopenia). If you agree with our clarification and the proposed minor revision, we would appreciate your consideration to make this PI change as part of the current labeling supplement under review.

The current package insert for Gleevec contains the Table 7 (Attachment 1), in which guidance is provided for the adjustment of dosing in the event of abnormal neutrophil and platelet counts. This dose adjustment scheme was originally generated based on data and experience in CML. After the approval of Gleevec for the GIST indication this table was modified to incorporate a similar scheme for GIST patients experiencing these adverse events. It has come to our attention that the way this information is provided for GIST dosing adjustments is not entirely clear. At the present time we do not feel that this presents a safety risk for these patients, but we would like this opportunity to amend the recommendations.

As it currently reads, Table 7 proposes that GIST patients receiving 400 mg daily with an ANC <1.0 x 10^9/L and/or platelet count of <50 x 10^9/L suspend dosing until an appropriate resolution, at which time reinstitution of the same dose is allowed. On the other hand, the table also reads that GIST patients receiving 600 mg daily only reduce their dose if they reach an ANC <0.5 x 10^9/L and/or platelet count <10 x 10^9/L, which are much lower and more severe toxicities.

Since the approved starting dose for Gleevec in treating GIST is 400 or 600 mg, the above described different thresholds for reducing the doses appears inconsistent. Our proposal to clarify this dose reduction recommendation is a minor revision to this table as provided in Attachment 2.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh
enclosures

Desk Copy via fax: A. Staten (301-827-4590)

East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS
ONCOLOGY

DUPLICATE

SUPPL-NEW CONCEP

SE1-004 (C)

November 20, 2002

NDA No. 21-335 / S-004

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

GLEEVEC ™ (imatinib mesylate) Capsules

GENERAL CORRESPONDENCE

OTHER: Rewording of Proposed Indication & Request to Extend Submission Deadline for Promotional Materials

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-004 for Gleevec™, which provides data for the treatment of patients with newly diagnosed Ph+ CML. Reference is also made to our teleconference held on November 19, 2002 which provided a review status of this SNDA. As a follow-up to the teleconference, we would like to provide alternative indication wording and request an extension of the deadline for submission of promotional materials required under the subpart H requirements for accelerated approval.

I. INDICATION

During the November 19th teleconference you informed Novartis that S-004 would now be considered a subpart H drug subject to the accelerated approval regulations. Since the new indication and the previously approved indications are now all considered under these accelerated approval regulations, we would like to consolidate the indication wording into one sentence as follows:

Original Proposed Text: (underlines and cross-outs reflect changes from currently approved wording)

[redacted]

New Proposed Text:

[redacted]

OR (without revision marks)

[redacted]

II. Filing of Promotional Materials

We understand that new indications approved under the accelerated approval regulations require that all promotional materials be pre-submitted to DDMAC for review prior to its approval. We further understand that after approval no new promotional pieces can be submitted for 120 days.

Due to the short notice of being informed that this pending indication was subject to the accelerated approval regulations we would like to request an extension to this pre-submission deadline for one promotional piece. This consists of which will be available for pre-submission on or before January 31, 2002. All other materials intended for use during the first 120 days will be ready for submission in December prior to the anticipated approval of this new indication. Your consideration in this one exemption would be greatly appreciated.

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/vh

Desk Copy: Joseph A. Grillo, Pharm.D.
Regulatory Review Officer
Division of Drug Marketing, Advertising and Communications (HFD-42)
Food and Drug Administration
5600 Fishers Lane, Room 8B-45
Rockville, Maryland 20857

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

Tel 973 781 8300

NOVARTIS
ONCOLOGY

SE1-004
BH

September 4, 2002

NDA No. 21-335

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

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-004)

OTHER: Request for Information

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-004 for Gleevec™ (imatinib mesylate, formerly STI571), which provides data for the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML). Reference is also made to a verbal request on July 25, 2002 from Ms. Ann Staten for an electronic version of the following study protocol, including all amendments:

> Study 106: A phase III study of STI571 versus Interferon-α (IFN-α) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP).

The above protocol (including all amendments) is provided on the attached CD in accordance with current FDA electronic submission guidelines. Please note that while this part of the report is bookmarked, there is no hyperlinking due to the elimination of all appendices and post-text tables, etc. The overall size of the electronic file contained is approximately 11 MB. The virus scanning software used for the submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/da

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

One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS
ONCOLOGY

SE1-004
BH

August 30, 2002

NDA No. 21-335

Electronic Document Room Staff
Food and Drug Administration
Center for Drug Evaluation and Research
12229 Wilkens Avenue
Rockville, Maryland 20852

Attn: Richard Pazdur, MD
Director
Division of Oncology Drug
Products/HFD-150

GLEEVEC ™ (imatinib mesylate)
Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-004)

OTHER: CRT Files

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-004 for Gleevec™ (imatinib mesylate, formerly STI571), which provides data for the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML). Reference is also made to a verbal request on July 29, 2002 from Ms. Ann Staten for SAS file "a_effsbj".

This submission provides two updated CDs containing the entire Clinical Report Tabulation (CRT) files including the missing SAS file "a_effsbj". This single file was inadvertently not copied during the creation of the original CDs for this SNDA. We have checked the dataset folder and confirmed that no other files are missing. Additional steps are being taken to prevent a similar occurrence in future submissions.

The attached CDs are submitted in accordance with current FDA electronic submission guidelines. The virus scanning software used for the submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

/da

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

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

Tel 973 781 8300

NOVARTIS

SE1-004-BB

SUPPLEMENT AMENDMENT

August 26, 2002

NDA No. 21-335

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

GLEEVEC ™ (imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION (S-004)

OTHER: Request for Information

DUPLICATE

Dear Dr. Pazdur:

Please refer to our Supplemental NDA 21-335 / S-004 for Gleevec™ (imatinib mesylate, formerly STI571), which provides data for the treatment of patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (CML) Reference is also made to a verbal request on July 25, 2002 from Ms. Ann Staten for an electronic version of the narrative portion for the following study report:

> Study 106: A phase III study of STI571 versus Interferon-α (IFN-α) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP).

The narrative portion of the above report is provided on the attached CD in accordance with c[illegible] electronic submission guidelines. Please note that while this part of the rep[illegible]t, there is no hyperlinking due to the elimination of all appendices an[illegible]es, etc. The overall size of the electronic file contained is approximately 3.11 MB. The virus scanning software used for the submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

If you have any questions or comments regarding this submission, please contact me at (973) 781-2282.

Sincerely

Robert A Miranda

Robert A Miranda
Director
Drug Regulatory Affairs

vh

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

DUPLICATE

One Health Plaza
East Hanover, NJ 07936-1080

Tel 973 781 8300

NOVARTIS
ONCOLOGY

SUPPL NEW CORRESP
DEC 2004
(C)

August 15, 2002

RECEIVED
AUG 16 2002
HFD-150 / CDER

NDA No. 21-335/S-004

Richard Pazdur, MD
Director
Division of Oncology Drug Products
(HFD-150)
Food and Drug Administration
Woodmont FDA Oncology Drug Group
Attn: Document Control Room #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

GLEEVEC ™ (imatinib mesylate) Capsules

OTHER: Letter of Authorization for Foreign Government

Dear Dr. Pazdur:

On behalf of Novartis Pharmaceuticals Corporation, the sponsor of the above referenced regulated product, New Drug Application (NDA) and supplemental NDA/S-004, I authorize the sharing of certain information by the United States Food and Drug Administration (FDA) to the following foreign government regulatory health authority, solely for the purpose of reviewing the registration application for Gleevec™ capsules (also known in some countries as Glivec®) in the treatment of patients with newly diagnosed chronic myeloid leukemia (CML).

Australia
Dr. Jamie McGinness
TGA Delgate
Clinical Evaluation Section 4
Therapeutic Goods Administration
Drug, Safety & Evaluation Branch
PO Box 100
WODEN ACT 2602
Australia

Telephone: +61 2 6232 8113
Fax: +61 2 6232 8140
e-mail: James.McGinness@health.gov.au

I understand that the information may contain confidential commercial or financial information or trade secrets within the meaning of 18 U.S.C.§331(j), and 5 U.S.C. §552(b)(4) and that is exempt from public disclosure. I agree to hold FDA harmless for any injury caused by FDA's

sharing the information to the above mentioned foreign government regulatory health authority.

Information to be shared:

- Supplemental NDA 21-335/S-004 dated June 28, 2002 and any subsequent amendments
- Pre-decisional and final review information or other non-public information as it relates to the review of this supplemental NDA

Authorization is given to the information being sent without deletion of confidential commercial or trade secret information. As indicated by my signature, I am the authorizing official for the sponsor and my full name, title, address, telephone number, and facsimile number are set out below for verification. I am sending a copy of this letter to the foreign government regulatory agency identified above, with which FDA may share the information.

Sincerely,

Robert A. Miranda

Robert A. Miranda
Director
Drug Regulatory Affairs

973/781-2282 (telephone)
973/781-5217 (fax)

cc: Foreign government health agency in Australia as listed above

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-335/S-004

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-004

Review Priority Classification: Priority (P)

Date of Supplement: June 28, 2002

Date of Receipt: June 28, 2002

This supplement proposes the following change: treatment of newly diagnosed Ph+ CML patients.

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}

/S/

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 03:43:25 PM
Signed for Dotti Pease

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NOVARTIS
ONCOLOGY

NDA NO 21-335 REF NO 004
INFO NUMBER SE1-004

June 28, 2002

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Wilkins Avenue
Rockville, MD 20852-1833

NDA No. 21-335 / S-002 4x per CSO

GLEEVEC ™ (imatinib mesylate) Capsules

EFFICACY SUPPLEMENT – CHANGES REQUIRING PRIOR APPROVAL

NEW INDICATION: Newly Diagnosed CML

Dear Sir/Madam: -

Reference is made to our NDA 21-335 for Gleevec™ (imatinib mesylate, formerly STI571 and CGP57148B) Capsules 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). At this time Novartis Pharmaceuticals Corporation submits a supplemental New Drug Application (SNDA) for the use of Gleevec in a new indication for the treatment of patients with newly diagnosed Ph+ CML.

As you know, Gleevec is a small molecule inhibitor of the Bcr-Abl tryosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Gleevec was approved on May 10, 2001 in late chronic and advanced stages of Ph+ CML. The current new indication is a logical development step to treat an earlier form of Ph+ CML.

This SNDA consists of the results from a phase III, multinational, two-arm randomized study (STI571A 0106) comparing the efficacy and safety of Gleevec versus interferon (IFN) plus cytarabine (Ara-C), in newly diagnosed Ph+ CML patients. This study in over 1,100 patients fully adheres to GCP guidelines and is closely monitored by Novartis personnel for compliance to the protocols and procedures described therein.

This SNDA has been prepared in a manner that is consistent with existing regulations relevant guidelines and understandings that were reached at our EOP2 and pre-SNDA meetings. A copy of the relevant correspondence related to these meetings is located in Volume 1 of the SNDA.

The Gleevec formulation is the same as previously approved for CML and GIST. The dose and schedule are similar. Therefore, there is no technical information in this SNDA. The CMC section is limited to a categorical exclusion for an environmental assessment in accordance with 21 CFR Part 25.31(b). For these reasons, the PAI requirements are not applicable and no certified copy of Section 3 is being provided to our district office.

As there have been no changes in dosage form, strengths, or manufacturing procedure, and the daily recommended doses remain unchanged, all of the pertinent preclinical safety data was submitted in the original NDA dated February 27, 2001. Since the original submission, the reproductive toxicity study program has been completed with an oral pre- and postnatal development study in rats [Study no. 017021]. Also, the metabolism of imatinib in milk and plasma after single peroral administration of ^{14}C-labeled STI571 to lactating rats has been investigated [Study no. 00-097-01]. Both of these preclinical studies are included in this SNDA.

In support of the expected longer treatment duration of newly diagnosed CML patients compared to the currently approved patient population, a carcinogenicity study program has been initiated and final study reports should be available by mid 2005. This program and its timelines were reviewed and agreed with the FDA in a Special Protocol Review Request (IND [redacted] Serial Nos. 467 & 468) and in the pre-SNDA communication.

Electronic Sections

As proposed in our pre-SNDA correspondence of March 2002, this submission includes the following SNDA components in electronic form only, and is contained on three CD-ROMs that are located in Volume E1 of the paper submission:

Item 2: Labeling
Item 11: Case Report Tabulations
Item 12: Case Report Forms

The overall size of the electronic file contained in Volume E1 is approximately 1.44 GB. The virus scanning software used for the submission is Network Associates VirusScan version 4.0.3a (formerly known as McAfee VirusScan).

Request for Priority Review
Gleevec is intended to treat newly diagnosed CML, which is a serious and life-threatening disease. The clinical study demonstrates that Gleevec provides unprecedented efficacy in this patient population over existing standard therapy. It is a convenient oral mediation that is generally well tolerated and administered on an outpatient basis.

Given this profile, Novartis believes that this application qualifies for priority review according to CDER's MAPP 6020.3, in that Gleevec offers a significant improvement in the treatment of newly diagnosed CML, a serious and life-threatening condition, compared to available therapies as demonstrated in our study.

Pediatric Waiver
A request for a waiver from pediatric labeling for Gleevec in CML is requested on the basis that Gleevec was designated as an Orphan Drug on January 31, 2001 for the treatment of CML. Orphan designation correspondence is provided in Volume 1.

User Fee
A waiver of the FDA User Fee for this application is requested on the basis of the orphan designation granted to Gleevec on January 31, 2001 for the treatment of CML. The FDA User Fee Cover Sheet is provided in Volume 1, along with the orphan designation correspondence.

90-Day Conference
We would like to request a 90-day post-submission conference (or earlier, if deemed appropriate) as provided for by 21 CFR 314.102. We would like to have the opportunity to meet with you and be advised of the general status of your review of this application and to discuss the review classification and potential for an advisory committee hearing.

SNDA Presentation to CDER's Division of Oncology
We would like to present the data from this SNDA to the reviewing Division personnel as requested in the pre-SNDA correspondence.

We propose the following available dates: August 14 or 15, 2002.

Please note that outside of the United States Gleevec™ may be known as Glivec®.

If you have any questions or comments regarding this SNDA, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

Attachments: Form FDA 356h
Form FDA 3397
Volumes 1-46 and E1

14 Desk Copies of Volume 1: Ann Staten (HFD-150)

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

NOVARTIS
ONCOLOGY

June 18, 2002

NDA No. 21-335

Marlene Haffner, MD
Director
Office of Orphan Products Development
Food and Drug Administration (HF-35)
5600 Fishers Lane, Room 8-73
Rockville, Maryland 20857

GLEEVEC ™ (imatinib mesylate) Capsules

ORPHAN DRUG DESIGNATION
(Notification of SNDA Submissions)

Reference No. 00-1401

Dear Dr. Haffner:

Please refer to the orphan drug designation for Gleevec™ (formerly Glivec™ or zimakastine/zimapapkine) for the treatment of patients with chronic myelogenous leukemia (CML) dated January 31, 2001. As you know, a marketing application (NDA 21-335) was submitted on February 27, 2001 and Gleevec was subsequently approved on May 10, 2001 for the treatment of Philadelphia chromosome positive CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. At this time we would like to notify your Office of additional marketing applications in this indication.

In continuing our development of Gleevec in the treatment of CML, we plan to submit a supplemental NDA 21-335 for the treatment of newly diagnosed Philadelphia positive CML.

SNDAs are to be submitted to the Division of Oncology by the end of this month.

If you have any questions or comments regarding this matter, please contact me at (973) 781-2282.

Sincerely,

Robert A. Miranda
Director
Drug Regulatory Affairs

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

Drug Regulatory Affairs East Hanover, NJ 07936-1080

NOVARTIS

Tel 973-781-4567
Fax 973-781-6325
Internet ann.shea@pharma.novartis.com

April 26, 2001

Marlene Haffner, M.D.
Director
Office of Orphan Products Development
Food and Drug Administration, HF-35
5600 Fishers Lane, Room 8-73
Rockville, Maryland 20857

STI 571

ORPHAN DRUG DESIGNATION
Amendment to Tradename

Reference No. 00-1401

Dear Dr. Haffner,

This is in reference to the January 31, 2001 letter in which Glivec™ (STI 571) qualified for Orphan Drug Designation for the treatment of chronic myelogenous leukemia, and our letter dated March 6, 2001 notifying you that a marketing application for Glivec™ (imatinib mesylate, formerly STI571) Capsules was submitted on February 27, 2001, NDA #21-335.

This is to inform you that our proposed tradename (Glivec™) has been reviewed by the Division of Oncology Drug Products and the Office of Post-Marketing Drug Risks and Assessments (OPDRA) and a change in the tradename to Gleevec™ was requested. We therefore request that Gleevec™ be used in future correspondence.

Should you have any questions or comments, please contact me at (973) 781-4567.

Sincerely,

Ann Shea
Associate Director
Drug Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development (*HF-35*)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

January 31, 2001

Novartis Pharmaceutical Corporation
59 Route 10
East Hanover, New Jersey 07936-1080

Attention: Ellen Cutler
Assistant Director, Drug Regulatory Affairs

Dear Ms. Cutler:

Reference is made to the orphan drug application dated November 22, 2000, submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of zimakastine/zimapapkine (Glivec™) as an orphan drug (application #00-1401).

We have completed the review of this application and have determined that zimakastine/zimapapkine qualifies for orphan designation for the treatment of chronic myelogenous leukemia.

Please be advised that if zimakastine/zimapapkine is approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of zimakastine/zimapapkine as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact John McCormick, M.D. at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

MEETING MINUTES

MEETING DATE: August 31, 2000 **TIME:** 9am **LOCATION:** Conference Room G

IND/NDA IND [redacted] Meeting Request Submission Date: July 26, 2000 (N088)
Briefing Document Submission Date: August 15, 2000 (N097)

DRUG: STI571

SPONSOR/APPLICANT: **Novartis**

TYPE of MEETING:

1. Other – follow-up from EOP2 (see meeting minutes 12/7/99 and 5/3/00)

2. **Proposed Indication:** Newly diagnosed previously untreated Philadelphia chromosome posistive (Ph+) chronic myelogenous leukemia in chronic phase.

FDA PARTICIPANTS:

Robert Temple, M.D., Director, Office of Drug Evaluation I
Richard Pazdur, M.D. Division Director
John Johnson, M.D., Medical Team Leader
Martin Cohen, M.D., Medical Reviewer
Gang Chen, Ph.D., Team Leader, Statistics
Mark Rothmann, Ph.D., Statistics
Atiqur Rahman, Ph.D., Team Leader, Clinical Pharmacology and Biopharmaceutics (internal meeting only)
Lydia Kieffer, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Ann Staten, R.D., Regulatory Project Manager
Donna Przepiorka, M.D., ODAC consultant (internal meeting only)
Bruce Cheson, M.D., ODAC consultant
Patty DeLaney, Office of Special Health Issues (internal meeting only)
Joann Minor, Office of Special Health Issues

INDUSTRY PARTICIPANTS:

Renaud Capdeville, M.D., Clinical Research
David Parkinson, M.D., Clinical Research
Elisabeth Wehrle, Ph.D., Statistics
Ellen Cutler, Drug Regulatory Affairs
Sharon Olmstead, Drug Regulatory Affairs

MEETING OBJECTIVES:

1. To discuss and resolve outstanding issues for protocol 0106

DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Primary Endpoint –

FDA:

A. Time to Treatment Failure (TTF) is not accepted as an endpoint for the following reasons:
   - Intolerance to treatment (inability to take the drug) cannot be an efficacy endpoint.
   - CHR (complete hematologic response) is not a compelling endpoint [responder vs. non-responder argument, not a surrogate for survival in most European randomized trial reports (see attachment 1), capacity to respond may be a good prognostic feature.
   - McyR is not a compelling endpoint (No data to support McyR as a surrogate endpoint for survival, similar arguments as for CHR, may influence tail of survival curve but not median survival)

B. Time to Progression (TTP) is recommended endpoint and suggestions include:
   - Loss of CHR
   - Loss of cytogenetic response
   - Inability to maintain peripheral blood counts (needs to be defined)
   - Increasing organomegaly
   - Accelerated phase CML
   - Blast crisis
   - Death from CML

Novartis Response: Concurs with the Agency's recommendation to substitute TTP (FDA definition) for TTF as the primary study endpoint.

2. Non-inferiority versus Superiority Statistical Analysis

FDA and Novartis discussed the effect of crossovers. Using TTP as the primary endpoint there will be fewer crossovers overall and much fewer early crossovers. Therefore, Novartis will design the trial to demonstrate superiority.

Novartis Response: Protocol will be amended to be a superiority trial.

3. Treatment Intolerance

FDA: Patients intolerant of study treatment will be censored at the time they discontinue treatment. Subsequent treatment can be at the investigator's discretion.

Novartis Response: Concurs with the Agency's recommendation.

4. Food Effect

FDA : Clinical Pharmacology and Biopharmaceutics Comments

We remind you of:

1. All the Clinical Pharmacology and Biopharmaceutics issues previously discussed that should be addressed regarding the development of STI 571.
2. The recent communication in which we asked you to provide the raw data and summary for the food effect study performed.
3. Submitting the data from the preliminary human PK results that indicates that STI 571 is rapidly absorbed when the drug is administered 2 hours after breakfast.
4. Submitting the solubility data that indicates that STI 571 is highly soluble in acid but has low solubility at a low pH 7.4

Novartis Response: Data from food effect study will be submitted in the near future.

ACTION ITEMS:

1. Novartis will submit an amended protocol mid-October.
2. Novartis will submit an amended statistical analysis plan to change to a superiority trial.
3. Novartis will assess the data on McyR at 12 months and may request another meeting to discuss whether this as an acceptable surrogate endpoint for accelerated approval.
4. The informed consent currently being used will be reviewed and revised, as appropriate. Patients already on study may have to be re-consented.

The meeting was concluded at 10:30 am. There were no unresolved issues or discussion points.

/S/ /S/

Ann Staten Date
Project Manager
Minutes preparer

Concurrence Chair: Martin Cohen Date
Medical Officer

Attachments: #1 FDA overhead; #2 Novartis overheads

cc:
Original IND [redacted]
HFD-150/Div File
/Staten/Pease
/Minor/Delaney
Copies distributed to attendees electronically

MEETING MINUTES

MEETING MINUTES

MEETING DATE: May 3, 2000 **TIME:** 10:30 am **LOCATION:** Conference Room G

IND/NDA IND [redacted] Meeting Request Submission Date: February 2, 2000(N034)
Briefing Document Submission Date: February 10, 2000(N035); March 2, 2000(N040); April 17, 2000(N62).

DRUG: STI571 (formerly CGP 57148B)

SPONSOR/APPLICANT: Novartis Pharmaceuticals Corporation

TYPE of MEETING:

1. End of Phase 1 / End of Phase 2

2. **Proposed Indication:**
   1. Treatment of patients with CML in blast cell crisis, accelerated phase and chronic phase refractory to interferon.
   2. Treatment of patients with early chronic phase CML.

FDA PARTICIPANTS:
Robert Temple, M.D., Office Director, Office of Drug Evaluation I (internal meeting only)
Richard Pazdur, M.D., Director, Division of Oncology Drug Products
Robert Justice, M.D., Acting Director, Division of Oncology Drug Products
John Johnson, M.D., Medical Team Leader
Martin Cohen, M.D., Medical Reviewer (internal meeting)
Dianne Spillman, Project Manager (internal meeting)
Amy Baird, Project Manager (industry meeting)
Gang Chen, Ph.D., Biometrics Team Leader (internal meeting only)
Mark Rothmann, Ph.D., Biometrics Reviewer
Lydia Kieffer, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Atiqur Rahman, Ph.D., Clin. Pharm. and Biopharm., Team Leader
Patricia DeLaney, Office of Special Health Issues
Donna Prezpiorka, M.D., ODAC consultant (internal meeting only)

INDUSTRY PARTICIPANTS:
Philip Bentley, Ph.D., Preclinical Safety
GregBurke, M.D., Ph.D., Clinical Research
Renaud Capdeville, M.D.,Clinical Research
Ellen Cutler, Regulatory Affairs
Insa Gathmann, Biostatistics
Russ Humme, Drug Regulatory Affairs
John Ketchum, Ph.D., Project Manager
Thomas Koestler, Ph.D., Drug Regulatory Affairs
David Parkinson, M.D., Clinical Development , Clinical Research
Bin Peng, Ph.D., Clinical Pharmacology
Brian Druker, M.D., Consultant, Oregon Health Sciences Univarsity
Anthony Murgo, M.D., NCI

IND

MEETING OBJECTIVES:

1. To obtain the Division's feedback regarding the adequacy of Novartis' proposed program to support the registration of STI571 for the treatment of patients with chronic myeloid leukemia.

BACKGROUND:

The sponsor's questions with the Agency's response were communicated via facsimile on May 2, 2000 (attached).

DISCUSSION and DECISIONS REACHED:

FDA encouraged the full data package (all three studies) for the initial submission as the length of follow up would not be sufficient in 3Q00 to assess durability of response in patients with accelerated disease. Exceptional efficacy demonstrated by a median survival of 12 months would be needed to support an earlier filing based on a single phase 2 study in patients with accelerated disease.

Question 1a. The patient populations are adequately defined.
Question 1b.

- FDA clarified that approval under Subpart H is likely for all subpopulations.

- Novartis would appreciate clarification regarding the acceptability of the endpoint for studies 0102 and 0109 as defined in the briefing book

For studies 0102 and 0109 response is defined as one of the following 3 outcomes:

1. Complete hematologic response, with < 5% blasts in the bone marrow and recovery of peripheral blood counts
2. No evidence of leukemia, but without recovery of peripheral blood counts
3. Return to chronic phase CML

Hematologic response must be confirmed after $\geq$ 4 weeks. Further definition of each of the categories can be found on page 13 of the briefing book.

- The NDA must include the rationale for the use of uncontrolled studies and support from the literature (historical data) regarding the expectations for response rate, duration of response and survival expectations.

Question 1c,
Time to treatment failure was not specified as an endpoint in these protocols and was erroneously stated in the question. A discussion of the minimum duration of follow up to obtain an initial evaluation of response duration for the filing followed.

A 1QO1 filing would include the following ranges of follow up:

0102 (blast crisis): 3-15 months
0109 (accelerated): 8-16 months
0110 (IFN-refractory): 6-11 months

All patients will be followed until disease progression and then for survival.

FDA stated that most patients should be followed for a minimum of 6 months. Novartis would appreciate feedback regarding whether additional follow up data for study 0102 would be acceptable prior to an advisory committee meeting.

Ultimately, FDA reserves final judgement regarding the acceptability of the proposal (regarding an acceptable durability of response) until additional data from the ongoing studies can be provided. A pre-NDA meeting should occur mid-summer.

ACTION ITEMS:

1. Novartis will submit a revised protocol for study 0106 for the Agency to review.
2. Novartis will provide a response to the statistical and clinical pharmacology comments.

The meeting was concluded at 3:30pm. There were no unresolved issues or discussion points.

/S/

Ann Staten, RD Date
Project Manager
Minutes preparer

/S/

Concurrence Chair: _____/____
Richard Pazdur, MD Date
Division Director

Attachment : FDA facsimile dated May 2, 2000

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Parklawn Building
5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler	**From:** Dianne Spillman
Fax: (301) 468-5614	**Fax:** (301) 594-0499
Phone: (301) 468-5602	**Phone:** (301) 594-5746
Pages (including cover): 27	**Date:** May 2, 2000
Re: IND [redacted] FDA bullets & overheads	

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

- **Comments:**

Ellen:

As promised, here are the Division's internal bullets (13 pages) and the overheads (13 pages) that may be presented by Drs. John Johnson & Marty Cohen prior to discussion of the internal bullets. Please distribute copies of this fax to the attendees on your end.

At the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request.

Sincerely,

Dianne Spillman, Project Manager
Division of Oncology Drug Products

IND [redacted] STI571
May 3, 2000

Topics for Discussion

1. Regarding the initial registration in patients with advanced CML:

We propose to register STI571 according to the provisions described in 21 CFR 314, Subpart H - Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses. We believe that STI571 promises to provide a meaningful therapeutic benefit to patients (e.g., ability to treat patients for whom no reasonable alternative exists or patients who are unresponsive to, or intolerant of, available therapy). A randomized controlled trial in patients with chronic stage CML will subsequently provide confirmatory evidence of activity.

a. Are the three subpopulations adequately defined (Sections 3.2, 3.3, 3.4)?

FDA Response:

Patients with blast crisis, accelerated phase, and interferon refractory chronic phase are adequately defined.

Question 1:

b. Do you agree that the primary efficacy endpoint of response rate (complete hematologic response in Protocols 0102 and 0109 or complete plus major cytogenetic response in Protocol 0110) is an appropriate surrogate endpoint that is reasonably likely to predict clinical benefit in the proposed populations?

FDA Response:

For blast crisis and accelerated phase CML, CHR is an adequate endpoint. For chronic phase CML (protocol 0110), and interferon failure/intolerant/resistant patients, complete plus major cytogenetic response is an adequate endpoint for accelerated approval. There are other drugs, available for use in these conditions, that produce responses. This is the reason the FDA recommended RCTs at the prior FDA/Novartis meeting (6-15-99). However, if responses in the Phase II trials are very good and are reasonably durable, it may be possible to conclude that STI 571 is better than available therapy without RCTs.

Question 1:

c. For responding patients, would a median duration of response (Protocol 0110) or time to treatment failure (Protocols 0102 and 0109) of at least 6 months be sufficient to demonstrate durability?

FDA Response:

Treatment Failure is not defined in these protocols.

We do not believe that time to treatment failure (TTF) as defined in protocol 106 (Initial Rx of CML) is an acceptable efficacy endpoint.

Durability of response is a review issue and would depend on results with other available therapy.

- **For study 0102 (Blast crisis CML), most patients should be followed for at least 6 months or until progression.**

- **In all studies, you should follow responding patients until progression. Six months would probably not be sufficient follow-up for the accelerated phase or the chronic phase Interferon refractory patients. We suggest meeting with the Division at a pre-NDA meeting to further discuss the issue of response duration.**

Question 1:

d. Does the proposed Phase II program support an initial registration in patients with the defined stages of CML?

FDA Response:

Hopefully.

See answers to Question 1a, 1b and 1c.