

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To: Bob Miranda

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 7

Date: April 17, 2001

Re: NDA 21-335 – Tradename consult

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

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Dear Bob,

As agreed upon in today's telephone conversation, the Division and OPDRA approve the use of "Gleevec" as a tradename.

Attached is a copy of the reviewer's comments from OPDRA.

Sincerely,

/s/

Ann

April 17, 2001

1. *Sponsor's Comments:*

Novartis will ship supplies of () in a controlled manner. There will be no automatic shipments of () made to retail pharmacies. For a variety of reasons, among them a relatively small chronic myeloid leukemia (CML) patient population of approximately 23,000 individuals, Novartis has identified a number of select wholesalers that have the technical capability and resources to provide patient-specific delivery service to retail pharmacies on an as needed basis. These wholesalers will maintain inventories of () and will provide adequate patient service at the retail level without the need for retail pharmacies to maintain shelf inventories of (). Consequently, we believe that the absence of shelf inventories of () at the retail level essentially eliminates the potential for confusion with *Glyset*, a product that is not widely used in the management of diabetes. The reported new prescriptions written for *Glyset* is very low and is reported at about an average of () per month since its launch in Feb 1999.

OPDRA's Comments:

Even though () is geared towards a small population and is ordered on an "as needed" basis, pharmacies may order the drug ahead of the next prescription so that if the patient is suddenly out of the medication, he or she will not have to wait another day to receive the medication. In this case, the drug product would be placed on the shelf in close proximity of the *Glyset* product. However, the source of the potential confusion does not lie on whether or not the product is on the shelf, but whether there is a potential error made by practitioners in prescribing the medication or by pharmacists who may interpret the *Glyset* as () or vice versa. A limited distribution of () does not prevent the practitioner from verbally communicating the wrong prescription to the pharmacist.

Of great concern is the patient's exposure to the dangerous side effects if () was given instead of *Glyset*. Such dangerous side effects include neutropenia and thrombocytopenia.

2. *Sponsor's Comments:*

A visual comparison between () and *Glyset* shows a number of distinctions between the two products that should reduce the likelihood of confusion at the pharmacy and patient level. *Glyset* is available as 25 mg, 50 mg and 100 mg white, round, film-coated tablets. These tablets are debossed with the word "Glyset" on one side and the strength on the other side. () will be marketed as a light yellow to orange yellow opaque capsule in a 100 mg strength, with an imprinted alpha-numeric code. These visual distinctions should allow patients to immediately identify any difference during prescription refills.

OPDRA's Comments:

The differences in the physical appearances of () and *Glyset* are not relevant in this case

April 17, 2001

since the source of error exists in the interpretation of the name when the prescription is given by the practitioner to the pharmacist. The two names have sound-alike qualities where the prefix (Gli with the long "i" and Gly) and the suffix (ec and et) sound similar. Both have an overlapping strength and the same route of administration. These similar qualities increase the potential for medication errors to occur. Of one concern noted from the Med-ERRS study is the pronunciation of "Glyvek" (glee' vek) which prompted a hit for *Glyset*. However, the look-alike similarity between these two names are stronger than the sound-alike similarity since "glee" and "gly" sound different.

Post-marketing experience with the drug product "Celebrex" has demonstrated that having *noteworthy differences* between products *does not eliminate* the potential error, as the Agency has received 116 reported cases of medication errors involving Celebrex, Celexa, and Cerebyx. Celebrex is an NSAID, cox-2 inhibitor indicated for the relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis. Celexa is a serotonin reuptake inhibitor indicated for the treatment of depression. Cerebyx is a prodrug and its active metabolite is phenytoin. Table 1 describes the FDA approved dosage forms, strengths, and usual dosages of each product. Celebrex and Cerebyx share none of the common factors mentioned above, and, therefore, one would perceive that these three drug products would never be confused. Also, the only commonality that Celebrex and Celexa share is a dosing interval of once daily. The only *common factor* that these names share is the *sound-alike and look-alike properties of their names*.

TABLE 1

Name of Drug	Available Strength and Dosage Form	Usual Dosage
Celebrex	100 mg and 200 mg Capsules	200 mg once daily or 100 mg to 200 mg twice daily
Cerebyx	50 mg PE/mL Injection 10 mL and 2 mL vial	Varies depending on indication. Average of 10-20 mg PE/kg
Celexa	20 mg and 40 mg Tablets	20 mg to 40 mg once daily. Up to 60 mg daily

Therefore, based on previous post-marketing experience, OPDRA does not believe that differences such as differentiating dosage forms, different routes of administration, different doses, and different indications rule out any potential for confusion when the names clearly sound or look alike to a currently marketed drug product. The errors for Celebrex are not overwhelmingly related to other confounding factors such as illegible handwriting, overlapping indications for use, overlapping strengths, mispronunciation of the product names, similar prescribing environments but rather to a cognitive error. It is evident from the case reports that the sound-alike/look-alike properties of the name alone are not the source of confusion in the minds of healthcare providers. The reports describe healthcare providers thinking, seeing, and hearing one product name but prescribing, transcribing, and dispensing another. There are numerous case reports that describe prescriptions being written correctly, typed correctly, but filled incorrectly on initial fills as well as product refills. Also, physicians have reported of thinking of one drug product but prescribing another. These errors cannot be blamed on incompetence since the same errors are occurring to

numerous individuals on a large scale.

3. *Sponsor's Comments:*

As described in the second Med-ERRS Failure Mode and Effects Analysis, there is a low risk of confusion between () and *Glyset* that could lead to medication errors. This report is based on a detailed, side by side comparison of the two products that tracked them from the wholesaler, pharmacy storage, prescribing physician, techniques for prescribing, order entry at the pharmacy, selection of product at pharmacy, dispensing, and finally patient administration. At each step in this eight-step sequence, the report describes a "low risk of confusion", with the exception of pharmacy shortage, where the risk of confusion was described as "moderate". The controlled distribution procedures described above further reduce this moderate risk in practice.

OPDRA's Comments:

It is unclear on how the second Med-ERRS evaluation was conducted. No details of the methodology was given, no information on the criteria used to determine whether or not the situation was a low, moderate, or high risk of confusion, no indication of who determined the levels of confusion and how those levels were determined, and no validation of method was indicated. The evaluation lacks pertinent information and cannot be accurately evaluated by OPDRA.

However, in evaluating the second Med-ERRS analysis, OPDRA has the following comments:

- a) **Storing drug on pharmacy shelf:** Med-ERRS state that there would be three drug products between () and *Glyset* when placed alphabetically on the shelf. The distance between the two products is still relatively close. Even though () is not automatically shipped to the retail pharmacy, a pharmacy will keep it in stock if a patient is on the medication. Please refer to the above comment 1.
- b) **Physician type:** The general practice physicians would be at higher risk for mistakenly prescribing () instead of *Glyset* due to name confusion since they treat a wider population of patients that may include patients with diabetes and/or cancer. The chance of a general practitioner being familiar with both () and *Glyset* may be higher than an oncologist knowing about both () and *Glyset* due to the specialty of practice.
- c) **How physicians prescribe:** Practitioners may communicate verbally to the patient on how to take the medications while giving the directions on the prescription as "use as directed". Please refer to the above example regarding Celebrex, Celexa, and Cerebyx. As indicated in the first Med-ERRS evaluation, respondents commented that they would pronounce () with a long "i" if they were not given a pronunciation guide. In reality, not every practitioner and pharmacist will pronounce () as glee' vek, but () with a long "i". The sound-alike similarity would still exist.

According to Webster's New World Dictionary (third college edition), the usual pronunciation of "i" can be found in "is", "hit", and "mirror" and the pronunciation of a long "i" can be found in "ice", "bite", "high", and "sky". Your proposed pronunciation of () as "Gleevec" is not a normal pronunciation of "i" and this was confirmed in both FDA and Med-ERRS analysis.

- d) **Order entry into pharmacy computer:** Different mnemonics is irrelevant when a pharmacist misinterprets or is given the wrong drug name. In a retail setting, the proprietary drug name is usually given instead of the generic name.
- e) **Drug administration:** "Physical characteristics of dosage form are very dissimilar, and would be recognized by a patient or caregiver familiar with its use." OPDRA wants to prevent having the wrong drug product get into the patient's hands. A patient or caregiver may not be paying close attention to what is being given, especially when a patient could be taking more than one medication. When the drug is used the first time by the patient or administered the first time by the caregiver, they may not be able to recognize the drug.

4. *Sponsor's Comments:*

The dose and administration guidelines will also serve to minimize confusion. The usual maintenance dose of *Glyset* is 50 mg 3 times daily, with a maximum recommended dose of 100 mg 3 times daily () will be prescribed for chronic phase CML as 400 mg (4 capsules) given once daily, for advance phase CML 600 mg (6 capsules) given once daily.

OPDRA's Comments:

The different dosing and administration guidelines do not rule out the possibility of a medication error occurring. Both products can be prescribed as 100 mg, use as directed. As seen in the above Celebrex, Celexa, and Cerebyx example, there was confusion among them even though the dosing and directions are different.

5. *Sponsor's Comments:*

In the first Med-ERRS evaluation, all 37 pharmacist respondents were given the Novartis pronunciation (GLEE-VEK), and none of them mentioned *Glyset* as a potential problem with a verbal order. US practitioners did point out that without specific instructions the tendency was to pronounce () with the long "i" sound, as it would sound with a "gly" prefix. However, based on the second Med-ERRS Failure Mode and Effects Analysis, we believe the risk is low for creating confusion that would lead to medication errors. To further reduce any potential risk we also plan to include a pronunciation guide in our educational programs.

OPDRA's Comments:

The first Med-ERRS report cannot be accurately evaluated by OPDRA due to a lack of important

April 17, 2001

information. Such information include the details on the methodology of the study, the criteria for the selection of the participants, the demographics of the participants, the practice setting of each participant, how the participants were selected (sampling frame), how the prescriptions were distributed, how the prescriptions were given (eg. Was the name given as part of a full prescription as in the real world?), the environment of the study (eg. Did it take place in a busy setting as in the real world?), how the scores were derived and how do the scores relate to actual events. The validation of the techniques used is also not given. The sample size used (37) in the study is quite small; not enough to detect all possible name confusions that might occur when the proprietary is put out in the real world. Also, this study cannot be applied to the review of () when pronounced with a long "i" and *Glyset* since the study uses the pronunciation as glee' vek. Even comments from the respondents in the sponsor's study stated that they would have pronounced it () with a long "i". The general population may also pronounce () with a long "i".

One note, with the pronunciation of glee' vek, but spelled "Glyvek", the study indicated that *Glyset* sounded slightly similar. *Guaivent* was also indicated as sounding similar to () (glee' vek); however, it sounds more like () (gly' vek) instead of () (lee'vek).

According to USAN, the use of "gli" as a prefix in a drug name indicates that the drug is a hypoglycemic agent. Using the name () would be misleading healthcare practitioners to believing that the drug product is a hypoglycemic agent.

6. Sponsor's Comments:

The extensive exchange of information within the media (print & TV) concerning () over the past four months, and particularly in the most recent period surrounding the publication of our Phase I studies in the *New England Journal of Medicine*, many health practitioners and CML patients are aware of () as a promising new treatment for the selected indications. This awareness translates to extraordinary name recognition, and this should further reduce the likelihood of prescription-writing or dispensing errors at launch and beyond. Finally, reference is made to over 630 million references made over the last four months surrounding the use () plus CML patient internet sites which have prominently featured this trademark (e.g. newcmldrug.com).

OPDRA's Comments:

Not every healthcare professional will be educated on the actual pronunciation of () Even existing drugs that have been on the U.S. market for years are mispronounced by healthcare professionals. Just recently, an NBC (Channel 4, Washington D.C.) newscaster on the 11 o'clock evening news pronounced the drug as () with a long "i". Not everyone will pronounce the name correctly even when there is an extensive exchange of information within the media.

RECOMMENDATIONS:

April 17, 2001

After review of the information submitted by the sponsor, OPDRA does not recommend the use of the name _____ since most healthcare professionals will pronounce the drug name with a long "i" (gly' vek). This pronunciation would sound similar to *Glyset*. Also, _____ uses a USAN prefix, gli-, which indicates that the drug is a hypoglycemic agent. It is against Agency's policy to use a USAN prefix and/or suffix when its meaning is not indicated for that drug product. Using the name (_____) would be misleading healthcare practitioners to believing that the drug product is a hypoglycemic agent.

However, OPDRA recommends the sponsor to revise the spelling of the proprietary name to "Gleevec" so that it is spelled the way it is pronounced. Even though the sponsor's study indicated that *Glyset* and *Guaivent* sound slightly similar to (_____) (glee' vek), OPDRA believes that the names sound different enough to reduce the potential risk of confusion. Also, the sponsor's study indicated that *Glucose* looks similar to "Gleevec"; however, glucose tablets are over-the-counter products, which would decrease the potential risk of confusion.

APPEARS THIS WAY
ON ORIGINAL

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DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To: Bob Miranda

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: April 17, 2001

Re: NDA 21-335 – information request - clinical pharmacology and Medical

Urgent For Review Please Comment Please Reply Please Recycle

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Dear Bob,

We have the following information requests:

The following is a question from the PK reviewer:

Question: For ID=21 (see data below), the concentrations were measured at 4.75hr, 8.5 hr, 9.5 hr, etc. The first dose, however, appears to be given at 11.5 hr. Could the sponsor check if the dose record(s) is (are) missing at or before 4.75 hr, since there are detectable levels of _____ for this and if necessary, for other patients?

The medical reviewer has the following question:

In your submission, you state that duration of hematologic response was censored at the last examination date when patients were still on study without evidence of progression. Were hematology examinations performed on these dates? Are these data in the NDA?

Sincerely,

Ann

AS

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Bob Miranda

From: Ann Staten, Project Manager

Fax: 973-781-6325

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Date: April 16, 2001

Re: NDA 21-335 - information request - clinical pharmacology

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Dear Bob,

We have the following information request:

During the development of the formulation of 50 mg has been changed from No. 3752417.00.001 to 3752417.00.002, to 3752417.00.003, to 3752417.00.004. Although the last three formulations do not have big differences, the first one 3752417.00.001 is quite different from the to-be-marketed.

Based on the information provided in the CMC section, this formulation was used in pivotal trials 102, 109 and PK study 03 001. We need the following information.

1. How many (and which) patients used this formulation?
2. In pivotal trials 102, 109 and PK study 03 001, 25 mg formulation was also used. How many (and which) patients used this 25 mg formulation?
3. Is there any equivalence study between the old formulation (25 mg and 50 mg used in pivotal trails) and to-be-marketed formulation conducted?

Sincerely,

Ann



Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

13-APR-01

DUPLICATE

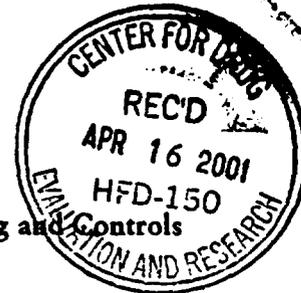
NDA 21-335

(imatinib mesylate)

Capsules

Minor Amendment to a Pending NDA- Chemistry, Manufacturing and Controls
FDA Information Request

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



ORIG AND
BC

Dear Dr. Pazdur:

Please refer to the above cited Original NDA for (imatinib mesylate) Capsules which was submitted on 27-FEB-01. This minor amendment contains the requested drug substance stability commitment report and the long-term registration stability data for the remaining one (1) batch of drug product. Desk copies were provided via two separate secure e-mails to Ms. Ann Staten on 11-April-01.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-3758. If there are any general or Clinical related issues please contact Mr. Robert A. Miranda, the DRA Therapeutic Area representative at (973) 781-2282.

Sincerely,

Leslie Martin-Hischak
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

cc: Ms. Regina Brown, New Jersey District Office, North Brunswick
Resident Post - Certified Field Copy (Cover Letter Only)

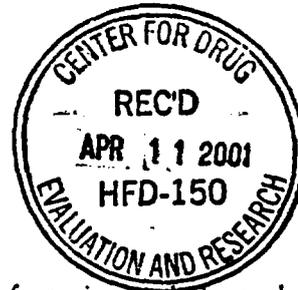
NOVARTIS

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

10-APR-01

NDA 21-335
() (imatinib mesylate)
Capsules



Minor Amendment to a Pending NDA- Chemistry, Manufacturing and Controls
FDA Information Request

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

Dear Dr. Pazdur:

Please refer to the above cited Original NDA for () (imatinib mesylate) Capsules which was submitted on 27-FEB-01. This minor amendment contains the Novartis response to the Clinical Pharmacology request received via secure e-mail on 04-April-01. A desk copy was provided (via secure e-mail) to Ms. Ann Staten on 06-April-01.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-3758. If there are any general or Clinical related issues please contact Mr. Robert A. Miranda, the DRA Therapeutic Area representative at (973) 781-2282.

Sincerely,

Leslie Martin-Hischak
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

cc: Ms. Regina Brown, New Jersey District Office, North Brunswick
Resident Post - Certified Field Copy (Cover Letter Only)

NOVARTIS

DUPLICATE



April 10, 2001

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 #20N
1451 Rockville Pike
Rockville, Maryland 20852-1448

() (Imatinib mesylate) Capsules

MINOR AMENDMENT TO A PENDING APPLICATION

OTHER: TRADEMARK REVIEW

NEW CORRECTION
NC

Dear Dr. Pazdur:

Please refer to our original NDA 21-335, dated February 27, 2001 for () (imatinib mesylate, formerly STI571, CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Reference is also made to a fax dated April 2, 2001 from Ms. Ann Staten, which included the OPDRA review comments as reasons why the trademark () is not acceptable. The main reason given was because of the phonetic similarities between () and GLYSET. The trademark () was originally submitted for review to our IND () on July 26, 2000 (Serial No. 089).

At this time we would like to provide additional information that may not have been available to OPDRA when it did its risk benefit analysis. We believe that this information supports the use of our preferred trademark ().

We ask for your expedited consideration of this information. We recognize the accelerated review assigned to this NDA and the potential importance to patients for this drug. As such we appreciate your immediate attention to this issue to avoid any potential delay in providing the product to patients in a timely fashion immediately after approval.

An international interdisciplinary group from Novartis has carefully reviewed the OPDRA evaluation, along with two error potential evaluations performed by Med-ERRS, a subsidiary of the Institute for Safe Medication Practices (ISMP). The first of the Med-ERRS evaluations was completed on March 23, 2001 and supported the Novartis decision to adopt () as the trademark for imatinib mesylate. The second Med-ERRS evaluation was completed on April 4, 2001 in response to the OPDRA evaluation that surfaced a concern about GLYSET. This second evaluation was a Failure Mode and Effects Analysis of () versus GLYSET and continues to support the use of the trademark ().

on the information from the two Med-ERRS evaluations (attached) and for other reasons, we believe the trademark () is a low risk for confusion with GLYSET. This is summarized in the following six topic areas:

Distribution of GLIVEC

Novartis will ship supplies of () in a controlled manner. There will be no automatic shipments of () made to retail pharmacies. For a variety of reasons, among them a relatively small chronic myeloid leukemia (CML) patient population of approximately 23,000 individuals, Novartis has identified a number of select wholesalers that have the technical capability and resources to provide patient-specific delivery service to retail pharmacies on an as needed basis. These wholesalers will maintain inventories of () and will provide adequate patient service at the retail level without the need for retail pharmacies to maintain shelf inventories of (). Consequently, we believe that the absence of shelf inventories of () at the retail level essentially eliminates the potential for confusion with GLYSET, a product that is not widely used in the management of diabetes. The reported new prescriptions written for GLYSET is very low and is reported at about an average of () per month since its launch in Feb 1999.

Visual Distinctions between () and GLYSET

A visual comparison between () and GLYSET shows a number of distinctions between the two products that should reduce the likelihood of confusion at the pharmacy and patient level. GLYSET is available as 25 mg, 50 mg and 100 mg white, round, film-coated tablets. These tablets are debossed with the word "Glyset" on one side and the strength on the other side. () will be marketed as a light yellow to orange yellow opaque capsule in a 100 mg strength, with an imprinted alpha-numeric code. These visual distinctions should allow patients to immediately identify any differences during prescription refills.

Low Risk Potential for GLIVEC and GLYSET Confusion

As described in the second Med-ERRS Failure Mode and Effects Analysis (attached), there is a low risk of confusion between () and GLYSET that could lead to medication errors. This report is based on a detailed, side by side comparison of the two products that tracked them from the wholesaler, pharmacy storage, prescribing physician, techniques for prescribing, order entry at the pharmacy, selection of product at pharmacy, dispensing, and finally patient administration. At each step in this eight-step sequence, the report describes a "low risk of confusion", with the exception of pharmacy storage, where the risk of confusion was described as "moderate". The controlled distribution procedures described above further reduce this moderate risk in practice.

Medical Differences

The dose and administration guidelines will also serve to minimize confusion. The usual maintenance dose of GLYSET is 50 mg 3 times daily, with a maximum recommended dose of 100 mg 3 times daily. () will be prescribed for chronic phase CML as 400 mg (4 capsules) given once daily, for advanced phase CML 600 mg (6 capsules) given once daily.

Pronunciation and Verbal Orders

In the first Med-ERRS evaluation (attached), all 37 pharmacist respondents were given the Novartis pronunciation (GLEE-VEK), and none of them mentioned GLYSET as a potential problem with a verbal order. US practitioners did point out that without specific instructions the tendency was to pronounce [redacted] with the long "i" sound, as it would sound with a "GLY" prefix. However, based on the second Med-ERRS Failure Mode and Effects Analysis, we believe the risk is low for creating confusion that would lead to medication errors. To further reduce any potential risk we also plan to include a pronunciation guide in our educational programs.

Public Awareness

The extensive exchange of information within the media (print & TV) concerning [redacted] over the past four months, and particularly in the most recent period surrounding the publication of our Phase I studies in the New England Journal of Medicine, many health practitioners and CML patients are aware of [redacted] as a promising new treatment for the selected indications. This awareness translates to extraordinary name recognition, and this should further reduce the likelihood of prescription-writing or dispensing errors at launch and beyond. Finally, reference is made to over 630 million references made over the last four months surrounding the use [redacted] plus CML patient internet sites which have prominently featured this trademark (e.g. newcmldrug.com).

the unlikely event that there is confusion with GLYSET and the risk of medication errors, in a post-launch period, Novartis is willing to work with the Agency in a cooperative way to carefully monitor the situation and immediately implement interventions so as to manage the risks in a manner acceptable to the Agency.

Because of the shared urgency on this matter, we respectfully request a conference call on or before April 16, 2001 (p.m.) or April 17, 2001 (a.m.) to discuss the contents of this letter and the attachments. We are enclosing six copies of the information package so that you can more easily share the information with OPDRA and others in a timely manner. Please let me know if you need additional copies.

If you have any questions or comments regarding this matter, please contact me at (73) 781-2282.

Sincerely,

Robert A. Miranda /suo

Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachments

Desk Copy via fax: Ann Staten (HFD-150 at 301/827-4590)
cc: Jerry Phillips (OPDRA)

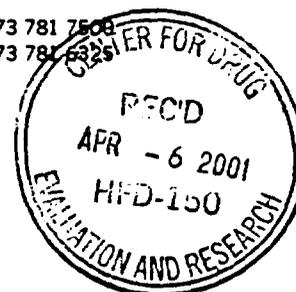
 **NOVARTIS**

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
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Tel 973 781 7500
Fax 973 781 6325

April 5, 2001

DUPLICATE



NDA No. 21-335

™ (Imatinib mesylate) Capsules

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

MINOR AMENDMENT TO A PENDING APPLICATION

OTHER: Nonclinical Toxicology Reports

ORIG AMENDMENT

Dear Dr. Pazdur:

BP

Reference is made to our original NDA 21-335, dated February 27, 2001 for (Imatinib mesylate, formerly STI571, CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. At this time we would like to provide the final report for the 39-week monkey toxicity study and a report amendment to the 26-week toxicity study in rats.

Attached is the final report entitled "39-week oral gavage (b.i.d.) toxicity study in monkeys with a 4-week recovery period", dated March 29, 2001. An interim report for this study was included in our original NDA. Submission of this final report at this time is in agreement with our pre-NDA meeting.

Attached is also an amendment no.1 to the final report entitled "26-week oral (gavage) toxicity study in rats with a 4-week recovery period", dated March 22, 2001. This amendment adds the stability result (60mg/mL STI571 aqueous solution), which was inadvertently omitted in the final report included in our original NDA. This change does not alter the interpretation or conclusion of the original final report.

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

Sincerely,



Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachment

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

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

NOVARTIS

04-APR-01

DUPLICATE

NDA 21-335

(imatinib mesylate)
Capsules

Amendment to a Pending NDA- Chemistry, Manufacturing and Controls
FDA Information Request

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



ORIG AMENDMENT

BC

Dear Dr. Pazdur:

Please refer to the above cited Original NDA for (imatinib mesylate) Capsules which was submitted on 27-FEB-01. This amendment contains the requested (FDA fax dated 02-Apr-01) drug substance stability information. The report containing the stability data was sent to Ms. Ann Staten via secured e-mail on 03-APR-01.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-3758. If there are any general or Clinical related issues please contact Mr. Robert A. Miranda, the DRA Therapeutic Area representative at (973) 781-2282.

Sincerely,

Leslie Martin-Hischak
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

cc: Ms. Regina Brown, New Jersey District Office, North Brunswick
Resident Post - Certified Field Copy (Cover Letter Only)

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To: Bob Miranda

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: April 3, 2001

Re: NDA 21-335 – Pharm/Tox information request

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

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Dear Bob,

The pharm/tox reviewer requests that the 39 day monkey study be submitted to the NDA in hard copy. This can be coded as a minor information amendment. The reviewer requests a desk copy of the electronic version, if have it available.

Could you please update me as to when the day 34 stability results for the 26 day rat study will be submitted?

Sincerely,

Ann

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

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

To: Leslie Martin-Hischak

From: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-3758

Phone: 301-594-5770

Pages: 1

Date: April 2, 2001

Re: NDA 21-335 – Information request - CMC

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

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Dear Leslie,

The chemistry reviewer has the following information request:

Please submit the stability data for the drug substance batches 1000006004, 1000009004 and 1000010004 ASAP.

Sincerely,

Ann

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325



30-MAR-01

DUPLICATE



NDA 21-335
(imatinib mesylate)
Capsules

Amendment to a Pending NDA- Chemistry, Manufacturing and Controls

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

BC

Dear Dr. Pazdur:

Please refer to the above cited Original NDA for (imatinib mesylate) Capsules which was submitted on 27-FEB-01. This amendment contains a previously agreed upon drug substance stability update. In addition, Novartis would like to clear up a discrepancy in the documentation regarding the re-test period for the drug substance. The documentation is not consistent in that different re-test periods have been listed in the Original NDA. The re-test period for the drug substance, imatinib mesylate is years.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-3758. If there are any general or Clinical related issues please contact Mr. Robert A. Miranda, the DRA Therapeutic Area representative at (973) 781-2282.

Sincerely,

Leslie Martin-Hischak
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

cc: Ms. Regina Brown, New Jersey District Office, North Brunswick
Resident Post - Certified Field Copy (Cover Letter Only)

Ms. Ann Staten, Division of Oncology Drug Products (2 Desk Copies)

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

 **NOVARTIS**

Tel 973 781 7500
Fax 973 781 6325

March 30, 2001

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

NDA No. 21-335

[(imatnib mesylate)
Capsules]

MINOR AMENDMENT TO A
PENDING APPLICATION

OTHER: USAN STATEMENT

Dear Dr. Pazdur:

Reference is made to our original NDA 21-335, dated February 27, 2001 for [(imatnib mesylate, formerly STI571, CGP57148B) Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. At this time we would like to provide documentation of the USAN adopted name for this drug.]

[Attached is a copy of the "Statement On A Nonproprietary Name Adopted By The USAN Council" dated January 31, 2001, which accepts the USAN name "Imatinib Mesylate" for (formerly STI571). We hope this meets your needs to complete the review of our product labels.]

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

Sincerely,



Robert A. Miranda
Associate Director
Drug Regulatory Affairs

Attachment

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

January 31, 2001

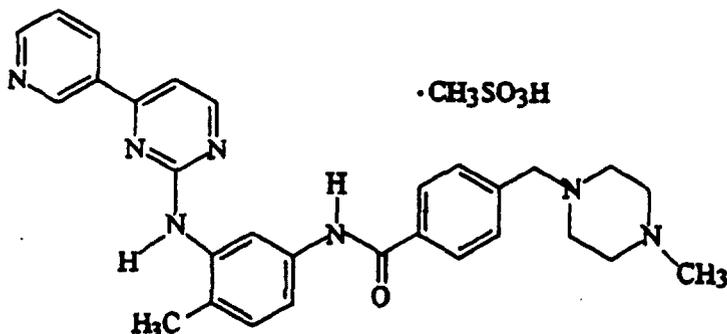
STATEMENT ON A NONPROPRIETARY NAME ADOPTED BY THE USAN COUNCIL:

USAN (MM-81)	IMATINIB MESYLATE
PRONUNCIATION	im at' in ib
THERAPEUTIC CLAIM	anti-leukemia and anti-tumor agent (tyrosine kinase inhibitor)

CHEMICAL NAME

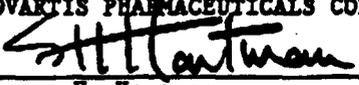
benzamide, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]aminophenyl]-, methanesulfonate salt

STRUCTURAL FORMULA



MOLECULAR FORMULA	$\text{C}_{29}\text{H}_{31}\text{N}_7\text{O} \cdot \text{CH}_4\text{O}_3\text{S}$ or $\text{C}_{30}\text{H}_{35}\text{N}_7\text{O}_4\text{S}$
MOLECULAR WEIGHT	589.71
TRADEMARK	Unknown as yet
MANUFACTURER	Novartis Pharma AG
CODE DESIGNATIONS	STI 571
CAS REGISTRY NUMBER	152459-95-5 (free base) (salt)
WHO NUMBER	8031

APPROVED
NOVARTIS PHARMACEUTICALS CORPORATIONS


Steven H. Hartman
Vice President, Trademarks & Copyrights

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Ann Shea **From:** Ann Staten, Project Manager

Fax: 973-781-6325 **Fax:** 301-827-4590

Phone: 973-781-4567 **Phone:** 301-594-5770

Pages: 1 **Date:** March 26, 2001

Re: NDA 21-335 – Clinical Pharmacology information request

Urgent For Review Please Comment Please Reply Please Recycle

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Dear Ann,

We need the following clinical pharmacology information ASAP.

Please let me know if this information is already provided in the NDA and where I can locate of the information.

1. *The in vitro metabolism studies and protein binding studies in Part 6. It will expedite our review if you can submit them electronically.*
2. *The justification for dissolution conditions.*
The justification of dissolution conditions should include:
 - pH solubility and stability profile.*
 - Drug permeability or water partition coefficient measurement.*
 - Justification for selecting the media.*
 - Justification for selecting the apparatus and speed.*

Sincerely,

/s/
Ann

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 7500
Fax 973 781 6325

 **NOVARTIS**

20-MAR-01

NDA 21-335

(imatinib mesylate)
Capsules

General Correspondence - Chemistry, Manufacturing and Controls

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

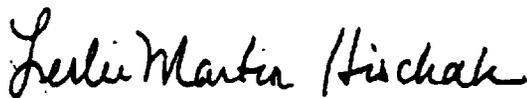
Dear Dr. Pazdur:

Please refer to the above cited Original NDA for (imatinib mesylate) Capsules which was submitted on 27-FEB-01. As requested by the Division at the March 16 NDA meeting this letter is a confirmation of inspection readiness for all Novartis sites in regards to the NDA.

All Novartis sites listed in the Original NDA with the exception of Novartis Ringaskiddy are ready for inspection now. Novartis Ringaskiddy will be ready for inspection as of April 2, 2001. In addition, Novartis is in contact with the (Switzerland) regarding their inspection participation on short notice and we do not expect this to be a problem.

Should you have any comments or questions regarding this submission or any other Chemistry, Manufacturing and Controls issue please contact me directly at (973) 781-3758. If there are any general or Clinical related issues please contact Ms. Ellen Cutler, the DRA Therapeutic Area representative at (973) 781-8180.

Sincerely,


Leslie Martin-Hischak
Chemistry, Manufacturing and Controls
Drug Regulatory Affairs

 **NOVARTIS**

Ellen Cutler
Associate Director
Regulatory Affairs

Tel 973-781-8180
Fax 973-781-6325

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

DUPLICATE

ORIG AMENDMENT

Ann Staten
Project Manager
Food and Drug Administration
Division of Oncology Drug Products, HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

March 9, 2001

NDA 21-335

[(imatinib mesylate)
Capsules

Replacement file (electronic)

AZ

Dear Ms. Staten,

Reference is made to our New Drug Application (NDA) for (imatinib mesylate) Capsules submitted February 27, 2001.

Enclosed is a disk containing replacement files N21335\clinstat\iss.pdf and clinstat\ise.pdf to substitute for these files included in the original NDA.

There are no new data or additional analyses provided in this submission.

If you have any questions or comments regarding this submission, please contact me at (973) 781-8180.

Sincerely,

Ellen Cutler

Ellen Cutler
Associate Director



Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080
Tel 973 781 8300

NOVARTIS

FAX

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936

TO

FROM

Name: Ann Staten	Name: Ellen Cutler
Company: FDA/DODP	Dept.: Drug Regulatory Affairs
Location: HFD-150	Phone No: 973-781-8180
Fax No. 301-827-4590	Fax No: 973-781-6325

Total pages (including cover sheet): 3

Date: March 6, 2001

Re: IND } STI571
Facsimile transmission

Dear Ann,

Attached is the letter from OPD confirming the orphan designation of _____ for treatment of CML.

Please let me know if anything additional is needed.

Kind regards,

Ellen

Mar 6 2001 13:21 P.01

9737816325
Fax: 9737816325

NOVARTIS



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 [redacted] as an orphan drug (application #00-1401).

We have completed the review of this application and have determined that [redacted] qualifies for orphan designation for the treatment of chronic myelogenous leukemia.

Please be advised that if [redacted] 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 FDCA (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 [redacted] 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

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: Ann Staten, Project Manager

Fax: 973-781-6325

Fax: 301-827-4590

Phone: 973-781-2282

Phone: 301-594-5770

Pages: 1

Date: March 5, 2001

Re: NDA 21-335 – Chemistry information request

Urgent For Review Please Comment Please Reply Please Recycle

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Ellen,

We need the following chemistry information ASAP to initiate inspection requests. Please let me know if this information is already provided in the NDA and where I can locate of the information.

The name and address of the facility(ies) and the contact person's name, title and telephone number. Please include all facilities involved in the manufacture, controls, stability testing and packaging of the drug substance and the drug product.

Sincerely,

Ann



NDA 21-335

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Attention: Ellen Cutler
Associate Director
Drug Regulatory Affairs

Dear Ms. Cutler:

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

Name of Drug Product: Imatinib mesylate) 50mg and 100mg capsules

Review Priority Classification: Priority (P)

Date of Application: February 27, 2001

Date of Receipt: February 27, 2001

Our Reference Number: NDA 21-335

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 April 28, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 27, 2001.

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 NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

Food and Drug Administration
Rockville MD 20857

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
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
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Ann Staten, Project Manager, at (301) 594-5770.

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

 **NOVARTIS**

Ellen Cutler
Associate Director
Regulatory Affairs

Tel 973-781-8180
Fax 973-781-6325

Novartis Pharmaceuticals Corporation
59 Route 10
East Hanover, NJ 07936-1080

Tel 973 781 8300

February 27, 2001

NDA 21-335

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

Imatinib mesylate Capsules

ORIGINAL NEW DRUG APPLICATION

Dear Sir/Madam,

In accordance with 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, Novartis Pharmaceuticals Corporation hereby submits an original New Drug Application (NDA) for **Imatinib mesylate, formerly STI571, CGP57148B** Capsules for the treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.

Imatinib mesylate is a new, rationally designed specific inhibitor of the Bcr-Abl tyrosine kinase, the gene product resulting from the translocated Philadelphia chromosome (Ph) which is the hallmark of chronic myeloid leukemia (CML). Results of extensive preclinical, technical, and clinical research are contained in this application. The clinical studies discussed in this NDA include one multiple dose tolerability/dose-finding study (phase I) and three large open, uncontrolled efficacy and safety studies (phase II), as an accelerated development to allow early registration in CML patients. A total of 1234 patients with CML and other Ph+ leukemias have been enrolled in these trials. The results of the Glivec studies are discussed in the perspective of the current state of knowledge in the treatment of CML as described with a comprehensive review of the literature for each target population (Appendix 4-6 of the Integrated Summary of Efficacy).

Request for Priority Review

Imatinib mesylate is intended for the treatment of patients with CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon (IFN)-based therapy. These are medical conditions for which there is a clear unmet medical need as demonstrated by the Fast Track designation of the myeloid blast crisis development program.

The clinical studies demonstrate that **Imatinib mesylate** provides hematologic control in all phases of the disease studied and cytogenetic response that appears higher than that obtained with any other available therapy. It is a convenient oral medication 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 [redacted] offers a significant improvement in the treatment of CML, a serious and life-threatening condition, compared to available therapies as demonstrated in comparison to historical controls.

Collaborative review

Please refer to our January 22, 2001 letter submitted to IND [redacted] and to our November 28, 2000 telephone conversation. Novartis encourages open and shared interactions between FDA and health authorities of Canada, Japan and Australia throughout the review of the NDA. Novartis remains committed to facilitate timely global review of our application and look forward to any suggestions the Division may have to support this initiative.

Electronic Submission

Archival versions of the following files are provided electronically to facilitate the review process. All files are formatted in accordance with the January 1999 Guidance for Industry - Providing Regulatory Submissions in Electronic Format - NDAs. The electronic submission is contained on [redacted] A Word file of the annotated draft package insert is provided on a diskette in volume 1. All electronic files accompanying this submission have been successfully scanned with [redacted]

Section 8: Clinical Data

The supportive post-text supplements containing tables, figures and listings are provided electronically for all clinical study reports and integrated summaries.

Section 11: Case Report Tabulations

SAS transport files are provided for all clinical trials (03 001, 0102, 0109, 0110). The SAS files are accompanied by the associated data definition tables and annotated CRFs. Data listings are also provided for the pivotal Phase II trials. In addition, SAS transport files and data definition tables of the pharmacokinetic data from the pivotal trials (03 001, 0102, 0109, 0110 population PK) are included.

Section 12: Case Report Forms

Scanned images of CRFs for patients as detailed in section 3.3.4 of our August 23, 2000 pre-NDA meeting briefing book are provided. (FDA comments/minutes are included in volume 1 of the NDA.)

This NDA has been prepared in a manner that is consistent with existing regulation, relevant guidelines, and understandings that were reached during meetings with the Agency. A copy of relevant correspondence is located in Volume 1 of the NDA.

We would like to request a 90-day post-submission conference 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.

This application contains technical documentation in support of 50 mg and 100 mg hard gelatin capsules.

A certified copy of Section 3 of this NDA is being provided to our district office in compliance with the pre-approval inspection (PAI) requirements.

A waiver of the FDA User Fee for this application is provided as received orphan designation for the treatment of CML on January 31, 2001.

Novartis Pharmaceuticals Corporation considers the information contained within this application to be confidential, and its contents are not to be disclosed without express written consent.

If you have any questions or comments regarding this submission, please contact me at (973) 781-8180.

Sincerely,



Ellen Cutler
Associate Director

Attachments: Form FDA 356H
Form FDA 3397
Volumes 1-73