

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-335/S-006

Approval Letter(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-335/S-006

Novartis Pharmaceuticals Corporation
One Health Plaza, Building 105/2W200
Hanover, New Jersey 07936-1080

Attention: Robert A. Miranda, Director
Drug Regulatory Affairs

Dear Mr. Miranda:

Please refer to your supplemental new drug application dated April 30, 2003, received May 2, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec (imatinib mesylate) Capsules, 100 mg.

We acknowledge receipt of your submissions dated May 2 and July 10, 2003 and correspondences dated October 28 and 29, 2003.

This "Changes Being Effected" supplemental new drug application provides for additional information to be included in the Post Marketing Experiences subsection of the ADVERSE REACTIONS section of the package insert.

We completed our review of this supplemental new drug application, as amended. It is approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on April 30, 2003.

However, we remind you of your October 28 and 29, 2003 agreement to make the following changes to the package insert at the next printing or within 6 months, whichever comes first.

1. Under **PRECAUTIONS, General** subsection, the following paragraph should be added as the first paragraph and read as follows:

Dermatologic Toxicities:

Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, have been reported with use of Gleevec. In some cases reported during post-marketing surveillance, a recurrent dermatologic reaction was observed upon rechallenge. Several foreign post-marketing reports have described cases in which patients tolerated the reintroduction of Gleevec therapy after resolution or improvement of the bullous reaction. In these instances, Gleevec was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

2. Under **ADVERSE REACTIONS**, following the **Gastrointestinal Stromal Tumors** subsection, the following subsection should read as:

Additional Data From Multiple Clinical Trials

The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare (estimated less than 0.1%) adverse events have been reported during clinical trials of Gleevec. These events are included based on clinical relevance.

Cardiovascular: *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness

Clinical Laboratory Tests: *Infrequent:* blood CPK increased, blood LDH increased

Dermatologic: *Less common:* dry skin, alopecia *Infrequent:* exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura *Rare:* vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis

Digestive: *Less common:* abdominal distension, gastroesophageal reflux, mouth ulceration *Infrequent:* gastric ulcer, gastroenteritis, gastritis *Rare:* colitis

Hematologic: *Infrequent:* pancytopenia *Rare:* aplastic anemia

Hypersensitivity: *Rare:* angioedema

Infections: *Infrequent:* sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: *Infrequent:* hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased *Rare:* hyperkalemia, hyponatremia

Musculoskeletal: *Less common:* joint swelling *Infrequent:* sciatica, joint and muscle stiffness

Nervous System/Psychiatric: *Less common:* paresthesia *Infrequent:* depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare:* increased intracranial pressure, cerebral edema (including fatalities)

Renal: *Infrequent:* renal failure, urinary frequency, hematuria

Reproductive: *Infrequent:* breast enlargement, menorrhagia, sexual dysfunction

Respiratory: *Rare:* interstitial pneumonitis, pulmonary fibrosis

Special Senses: *Less common:* conjunctivitis, vision blurred *Infrequent:* conjunctival hemorrhage, dry eye, vertigo, tinnitus *Rare:* macular edema, papilledema, retinal hemorrhage

If you issue a letter communicating important information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,


{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Grant Williams
10/31/03 02:27:42 PM
for Dr. Pazdur

PROJECT MANAGER REVIEW OF LABELING

NDA 21-335/S-006

Drug: Gleevec (imatinib mesylate) Capsules, 100mg
Applicant: Novartis Pharmaceuticals Corporation
Submission Date: April 30, 2003 CBE; July 10, 2003 BL (elect. word version);
May 2, 2003 BF
Receipt Date: May 2, 2003; July 11, 2003; May 5, 2003

BACKGROUND:

On February 26, 2003, the sponsor submission dated January 27, 2003 containing FPL for supplement 004 was acknowledged and retained.

Novartis submitted a "Changes Being Effected" (CBE) labeling supplement (S-006) dated April 30, 2003 to provide for additions to the **Post Marketing Experiences** subsection of the **ADVERSE REACTIONS** section of the package insert.

DOCUMENTS REVIEWED:

I compared the approved January 27, 2003 FPL against the FPL in the CBE supplement dated April 30, 2003 (electronic submission dated July 10, 2003).

REVIEW:

The following changes were identified.

Under the **ADVERSE REACTIONS** section, [

]

[

]

Cardiovascular: *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness

Clinical Laboratory Tests: *Infrequent:* blood CPK increased, blood LDH increased

Dermatologic: *Less common:* dry skin, alopecia *Infrequent:* exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura *Rare:* vesicular rash, Stevens-Johnson syndrome

Digestive: *Less common:* abdominal distension, gastroesophageal reflux, mouth ulceration *Infrequent:* gastric ulcer, gastroenteritis, gastritis *Rare:* colitis

Hematologic: *Infrequent:* pancytopenia

Hypersensitivity: *Rare:* angioedema

Infections: *Infrequent:* sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: *Infrequent:* hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased *Rare:* hyperkalemia, hyponatremia

Musculoskeletal: *Less common:* joint swelling *Infrequent:* sciatica, joint and muscle stiffness

Nervous System/Psychiatric: *Less common:* paresthesia *Infrequent:* depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare:* increased intracranial pressure, cerebral edema (including fatalities)

Renal: *Infrequent:* renal failure, urinary frequency, hematuria

Reproductive: *Infrequent:* breast enlargement, menorrhagia, sexual dysfunction

Respiratory: *Rare:* interstitial pneumonitis, pulmonary fibrosis

Special Senses: *Less common:* conjunctivitis, vision blurred *Infrequent:* conjunctival hemorrhage, dry eye, vertigo, tinnitus *Rare:* macular edema, papilledema, retinal hemorrhage

These changes were reviewed by the Medical Reviewer and the safety evaluator in the Office of Drug Safety (ODS). The safety evaluator and the medical review team recommended changes to the package insert and the following recommendations were shared with Novartis on October 15, 2003:

1. Under **PRECAUTIONS, General** subsection, the following paragraph should be added as the first paragraph:

Dermatologic Toxicities:

Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, have been reported with use of Gleevec. In some cases reported during post-marketing surveillance, a recurrent dermatologic reaction was observed upon rechallenge. Several foreign post-marketing reports have

described cases in which patients tolerated the reintroduction of Gleevec therapy after resolution or improvement of the bullous reaction. In these instances, Gleevec was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines.

2. Under **ADVERSE REACTIONS**, following the **Gastrointestinal Stromal Tumors** subsection, the following two subsections should read as:

□ **Data From Multiple Clinical Trials**

The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare (estimated less than 0.1%) adverse events have been reported during clinical trials of Gleevec. These events are included based on clinical relevance

Cardiovascular: *Infrequent:* cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness

Clinical Laboratory Tests: *Infrequent:* blood CPK increased, blood LDH increased

Dermatologic: *Less common:* dry skin, alopecia *Infrequent:* exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes, photosensitivity reaction, purpura *Rare:* vesicular rash, Stevens-Johnson syndrome

Digestive: *Less common:* abdominal distension, gastroesophageal reflux, mouth ulceration *Infrequent:* gastric ulcer, gastroenteritis, gastritis *Rare:* colitis

Hematologic: *Infrequent:* pancytopenia

Hypersensitivity: *Rare:* angioedema

Infections: *Infrequent:* sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: *Infrequent:* hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased *Rare:* hyperkalemia, hyponatremia

Musculoskeletal: *Less common:* joint swelling *Infrequent:* sciatica, joint and muscle stiffness

Nervous System/Psychiatric: *Less common:* paresthesia *Infrequent:* depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine,

memory impairment *Rare*: increased intracranial pressure, cerebral edema (including fatalities)

Renal: *Infrequent*: renal failure, urinary frequency, hematuria

Reproductive: *Infrequent*: breast enlargement, menorrhagia, sexual dysfunction

Respiratory: *Rare*: interstitial pneumonitis, pulmonary fibrosis

Special Senses: *Less common*: conjunctivitis, vision blurred *Infrequent*: conjunctival hemorrhage, dry eye, vertigo, tinnitus *Rare*: macular edema, papilledema, retinal hemorrhage

Post Marketing Experience

The following adverse events have been reported in association with post-approval use of Gleevec. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or to establish a causal relationship to drug exposure.

Dermatologic: acute generalized exanthematous pustulosis

Hematologic: aplastic anemia

On October 28, 2003, Novartis concurred with the changes but requested that the format be modified as follows (changes highlighted in yellow):

Under **ADVERSE REACTIONS**, following the **Gastrointestinal Stromal Tumors** subsection, the following one subsection should replace the FDA proposed two subsections and read as follows:

Additional Data From Multiple Clinical Trials

The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare (estimated less than 0.1%) adverse events have been reported during clinical trials of Gleevec. These events are included based on clinical relevance.

Cardiovascular: *Infrequent*: cardiac failure, tachycardia, hypertension, hypotension, flushing, peripheral coldness

Clinical Laboratory Tests: *Infrequent*: blood CPK increased, blood LDH increased

Dermatologic: *Less common*: dry skin, alopecia *Infrequent*: exfoliative dermatitis, bullous eruption, nail disorder, skin pigmentation changes,

photosensitivity reaction, purpura *Rare*: vesicular rash, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis

Digestive: *Less common*: abdominal distension, gastroesophageal reflux, mouth ulceration *Infrequent*: gastric ulcer, gastroenteritis, gastritis *Rare*: colitis

Hematologic: *Infrequent*: pancytopenia *Rare*: aplastic anemia

Hypersensitivity: *Rare*: angioedema

Infections: *Infrequent*: sepsis, herpes simplex, herpes zoster

Metabolic and Nutritional: *Infrequent*: hypophosphatemia, dehydration, gout, appetite disturbances, weight decreased *Rare*: hyperkalemia, hyponatremia

Musculoskeletal: *Less common*: joint swelling *Infrequent*: sciatica, joint and muscle stiffness

Nervous System/Psychiatric: *Less common*: paresthesia *Infrequent*: depression, anxiety, syncope, peripheral neuropathy, somnolence, migraine, memory impairment *Rare*: increased intracranial pressure, cerebral edema (including fatalities)

Renal: *Infrequent*: renal failure, urinary frequency, hematuria

Reproductive: *Infrequent*: breast enlargement, menorrhagia, sexual dysfunction

Respiratory: *Rare*: interstitial pneumonitis, pulmonary fibrosis

Special Senses: *Less common*: conjunctivitis, vision blurred *Infrequent*: conjunctival hemorrhage, dry eye, vertigo, tinnitus *Rare*: macular edema, papilledema, retinal hemorrhage

On October 29, 2003, the safety evaluator and medical review team concurred with the above proposal.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

This supplement should be approved and the sponsor reminded to make the agreed upon changes to the package insert at the next printing or within 6 months, whichever comes first.

___ *{See appended electronic signature page}*__

Ann Staten, Regulatory Health Project Manager

___ *{See appended electronic signature page}*__

Dotti Pease, Chief, Project Manager Staff

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this page is the manifestation of the electronic signature.**

/s/

Ann Staten
10/30/03 04:06:46 PM
CSO

Dianne Spillman
10/31/03 11:11:00 AM
CSO
Signing/Acting for Dotti Pease, CPMS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		ODS POSTMARKETING SAFETY REVIEW	
FROM: DDRE (HFD-430) Kathleen Phelan, R.Ph., Safety Evaluator		DATE: September 12, 2003 OPDRA PID # D030520	
TO: DODP (HFD-150) Richard Pazdur, M.D., Director		THROUGH: DDRE (HFD-430) Mark Avigan, M.D., Acting Director	
DRUG (Est)/APPROVAL: imatinib mesylate/May 10, 2001		NDA/IND # 21-335	SPONSOR: Novartis
DRUG NAME (Trade): Gleevec		THERAPEUTIC CLASSIFICATION: cytotoxic	
EVENT: Post marketing safety labeling change recommendations and response to CBE N21335\S006\2003-04-30			
Executive Summary: This document presents ODS' recommendations for Gleevec adverse event labeling based on <ul style="list-style-type: none"> • June 3, 2003 review of serious skin adverse events associated with Gleevec by Robert Pratt, Pharm D., Safety Evaluator, DDRE (review available in DFS under NDA 21-335); • March 14, 2003 review of serious hematological adverse events associated with Gleevec by Carol Pamer, R.Ph., Safety Evaluator, DDRE (review available in DFS under NDA 21-335); • January 30, 2003 review of interstitial lung disease associated with Gleevec by Robert Pratt, Pharm D., Safety Evaluator, DDRE (review available in DFS under NDA 21-335) and; • CBE N21335\S006 submitted by Novartis and Novartis' response to ODS' questions about the CBE (CBE N21335\S006\2003-04-30 available in EDR; ODS' questions and Novartis' response to ODS' questions available as Attachment 1 to this document). 			
ODS' recommendations for Gleevec adverse event labeling are <ul style="list-style-type: none"> • to add to Precautions a paragraph describing rechallenge experience in patients with serious skin events; • to add the adverse events acute exanthematous pustulosis and aplastic anemia to Post-Marketing Experience; and • to change the heading for the adverse events added in the CBE from that proposed by Novartis to one that more accurately explains the source of the adverse events. 			
Three reviews of adverse events associated with Gleevec were completed by ODS during the first 6 months of 2003. In April of 2003, Novartis submitted a CBE for major additions to the Post-Marketing adverse events section of the label. The CBE incorporated most of the events that ODS recommended adding and it also provided incidence rates for all events proposed for addition. The presence of incidence rates suggested a non-spontaneous source for the adverse events. Novartis confirmed that the events were gleaned from clinical trials but stated all but two had also been reported spontaneously.			
ODS agrees with Novartis' CBE with the exceptions that the heading <input type="checkbox"/> <input type="checkbox"/> to more accurately reflect the source of the data from clinical trials and that the additional events identified by ODS, namely acute exanthematous pustulosis and aplastic anemia, be added to the Post-Marketing Experience section of Gleevec labeling.			
On July 28, 2003, ODS presented some of the adverse events associated with Gleevec at an Oncology Monday meeting. The presentation included cases of serious skin reactions in which patients rechallenged with Gleevec tolerated a lower dose with concomitant steroids, antihistamines, or a second interruption of Gleevec therapy. It was decided at that meeting that ODS would draft a paragraph describing this clinical experience for possible inclusion in the Precautions section of Gleevec labeling. That draft paragraph is included in this document under <i>Recommendations for Gleevec labeling</i> .			

Background and Discussion:

Routine AERS in-box review found reports of serious skin reactions, serious hematological adverse events, and interstitial lung disease associated with Gleevec use. These safety issues were reviewed in-depth by Robert Pratt and Carol Pamer of ODS. Their reviews are available in DFS and the issues will not be extensively discussed in this document.

Serious skin reactions

ODS recommended the addition of erythema multiforme, Stevens Johnson syndrome (SJS), exfoliative dermatitis and acute exanthematous pustulosis to the product labeling based on R. Pratt's June 3, 2003 review of serious skin reactions with Gleevec. That review identified 32 cases of erythema multiforme (12), SJS (8), toxic epidermal necrolysis (TEN; 1), oculomucocutaneous syndrome (1), exfoliative dermatitis (7) and acute exanthematous pustulosis (3) with temporal association to Gleevec use at 300 to 600 mg per day to treat chronic myeloid leukemia or gastrointestinal stromal tumors. There were no deaths. In 31 of 32 cases, the adverse event subsided with Gleevec discontinuation and corticosteroid or antihistamine treatment in some cases. In 8 of 13 erythema multiforme, SJS or TEN cases, the reaction recurred with Gleevec reinitiation. However, five of eight rechallenged patients were ultimately able to tolerate a lower dose of Gleevec with concomitant steroids or antihistamines or a second interruption of Gleevec use.

Discussion of these cases at the July 28 Oncology Monday meeting ended with an agreement that R. Pratt would draft a descriptive paragraph for possible inclusion in the Precautions section of Gleevec labeling. That paragraph is below under *Recommendations for Gleevec labeling*.

In the CBE, Novartis proposes the addition of exfoliative dermatitis, bullous eruption, vesicular rash, and Stevens-Johnson syndrome to Gleevec labeling. We agree with these additions but suggest that acute exanthematous pustulosis be added also.

Hematological events

C. Pamer's March 14, 2003 review of serious hematological adverse events identified 71 cases of pancytopenia and 18 biopsied cases of aplastic anemia. Seven fatal cases were considered by the reporters to be related to Gleevec therapy. Novartis proposes adding pancytopenia to labeling in the CBE; we recommend adding aplastic anemia also.

Respiratory events

ODS recommended addition of "interstitial pneumonitis, including pulmonary fibrosis" to labeling based on a review of interstitial lung disease associated with Gleevec by R. Pratt dated January 30, 2003. Novartis' CBE proposes addition of interstitial pneumonitis and pulmonary fibrosis. We agree with this addition.

Section headings used in label

We recommend changing the heading used for the adverse reactions list that Novartis proposes adding to labeling. Novartis submitted a CBE for extensive additions to the Post-Marketing Experiences section that included incidence rates. Novartis' supporting documents consisted of counts of spontaneous reports. However, incidence rates cannot be determined using post-marketing spontaneous adverse event reports, indicating that Novartis used supporting data other than that submitted with the CBE. Upon ODS' request, Novartis provided additional information via e-mail, which is appended to this document as Attachment 1. The additional information states that the incidence rates were determined from pooled clinical trial data, that two of the adverse events they proposed for addition occurred only in trials and have not been reported spontaneously, and that the adverse events they propose adding were chosen on the basis of clinical significance and possible relatedness to Gleevec use. We recommend that the heading used in labeling to identify these adverse events be changed to accurately reflect their source. This will require clarifying whether the clinical trials included in the pooled data reflect all trials or only trials conducted after marketing. Also, this will require the reinsertion of a Post-Marketing Experiences section to contain spontaneously reported adverse events identified during post-marketing surveillance.

We also suggest confirming that the proposed adverse events all occurred in clinical trials, as the Novartis response to ODS' questions states. Specifically, the CBE includes "cerebral edema (including fatalities)" as an event with a frequency of <0.1% in a pool of post-marketing studies. Did fatalities occur due to cerebral edema in the studies or was this wording only retained from earlier labeling?

Recommendations for Gleevec labeling:

Add to Precautions section:

"Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, have been reported [] Gleevec. In some [] cases, [] Several foreign post-marketing reports have described cases in which patients tolerated the reintroduction of Gleevec therapy after resolution or improvement of the bullous reaction. In these instances, Gleevec was resumed at a dose lower than that at which the reaction occurred and some patients also received concomitant treatment with corticosteroids or antihistamines."

Change heading of adverse events section Novartis proposed [] to:

[] The following less common (estimated 1%-10%), infrequent (estimated 0.1%-1%), and rare (estimated less than 0.1%) adverse events have been reported during clinical trials of Gleevec. These events are included based on clinical relevance []

The final wording of the above heading must be developed in cooperation with Novartis to insure accurate reflection of the data source and appropriate distribution of adverse events between this section and the *Post-Marketing Experiences* section.

Reinsert Post-Marketing Experience section as follows:

"Post-Marketing Experiences

The following adverse events have been reported in association with post-approval use of Gleevec. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or to establish a causal relationship to drug exposure.

Dermatologic: acute generalized exanthematous pustulosis

Hematologic: aplastic anemia"

Reviewer's Signature / Date:

Team Leader's Signature / Date:

Division Director Signature / Date:

Attachments:

1. Novartis' response to ODS' questions regarding CBE N21335\S0006

Attachment 1
Novartis' response to ODS questions regarding CBE N21335\S006

FDA Question #1: Explain how events were chosen for inclusion in the Post-Marketing Experiences of the USPI.

Answer: All of the spontaneous, literature and post-marketing clinical trial data available in 2002 were reviewed for adverse event inclusion in the post-marketing experience section of the package insert (submitted as a CBE, NDA 21-335, S-006). Each new adverse event term was selected for inclusion based on the assessment of clinical relevance and possible causality. There were no other new adverse event terms reported from the spontaneous data that was not already included from the reports in the clinical trial data. The only difference in adverse event terms reported between the clinical trial data and the spontaneous data were the reports of Herpes simplex and macular edema, which had only been reported from clinical trial data and are included in the post-marketing experience section of the USPI. The adverse event terms included are also consistent with the Novartis global labeling for Gleevec®/Glivec®.

FDA Question #2: Explain the method used to determine the incidence rates proposed.

Answer: The incidence rates were determined from clinical trial data, where there is a known denominator value. This is the most reliable method of estimating the incidence rate. The table below specifically provides the AE incidence rates from the pool of the CML clinical trials, which was used for selecting the post-marketing adverse event terms.

Following the new updated data obtained from the GIST and CML clinical trials, the safety data was recently re-evaluated. The new data showed some small variations ($\leq 0.6\%$) in cumulative incidence rates, but these differences were expected and were not clinically significant. Therefore, the adverse event incidence rates reflected in the labeling remains unchanged from the 2002 data.

RATIONALE FOR AE FREQUENCIES - GLEEVEC POST-MARKETING EXPERIENCE STUDY 102, 106, 109, 110 DATABASE CUT-OFF JANUARY 31, 2002 UNLESS OTHERWISE INDICATED	
USPI POST-MARKETING SECTION	RELATED AE FREQUENCY (%) FROM POOL OF POST-MARKETING STUDIES
Cardiovascular: Infrequent AEs	
Cardiac Failure	0.2
Tachycardia	0.4
Hypertension	0.6
Hypotension	0.2
Flushing	1
Peripheral Coldness	0.5
Laboratory Tests: Infrequent AEs	
Blood CPK increased	0.4
Blood LDH increased	0.3
Dermatologic: Less Common AEs	
Dry Skin	4.2
Alopecia	2.9

USPI POST-MARKETING SECTION	RELATED AE FREQUENCY (%) FROM POOL OF POST-MARKETING STUDIES
Dermatologic: Infrequent AEs	
Exfoliative Dermatitis/Bullous Eruption	0.3
Nail Disorder	0.3
Skin Pigmentation Changes (Hyperpigmentation)	0.3
Photosensitivity Reaction	0.6
Purpura	0.2
Dermatologic: Rare AEs	
Vesicular Rash	<0.1
Stevens-Johnson Syndrome	<0.1*
Digestive: Less Common AEs	
Abdominal Distention	3
Gastroesophageal Reflux	1.7
Mouth Ulceration	1.1
Digestive: Infrequent AEs	
Gastric Ulcer	0.3
Gastroenteritis	0.3
Gastritis	1
Digestive: Rare AEs	
Colitis	<0.1
Hematologic: Infrequent AEs	
Pancytopenia	1
Hypersensitivity: Rare AEs	
Angioedema	<0.1
Infections: Infrequent AEs	
Sepsis	0.2*
Herpes simplex	0.6
Herpes zoster	0.4
Metabolic/Nutritional: Infrequent AEs	
Hypophosphatemia	0.2
Dehydration	0.3
Gout	0.3
Appetite Disturbance (Appetite Increased)	0.9
Weight Decreased	0.9

USPI POST-MARKETING SECTION	RELATED AE FREQUENCY (%) FROM POOL OF POST-MARKETING STUDIES
Metabolic/Nutritional: Rare AEs	
Hyperkalemia	<0.1
Hyponatremia	<0.1
Musculoskeletal: Less Common AEs	
Joint Swelling	1.7
Musculoskeletal: Infrequent AEs	
Sciatica	0.2
Joint & Muscle Stiffness (Joint stiffness)	0.4
Nervous S./Psychiatric: Less Common AEs	
Paresthesia	2.2
Nervous S./Psychiatric: Infrequent AEs	
Depression	0.3
Anxiety	0.3
Syncope	0.3
Peripheral Neuropathy	0.4
Somnolence	0.4
Migraine	0.5
Memory Impairment	0.3
Nervous S./Psychiatric: Rare AEs	
Increased Intracranial Pressure	<0.1
Cerebral Edema	< 0.1*
Renal: Infrequent AEs	
Renal Failure	0.7
Urinary Frequency	0.3
Hematuria	0.2
Reproductive: Infrequent AEs	
Breast Enlargement	0.6
Menorrhagia	0.3
Sexual Dysfunction	0.2
Respiratory: Rare AEs	
Interstitial Pneumonitis	<0.1*
Pulmonary Fibrosis	<0.1*

USPI POST-MARKETING SECTION	RELATED AE FREQUENCY (%) FROM POOL OF POST-MARKETING STUDIES
Special Senses: Less Common AEs	
Conjunctivitis	1.4
Vision Blurred	1.1
Special Senses: Infrequent AEs	
Conjunctival Hemorrhage	1
Dry Eye	1
Vertigo	0.8
Tinnitus	0.3
Special Senses: Rare AEs	
Macular Edema	<0.1
Papilledema	<0.1
Retinal Hemorrhage	<0.1
* Database cut-off June 5, 2003	

FDA Question #3: Explain why erythema multiforme was not included.

Answer: Erythema multiforme was not included because it was adequately covered by two other terms used in the Post-Marketing Experiences section of the USPI, which were bullous eruption and Stevens-Johnson Syndrome.

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/s/

Kathleen Phelan
9/12/03 10:46:19 AM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
9/12/03 06:43:55 PM
DRUG SAFETY OFFICE REVIEWER

Staten, Ann M

From: Staten, Ann M
Sent: Monday, June 02, 2003 3:06 PM
To: Robert Miranda (E-mail)
Subject: FW: e-mail to send to Novartis

Importance: High

Dear Bob,

Please refer to your CBE submitted to NDA 21-335/S-006. We have the following request from the postmarketing reviewer:

Please describe in greater detail how you decided which adverse events to include in the proposed Post-marketing Experiences section, as well as the method used to determine incidence rates. The following information supports the request:

If raw event counts were used as the basis of your decisions, the counts in Appendices 1, 2, and 3 that you provided in support of the changes appear to conflict with the incidence categories proposed. For example, you report 7 cases of dry skin and categorize dry skin as a less common event. By your definition, less common means the estimated incidence is 1 to 10% of imatinib-treated patients. However, you report 64 cases of pancytopenia, which you classify as an infrequent event (0.1 to 1% estimated incidence). Similarly, you report 6 cases of Stevens-Johnson syndrome, which you classify as a rare event. Renal failure, with 28 cases, is classified as infrequent while alopecia, with 1 case, is classified as less common.

Also, how were the events to be included chosen? For example, you report 13 erythema multiforme cases and do not propose it's addition, while proposing addition of Stevens-Johnson syndrome based on 6 reports.

Thanks,
Ann

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ON ORIGINAL**

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this page is the manifestation of the electronic signature.**

/s/

Ann Staten
6/2/03 03:04:21 PM
CSO

Staten, Ann M

From: Staten, Ann M
Sent: Monday, October 20, 2003 12:53 PM
To: Robert Miranda (robert.miranda@pharma.novartis.com)
Subject: FW: Gleevec and aplastic anemia, AGEF backgrounds

Importance: High

Dear Bob,

As a follow-up to your request for additional information on the Post-Marketing Experience section, attached is from our safety monitor.

Please let me know if you have any questions.

ann

With the information below, Novartis should be able to obtain the adverse event cases upon which the request for addition of aplastic anemia and acute generalized exanthematous pustulosis to Gleevec labeling was based. In order to obtain the Office of Drug Safety reviews themselves, Novartis must request them from FOI. ODS can expedite the request.

These are the published references containing the reports of acute generalized exanthematous pustulosis upon which the request for its addition was based:

- Schwarz M, Kreuzer K, Baskaynak G, et al. Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. *Eur J Haematol* 2002; 69:254-256.
- Brouard MC, Prins C, Mach-Pascual S, et al. Acute generalized exanthematous pustulosis associated with STI571 in a patient with chronic myeloid leukemia. *Dermatology* 2001; 203:57-59

These are the manufacturer's cases of pancytopenia with hypocellularity on bone marrow biopsy upon which the request for addition of aplastic anemia was based:

APPEARS THIS WAY
ON ORIGINAL

CSENUM	AGE	SEX	MFRCTRL	CNTRY	STUDY	OUTC1	OUTC2	OUTC3	OUTC6	MET CASE CRIT?	BONE MAR BX +
3676225	70	Female	PHHO2001AU05310	AU	Y	MS				Y	Y
3676833	38	Male	PHHO2001CA04550	CA	Y	HO				Y	Y
3660758	23	Male	PHHO2001ES03347	ES	Y	HO				Y	Y
3665449	71	Male	PHHO2001GB04666	GB	Y	HO				Y	Y
3761020	58	Male	PHBS2002JP01200	JP		MS				Y	Y
3855131	50	Female	PHBS2002JP11711	JP	LIT	MS				Y	Y
3755200	72	Male	PHBS2001JP13042	JP		DE				Y	Y
3784956	36	Male	PHBS2002JP01068	JP		MS				Y	Y
3762458	36	Female	PHBS2002JP01696	JP		HO				Y	Y
3795769	70	Female	PHBS2002JP05690	JP		HO				Y	Y
3858291	40	Female	PHBS2002JP04425	JP	LIT	HO				Y	Y
3665426	73	Female	PHHO2001SE03009	SE	Y	HO	MS			INC	Y
3662749	62	Female	PHHO2001SE03467	SE	Y	HO				Y	Y
3820017	46	Female	PHBS2002SG08064	SG		HO				Y	Y
3693821		Female	PHEH2001US06288	US		LT	HO			Y	Y
3676951	15	Female	PHEH2001US05323	US	Y	MS				Y	Y
3706090	56	Female	PHEH2001US07235	US		LT	HO			Y	Y
3664779	58	Male	PHHO2001ZA04440	ZA	Y	HO				INC	Y

The case definitions for pancytopenia and aplastic anemia are:

Clinical diagnosis (by reporter) of pancytopenia or aplastic anemia **-or-**

Presence of the following: WBC $\leq 3,500/\mu\text{L}$, platelets $\leq 55,000/\mu\text{L}$ & hemoglobin ≤ 10 g/dL

For aplastic anemia, bone marrow biopsy indicating hypocellularity, in addition to the above

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this page is the manifestation of the electronic signature.**

/s/

Ann Staten
10/22/03 11:18:46 AM
CSO

Staten, Ann M

From: Staten, Ann M
Sent: Wednesday, October 15, 2003 4:23 PM
To: Robert Miranda (robert.miranda@pharma.novartis.com)
Cc: Vena Herald (vena.herald@pharma.novartis.com)
Subject: Gleevec CBE dated 4-30-03 - FDA changes to the PI
Importance: High

Dear Bob,

Please refer to your NDA 21-335/S-006 (labeling supplement – CBE) dated 4-30-03. Please also refer to your submission dated July 10, 2003. We have reviewed the submissions and attached is our recommended wording (package insert attached).

Please let me know if your team agrees with these changes at your earliest convenience.

Thanks,
Ann

24 pages redacted from this section of
the approval package consisted of draft labeling

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

/s/

Ann Staten
10/22/03 11:13:30 AM
CSO
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