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Approval Package for:

APPLICATION NUMBER:

20-588/S005

Trade Name: Gleevac

Generic Name: Imatinib Mesylate

Sponsor: Novartis

Approval Date: March 14, 2005

Indications: Indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in chronic phase.

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APPLICATION NUMBER:

20-588 Supplement 5

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APPLICATION NUMBER:

20-588/S005

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-588/S-005

Novartis Pharmaceuticals Corporation
Drug Regulatory Affairs
One Health Plaza, Bldg. 105/Rm. 2W200
East Hanover, NJ 07936-1080

Attention: Robert A. Miranda, Director
Drug Regulatory Affairs

Dear Mr. Miranda:

Please refer to your supplemental new drug application dated September 7, 2004, received September 8, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gleevec® (imatinib mesylate) Tablets.

We acknowledge receipt of your correspondence dated February 15, 2005.

This supplemental new drug application provides for changes to the package insert to reflect additional data accumulated from the ongoing pivotal study (106) in newly diagnosed Ph+ CML.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission **"FPL for approved supplement NDA 21-588/S-005."** Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

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 reporting requirements for an approved NDA (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

Enclosure

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

/s/

Richard Pazdur
3/14/05 03:43:43 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-588/S005

LABELING

NOVARTIS

T2004-10
89019002

Gleevec®
(imatinib mesylate)

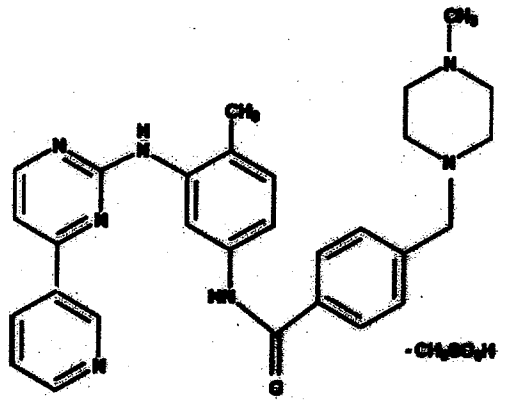
Tablets

Rx only

Prescribing Information

DESCRIPTION

Gleevec® (imatinib mesylate) film-coated tablets contain imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base. Imatinib mesylate is designated chemically as 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-phenyl]benzamide methanesulfonate and its structural formula is



Imatinib mesylate is a white to off-white to brownish or yellowish tinged crystalline powder. Its molecular formula is $C_{29}H_{31}N_7O \cdot CH_4SO_3$ and its molecular weight is 589.7. Imatinib mesylate is soluble in aqueous buffers ≤ pH 5.5 but is very slightly soluble to insoluble in neutral/alkaline aqueous buffers. In non-aqueous solvents, the drug substance is freely soluble to very slightly soluble in dimethyl sulfoxide, methanol and ethanol, but is insoluble in n-octanol, acetone and acetonitrile.

Inactive Ingredients: colloidal silicon dioxide (NF); crospovidone (NF); hydroxypropyl methylcellulose (USP); magnesium stearate (NF); and microcrystalline cellulose (NF). *Tablet coating:* ferric oxide, red (NF); ferric oxide, yellow (NF); hydroxypropyl methylcellulose (USP); polyethylene glycol (NF) and talc (USP).

CLINICAL PHARMACOLOGY

Mechanism of Action

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. In colony formation assays using *ex vivo* peripheral blood and bone marrow samples, imatinib shows inhibition of Bcr-Abl positive colonies from CML patients.

In vivo, it inhibits tumor growth of Bcr-Abl transfected murine myeloid cells as well as Bcr-Abl positive leukemia lines derived from CML patients in blast crisis.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. *In vitro*, imatinib inhibits proliferation and induces apoptosis in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.

Pharmacokinetics

The pharmacokinetics of Gleevec® (imatinib mesylate) have been evaluated in studies in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major active metabolite, the N-desmethyl derivative, are approximately 18 and 40 hours, respectively. Mean imatinib AUC increases proportionally with increasing doses ranging from 25 mg-1000 mg. There is no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-2.5 fold at steady state when Gleevec is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 95%, mostly to albumin and α_1-acid glycoprotein.

The pharmacokinetics of Gleevec are similar in CML and GIST patients.

Metabolism and Elimination

CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP1A2, CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. The main circulating active metabolite in humans is the N-demethylated piperazine derivative, formed predominantly by CYP3A4. It shows *in vitro* potency similar to the parent imatinib. The plasma AUC for this metabolite is about 15% of the AUC for imatinib.

Elimination is predominately in the feces, mostly as metabolites. Based on the recovery of compound(s) after an oral ^{14}C-labeled dose of imatinib, approximately 81% of the dose was eliminated within 7 days, in feces (68% of dose) and urine (13% of dose). Unchanged imatinib accounted for 25% of the dose (5% urine, 20% feces), the remainder being metabolites.

Typically, clearance of imatinib in a 50-year-old patient weighing 50 kg is expected to be 8 L/h, while for a 50-year-old patient weighing 100 kg the clearance will increase to 14 L/h. However, the inter-patient variability of 40% in clearance does not warrant initial dose adjustment based on body weight and/or age but indicates the need for close monitoring for treatment related toxicity.

Special Populations

Pediatric: As in adult patients, imatinib was rapidly absorbed after oral administration in pediatric patients, with a C_{max} of 2-4 hours. Apparent oral clearance was similar to adult values (11.0 L/hr/m^2 in children vs. 10.0 L/hr/m^2 in adults), as was the half-life (14.8 hours in children vs. 17.1 hr in adults). Dosing in children at both 260 mg/m^2 and 340 mg/m^2 achieved an AUC similar to the 400-mg dose in adults. The comparison of $AUC_{(0-24)}$ on Day 8 vs. Day 1 at 260 mg/m^2 and 340 mg/m^2 dose levels revealed a 1.5 and 2.2-fold drug accumulation, respectively, after repeated once-daily dosing. Mean imatinib AUC did not increase proportionally with increasing dose.

Hepatic Insufficiency: No clinical studies were conducted with Gleevec in patients with impaired hepatic function.

Renal Insufficiency: No clinical studies were conducted with Gleevec in patients with decreased renal function (studies excluded patients with serum creatinine concentration more than 2 times the upper limit of the normal range). Imatinib and its metabolites are not significantly excreted via the kidney.

Drug-Drug Interactions

CYP3A4 Inhibitors: There was a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) in healthy subjects when Gleevec was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor). (See PRECAUTIONS.)

CYP3A4 Substrates: Gleevec increased the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5- fold, respectively, indicating an inhibition of CYP3A4 by Gleevec. (See PRECAUTIONS.)

CYP3A4 Inducers: Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 8 days, followed by a single 400 mg dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold (90% confidence interval $\leq$ 3.5- to 4.3-fold), which represents mean decreases in C_{max}, $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ by 54%, 68% and 74%, of the respective values without rifampin treatment. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

In Vitro Studies of CYP Enzyme Inhibition: Human liver microsome studies demonstrated that Gleevec is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5 and 8 μM, respectively. Gleevec is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5. (See PRECAUTIONS.)

CLINICAL STUDIES

Chronic Myeloid Leukemia

Chronic Phase, Newly Diagnosed

An open-label, multicenter, international randomized Phase 3 study has been conducted in patients with newly diagnosed Philadelphia chromosome positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. This study compared treatment with either single-agent Gleevec® (imatinib mesylate) or a combination of interferon-alfa (IFN) plus cytarabine (Ara-C). Patients were allowed to cross over to the alternative treatment arm if they failed to show a complete hematologic response (CHR) at 6 months, a major cytogenetic response (MCyR) at 12 months, or if they lost a CHR or MCyR. Patients with increasing WBC or severe intolerance to treatment were also allowed to cross over to the alternative treatment arm with the permission of the study monitoring committee (SMC). In the Gleevec arm, patients were treated initially with 400 mg daily. In the IFN arm, patients were treated with a target dose of IFN of 5 MIU/m^2/day subcutaneously in combination with subcutaneous Ara-C 20 mg/m^2/day for 10 days/month.

A total of 1106 patients were randomized from 177 centers in 16 countries, 553 to each arm. Baseline characteristics were well balanced between the two arms. Median age was 51 years (range 18-70 years), with 21.9% of patients ≥60 years of age. There were 59% males and 41% females; 89.9% Caucasian and 4.7% Black patients. With a median follow-up of 31 and 30 months for Gleevec and IFN, respectively, 79% of patients randomized to Gleevec were still receiving first-line treatment. Due to discontinuations and cross-overs, only 7% of patients randomized to IFN were still on first-line treatment. In the IFN arm, withdrawal of consent (13.6%) was the most frequent reason for discontinuation of first-line therapy, and the most frequent reason for cross over to the Gleevec arm was severe intolerance to treatment (25.1%).

The primary efficacy endpoint of the study was progression-free survival (PFS). Progression was defined as any of the following events: progression to accelerated phase or blast crisis, death, loss of CHR or MCyR, or in patients not achieving a CHR an increasing WBC despite appropriate therapeutic management. The protocol specified that the progression analysis would compare the intent to treat (ITT) population: patients randomized to receive Gleevec were compared with patients randomized to receive interferon. Patients that crossed over prior to progression were not censored at the time of cross-over, and events that occurred in these patients following cross-over were attributed to the original randomized treatment.. The estimated rate of progression-free survival at 30 months in the ITT population was 87.8% in the Gleevec arm and 68.3% in the IFN arm ($p<0.001$), (Figure 1). The estimated rate of patients free of progression to accelerated phase (AP) or blast crisis (BC) at 30 months was 94.8% in the Gleevec arm compared to 89.6%, ($p=0.0016$) in the IFN arm, (Figure 2.) There were 33 and 46 deaths reported in the Gleevec and IFN arm, respectively, with an estimated 30-month survival rate of 94.6% and 91.6% respectively (differences not significant). The probability of remaining progression-free at 30 months was 100% for patients who were in complete cytogenetic response with major molecular response (≥3-log reduction in bcr-abl transcripts as measured by quantitative reverse transcriptase polymerase chain reaction) at 12 months, compared to 93% for patients in complete cytogenetic response

146 but without a major molecular response, and 82% in patients who were not in complete
147 cytogenetic response at this time point ($p<0.001$).

Figure 1 Time to Progression (ITT)

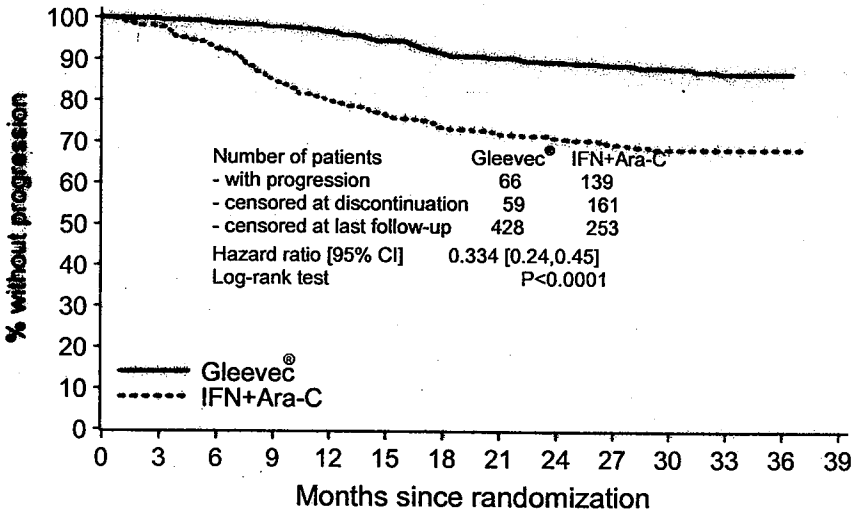


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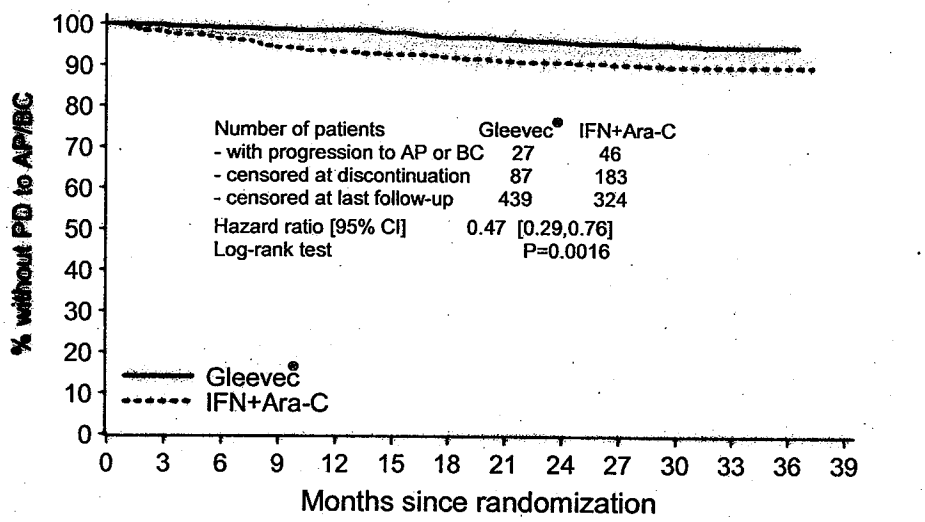
Figure 2 Time to Progression to AP or BC (ITT)



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153 Major cytogenetic response, hematologic response, evaluation of minimal residual
154 disease (molecular response), time to accelerated phase or blast crisis and survival were main
155 secondary endpoints. Response data are shown in Table 1. Complete hematologic response,
156 major cytogenetic response and complete cytogenetic response were also statistically
157 significantly higher in the Gleevec arm compared to the IFN + Ara-C arm.

Table 1 Response in Newly Diagnosed CML Study (First-Line) (30-month data)

(Best Response Rate)	Gleevec® n=553	IFN+Ara-C n=553
Hematologic Response[1]		
CHR Rate n (%)	527 (95.3%)*	308 (55.7%)*
[95% CI]	[93.2%, 96.9%]	[51.4%, 59.9%]
Cytogenetic Response[2]		
Major Cytogenetic Response n (%)	461 (83.4%)*	90 (16.3%)*
[95% CI]	[80.0%, 86.4%]	[13.3%, 19.6%]
Unconfirmed[3]	87.2%*	23.0%*
Complete Cytogenetic Response n (%)	378 (68.4%)*	30(5.4%)*
Unconfirmed[3]	78.8%*	10.7%*
Molecular response[4]		
Major response at 12 months (%)	40%*	2%*
Major response at 24 months (%)	54%*	NA[5]*

p<0.001, Fischer's exact test

[1] **Hematologic response criteria (all responses to be confirmed after ≥4 weeks):** WBC<10 x 10^9/L, platelet <450 x 10^9/L, myelocyte + metamyelocyte <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement.

[2] **Cytogenetic response criteria (confirmed after ≥4 weeks):** complete (0% Ph+ metaphases). or partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.

[3] Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic response on a subsequent bone marrow evaluation.

[4] **Major molecular response criteria:** in the peripheral blood, after 12 months of therapy, reduction of ≥3 logarithms in the amount of BCR-ABL transcripts (measured by real-time quantitative reverse transcriptase PCR assay) over a standardized baseline.

[5] Not Applicable: insufficient data, only two patients available with samples

Physical, functional, and treatment-specific biologic response modifier scales from the FACT-BRM (Functional Assessment of Cancer Therapy - Biologic Response Modifier) instrument were used to assess patient-reported general effects of interferon toxicity in 1067 patients with CML in chronic phase. After one month of therapy to six months of therapy, there was a 13%-21% decrease in median index from baseline in patients treated with interferon, consistent with increased symptoms of interferon toxicity. There was no apparent change from baseline in median index for patients treated with Gleevec.

Late Chronic Phase CML and Advanced Stage CML

Three international, open-label, single-arm Phase 2 studies were conducted to determine the safety and efficacy of Gleevec in patients with Ph+ CML: 1) in the chronic phase after failure of IFN therapy, 2) in accelerated phase disease, or 3) in myeloid blast crisis. About 45% of patients were women and 6% were Black. In clinical studies 38%-40% of patients were ≥60 years of age and 10%-12% of patients were ≥70 years of age.

Chronic Phase, Prior Interferon-Treatment

532 patients were treated at a starting dose of 400 mg; dose escalation to 600 mg was allowed. The patients were distributed in three main categories according to their response to prior interferon: failure to achieve (within 6 months), or loss of a complete hematologic response

(29%), failure to achieve (within 1 year) or loss of a major cytogenetic response (35%), or intolerance to interferon (36%). Patients had received a median of 14 months of prior IFN therapy at doses ≥25 x 10^6 IU/week and were all in late chronic phase, with a median time from diagnosis of 32 months. Effectiveness was evaluated on the basis of the rate of hematologic response and by bone marrow exams to assess the rate of major cytogenetic response (up to 35% Ph+ metaphases) or complete cytogenetic response (0% Ph+ metaphases). Median duration of treatment was 29 months with 81% of patients treated for ≥24 months (maximum = 31.5 months). Efficacy results are reported in Table 2. Confirmed major cytogenetic response rates were higher in patients with IFN intolerance (66%) and cytogenetic failure (64%), than in patients with hematologic failure (47%). Hematologic response was achieved in 98% of patients with cytogenetic failure, 94% of patients with hematologic failure, and 92% of IFN-intolerant patients.

Accelerated Phase

235 patients with accelerated phase disease were enrolled. These patients met one or more of the following criteria: ≥15%-<30% blasts in PB or BM; ≥30% blasts + promyelocytes in PB or BM; ≥20% basophils in PB; and <100 x 10^9/L platelets. The first 77 patients were started at 400 mg, with the remaining 158 patients starting at 600 mg.

Effectiveness was evaluated primarily on the basis of the rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia (i.e., clearance of blasts from the marrow and the blood, but without a full peripheral blood recovery as for complete responses), or return to chronic phase CML. Cytogenetic responses were also evaluated. Median duration of treatment was 18 months with 45% of patients treated for ≥24 months (maximum = 35 months). Efficacy results are reported in Table 2. Response rates in accelerated phase CML were higher for the 600-mg dose group than for the 400-mg group: hematologic response (75% vs. 64%), confirmed and unconfirmed major cytogenetic response (31% vs. 19%).

Myeloid Blast Crisis

260 patients with myeloid blast crisis were enrolled. These patients had ≥30% blasts in PB or BM and/or extramedullary involvement other than spleen or liver; 95 (37%) had received prior chemotherapy for treatment of either accelerated phase or blast crisis ("pretreated patients") whereas 165 (63%) had not ("untreated patients"). The first 37 patients were started at 400 mg; the remaining 223 patients were started at 600 mg.

Effectiveness was evaluated primarily on the basis of rate of hematologic response, reported as either complete hematologic response, no evidence of leukemia, or return to chronic phase CML using the same criteria as for the study in accelerated phase. Cytogenetic responses were also assessed. Median duration of treatment was 4 months with 21% of patients treated for ≥12 months and 10% for ≥24 months (maximum = 35 months). Efficacy results are reported in Table 2. The hematologic response rate was higher in untreated patients than in treated patients (36% vs. 22%, respectively) and in the group receiving an initial dose of 600 mg rather than 400 mg (33% vs. 16%). The confirmed and unconfirmed major cytogenetic response rate was also higher for the 600-mg dose group than for the 400 mg group (17% vs. 8%).

Table 2 Response in CML Studies

	Chronic Phase IFN Failure (n=532)	Accelerated Phase (n=235)	Myeloid Blast Crisis (n=260)
		600 mg n=158	600 mg n=223
	400 mg	400 mg n=77	400 mg n=37
		% of patients [$CI_{95\%}$]	
Hematologic Response[1]	**95% [92.3-96.3]**	**71%[64.8-76.8]**	**31% [25.2-36.8]**
Complete Hematologic Response (CHR)	95%	38%	7%
No Evidence of Leukemia (NEL)	Not applicable	13%	5%
Return to Chronic Phase (RTC)	Not applicable	20%	18%
Major Cytogenetic Response[2]	**60% [55.3-63.8]**	**21% [16.2-27.1]**	**7% [4.5-11.2]**
(Unconfirmed[3])	(65%)	(27%)	(15%)
Complete[4] (Unconfirmed[3])	39% (47%)	16% (20%)	2% (7%)

[1] **Hematologic response criteria (all responses to be confirmed after ≥4 weeks):**

CHR: Chronic phase study [WBC <10 x 10^9/L, platelet <450 x 10^9/L, myelocytes + metamyelocytes <5% in blood, no blasts and promyelocytes in blood, basophils <20%, no extramedullary involvement] and in the accelerated and blast crisis studies [ANC ≥1.5 x 10^9/L, platelets ≥100 x 10^9/L, no blood blasts, BM blasts <5% and no extramedullary disease]

NEL: same criteria as for CHR but ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L (accelerated and blast crisis studies)

RTC: <15% blasts BM and PB, <30% blasts + promyelocytes in BM and PB, <20% basophils in PB, no extramedullary disease other than spleen and liver (accelerated and blast crisis studies).

BM=bone marrow, PB=peripheral blood

[2] **Cytogenetic response criteria (confirmed after ≥4 weeks):** complete (0% Ph+ metaphases) or partial (1%-35%). A major response (0%-35%) combines both complete and partial responses.

[3] Unconfirmed cytogenetic response is based on a single bone marrow cytogenetic evaluation, therefore unconfirmed complete or partial cytogenetic responses might have had a lesser cytogenetic response on a subsequent bone marrow evaluation.

[4] Complete cytogenetic response confirmed by a second bone marrow cytogenetic evaluation performed at least one month after the initial bone marrow study.

The median time to hematologic response was 1 month. In late chronic phase CML, with a median time from diagnosis of 32 months, an estimated 87.8% of patients who achieved MCyR maintain their response 2 years after achieving their initial response. After 2 years of treatment, an estimated 85.4% of patients were free of progression to AP or BC , and estimated overall survival was 90.8% [88.3, 93.2]. In accelerated phase, median duration of hematologic response was 28.8 months for patients with an initial dose of 600 mg (16.5 months for 400 mg, p=0.0035). An estimated 63.8% of patients who achieved MCyR were still in response 2 years after achieving initial response. The median survival was 20.9 [13.1, 34.4] months for the 400 mg group and was not yet reached for the 600 mg group (p=0.0097). An estimated 46.2% [34.7, 57.7] vs. 65.8% [58.4, 73.3] of patients were still alive after 2 years of treatment in the 400-mg vs. 600-mg dose groups, respectively (p=0.0088). In blast crisis, the estimated median duration of hematologic response is 10 months. An estimated 27.2% [16.8, 37.7] of hematologic responders maintained their response 2 years after achieving their initial response. Median survival was 6.9 [5.8, 8.6] months, and an estimated 18.3% [13.4, 23.3] of all patients with blast crisis were alive 2 years after start of study.

Efficacy results were similar in men and women and in patients younger and older than age 65. Responses were seen in Black patients, but there were too few Black patients to allow a quantitative comparison.

Pediatric CML

One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to alpha interferon therapy. Patients ranged in age from 3 to 20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years old. Patients were treated at doses of 260 mg/m^2/day (n=3), 340 mg/m^2/day (n=4), 440 mg/m^2/day (n=5) and 570 mg/m^2/day (n=2). In the 13 patients for whom cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic response, and 2 had minimal cytogenetic response. At the recommended dose of 260 mg/m^2/day, 2 of 3 patients achieved a complete cytogenetic response. Cytogenetic response rate was similar at all dose levels.

In a second study, 2 of 3 patients with Ph+ chronic phase CML resistant to alpha interferon achieved a complete cytogenetic response at doses of 242 and 257 mg/m^2/day.

Gastrointestinal Stromal Tumors

One open-label, multinational study was conducted in patients with unresectable or metastatic malignant gastrointestinal stromal tumors (GIST). In this study 147 patients were enrolled and randomized to receive either 400 mg or 600 mg orally q.d. for up to 24 months. The study was not powered to show a statistically significant difference in response rates between the two dose groups. Patients ranged in age from 18 to 83 years old and had a pathologic diagnosis of Kit-positive unresectable and/or metastatic malignant GIST. Immunohistochemistry was routinely performed with Kit antibody (A-4502, rabbit polyclonal antiserum, 1:100; DAKO Corporation, Carpinteria, CA) according to analysis by an avidin-biotin-peroxidase complex method after antigen retrieval.

The primary outcome of the study was objective response rate. Tumors were required to be measurable at entry in at least one site of disease, and response characterization was based on Southwestern Oncology Group (SWOG) criteria. Results are shown in Table 3.

Table 3 Tumor Response in GIST Study

Total Patients	N	Confirmed Partial Response N (%)	95% Confidence Interval
400 mg daily	73	24 (33%)	22%, 45%
600 mg daily	74	32 (43%)	32%, 55%
Total	147	56 (38%)	30%, 46%

A statistically significant difference in response rates between the two dose groups was not demonstrated. At the time of interim analysis, when the median follow-up was less than 7 months, 55 of 56 patients with a confirmed partial response (PR) had a maintained PR. The data were too immature to determine a meaningful response duration. No responses were observed in 12 patients with progressive disease on 400 mg daily whose doses were increased to 600 mg daily.

INDICATIONS AND USAGE

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

Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). (See CLINICAL STUDIES: Gastrointestinal Stromal Tumors.) The effectiveness of Gleevec in GIST is based on objective response rate (see CLINICAL STUDIES). There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

CONTRAINDICATIONS

Use of Gleevec® (imatinib mesylate) is contraindicated in patients with hypersensitivity to imatinib or to any other component of Gleevec.

WARNINGS

Pregnancy

Women of childbearing potential should be advised to avoid becoming pregnant.

Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses ≥100 mg/kg, approximately equal to the maximum clinical dose of 800 mg/day (based on body surface area). Teratogenic effects included exencephaly or encephalocele, absent/reduced frontal and absent parietal bones. Female rats administered doses ≥45 mg/kg (approximately one-half the maximum human dose of 800 mg/day, based on body surface area) also experienced significant post-implantation loss as evidenced by either early fetal resorption or stillbirths, nonviable pups and early pup mortality between postpartum days 0 and 4. At doses higher than 100 mg/kg, total fetal loss was noted in all animals. Fetal loss was not seen at doses ≤30 mg/kg (one-third the maximum human dose of 800 mg).

Male and female rats were exposed *in utero* to a maternal imatinib mesylate dose of 45 mg/kg (approximately one-half the maximum human dose of 800 mg) from day 6 of gestation and through milk during the lactation period. These animals then received no imatinib exposure for nearly 2 months. Body weights were reduced from birth until terminal sacrifice in these rats. Although fertility was not affected, fetal loss was seen when these male and female animals were then mated.

There are no adequate and well-controlled studies in pregnant women. If Gleevec® (imatinib mesylate) is used during pregnancy, or if the patient becomes pregnant while taking (receiving) Gleevec, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

General

Dermatologic Toxicities: Bullous dermatologic reactions, including erythema multiforme and Stevens Johnson syndrome, have been reported with use of Gleevec® (imatinib mesylate). 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.

Fluid Retention and Edema: Gleevec is often associated with edema and occasionally serious fluid retention (see ADVERSE REACTIONS). Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. The probability of edema was increased with higher Gleevec dose and age >65 years in the CML studies. Severe superficial edema was reported in 1.1% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of other adult CML patients taking Gleevec. In addition, other severe fluid retention (e.g., pleural effusion, pericardial effusion, pulmonary edema, and ascites) events were reported in 0.7% of newly diagnosed CML patients taking Gleevec, and in 2%-6% of other adult CML patients taking Gleevec. There have been post-marketing reports, including fatalities, of cerebral edema, increased intracranial pressure, and papilledema in patients with CML treated with Gleevec.

Severe superficial edema and severe fluid retention (pleural effusion, pulmonary edema and ascites) were reported in 1%-6% of patients taking Gleevec for GIST.

GI Irritation: Gleevec is sometimes associated with GI irritation. Gleevec should be taken with food and a large glass of water to minimize this problem.

Hemorrhage: In the newly diagnosed CML trial, 1.1% of patients had grade 3/4 hemorrhage. In the GIST clinical trial seven patients (5%), four in the 600-mg dose group and three in the 400-mg dose group, had a total of eight events of CTC grade 3/4 - gastrointestinal (GI) bleeds (3 patients), intra-tumoral bleeds (3 patients) or both (1 patient). Gastrointestinal tumor sites may have been the source of GI bleeds.

Hematologic Toxicity: Treatment with Gleevec is associated with anemia, neutropenia, and thrombocytopenia. Complete blood counts should be performed weekly for the first month, biweekly for the second month, and periodically thereafter as clinically indicated (for example every 2-3 months). In CML, the occurrence of these cytopenias is dependent on the stage of

disease and is more frequent in patients with accelerated phase CML or blast crisis than in patients with chronic phase CML. (See DOSAGE AND ADMINISTRATION.)

Hepatotoxicity: Hepatotoxicity, occasionally severe, may occur with Gleevec (see ADVERSE REACTIONS). Liver function (transaminases, bilirubin, and alkaline phosphatase) should be monitored before initiation of treatment and monthly or as clinically indicated. Laboratory abnormalities should be managed with interruption and/or dose reduction of the treatment with Gleevec. (See DOSAGE AND ADMINISTRATION.) Patients with hepatic impairment should be closely monitored because exposure to Gleevec may be increased. As there are no clinical studies of Gleevec in patients with impaired liver function, no specific advice concerning initial dosing adjustment can be given.

Toxicities From Long-Term Use: It is important to consider potential toxicities suggested by animal studies, specifically, *liver and kidney toxicity and immunosuppression*. Severe liver toxicity was observed in dogs treated for 2 weeks, with elevated liver enzymes, hepatocellular necrosis, bile duct necrosis, and bile duct hyperplasia. Renal toxicity was observed in monkeys treated for 2 weeks, with focal mineralization and dilation of the renal tubules and tubular nephrosis. Increased BUN and creatinine were observed in several of these animals. An increased rate of opportunistic infections was observed with chronic imatinib treatment in laboratory animal studies. In a 39-week monkey study, treatment with imatinib resulted in worsening of normally suppressed malarial infections in these animals. Lymphopenia was observed in animals (as in humans).

Drug Interactions

Drugs that may alter imatinib plasma concentrations

Drugs that may **increase** imatinib plasma concentrations:

Caution is recommended when administering Gleevec with inhibitors of the CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, clarithromycin). Substances that inhibit the cytochrome P450 isoenzyme (CYP3A4) activity may decrease metabolism and increase imatinib concentrations. There is a significant increase in exposure to imatinib when Gleevec is coadministered with ketoconazole (CYP3A4 inhibitor).

Drugs that may **decrease** imatinib plasma concentrations:

Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, phenobarbital or St. John's Wort) may significantly reduce exposure to Gleevec. Pretreatment of healthy volunteers with multiple doses of rifampin followed by a single dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold, which significantly ($p<0.05$) decreased mean C_{max} and $AUC_{(0-\infty)}$. In patients where rifampin or other CYP3A4 inducers are indicated, alternative therapeutic agents with less enzyme induction potential should be considered. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION.)

Drugs that may have their plasma concentration altered by Gleevec

Gleevec increases the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) 2- and 3.5-fold, respectively, suggesting an inhibition of the CYP3A4 by Gleevec. Particular caution is recommended when administering Gleevec with CYP3A4 substrates that have a narrow therapeutic window (e.g., cyclosporine or pimozide). Gleevec will increase plasma concentration of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

Because *warfarin* is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin.

In vitro, Gleevec inhibits the cytochrome P450 isoenzyme CYP2D6 activity at similar concentrations that affect CYP3A4 activity. Systemic exposure to substrates of CYP2D6 is expected to be increased when coadministered with Gleevec. No specific studies have been performed and caution is recommended.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with imatinib mesylate.

Positive genotoxic effects were obtained for imatinib in an *in vitro* mammalian cell assay (Chinese hamster ovary) for clastogenicity (chromosome aberrations) in the presence of metabolic activation. Two intermediates of the manufacturing process, which are also present in the final product, are positive for mutagenesis in the Ames assay. One of these intermediates was also positive in the mouse lymphoma assay. Imatinib was not genotoxic when tested in an *in vitro* bacterial cell assay (Ames test), an *in vitro* mammalian cell assay (mouse lymphoma) and an *in vivo* rat micronucleus assay.

In a study of fertility, in male rats dosed for 70 days prior to mating, testicular and epididymal weights and percent motile sperm were decreased at 60 mg/kg, approximately three-fourths the maximum clinical dose of 800 mg/day, based on body surface area. This was not seen at doses ≤20 mg/kg (one-fourth the maximum human dose of 800 mg). When female rats were dosed 14 days prior to mating and through to gestational day 6, there was no effect on mating or on number of pregnant females.

In female rats dosed with imatinib mesylate at 45 mg/kg (approximately one-half the maximum human dose of 800 mg, based on body surface area) from gestational day 6 until the end of lactation, red vaginal discharge was noted on either gestational day 14 or 15.Pregnancy

Pregnancy Category D. (See WARNINGS.)

Nursing Mothers

It is not known whether imatinib mesylate or its metabolites are excreted in human milk. However, in lactating female rats administered 100 mg/kg, a dose approximately equal to the maximum clinical dose of 800 mg/day based on body surface area, imatinib and its metabolites were extensively excreted in milk. Concentration in milk was approximately

three-fold higher than in plasma. It is estimated that approximately 1.5% of a maternal dose is excreted into milk, which is equivalent to a dose to the infant of 30% the maternal dose per unit body weight. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should be advised against breast-feeding while taking Gleevec.

Pediatric Use

Gleevec safety and efficacy have been demonstrated only in children with Ph+ chronic phase CML with recurrence after stem cell transplantation or resistance to interferon-alpha therapy. There are no data in children under 3 years of age.

Geriatric Use

In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. In the study of patients with newly diagnosed CML, 22% of patients were 60 years of age or older. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. (See PRECAUTIONS.) The efficacy of Gleevec was similar in older and younger patients.

In the GIST study, 29% of patients were older than 60 years and 10% of patients were older than 70 years. No obvious differences in the safety or efficacy profile were noted in patients older than 65 years as compared to younger patients, but the small number of patients does not allow a formal analysis.

ADVERSE REACTIONS

Chronic Myeloid Leukemia

The majority of Gleevec-treated patients experienced adverse events at some time. Most events were of mild-to-moderate grade, but drug was discontinued for drug-related adverse events in 3.1% of newly diagnosed patients, 4% of patients in chronic phase after failure of interferon therapy, 4% in accelerated phase and 5% in blast crisis.

The most frequently reported drug-related adverse events were edema, nausea and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash (Table 4 for newly diagnosed CML, Table 5 for other CML patients). Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of Gleevec® (imatinib mesylate). (See DOSAGE AND ADMINISTRATION.) The frequency of severe superficial edema was 0.9%-6%.

A variety of adverse events represent local or general fluid retention including pleural effusion, ascites, pulmonary edema and rapid weight gain with or without superficial edema. These events appear to be dose related, were more common in the blast crisis and accelerated phase studies (where the dose was 600 mg/day), and are more common in the elderly. These events were usually managed by interrupting Gleevec treatment and with diuretics or other appropriate supportive care measures. However, a few of these events may be serious or life

525 threatening, and one patient with blast crisis died with pleural effusion, congestive heart
526 failure, and renal failure.

527 Adverse events, regardless of relationship to study drug, that were reported in at least
528 10% of the patients treated in the Gleevec studies are shown in Tables 4 and 5.

Table 4 **Adverse Experiences Reported in Newly Diagnosed CML Clinical Trial (≥10% of all patients)[1]**

	All Grades		CTC Grades 3/4	
Preferred Term	**Gleevec® N=551 (%)**	**IFN+Ara-C N=533 (%)**	**Gleevec® N=551 (%)**	**IFN+Ara-C N=533 (%)**
Fluid Retention	59.2	10.7	1.8	0.9
- Superficial Edema	57.5	9.2	1.1	0.4
- Other Fluid Retention Events	6.9	1.9	0.7	0.6
Nausea	47.0	61.5	0.9	5.1
Muscle Cramps	43.2	11.4	1.6	0.2
Musculoskeletal Pain	39.9	44.1	3.4	8.1
Diarrhea	38.5	42.0	2.0	3.2
Rash and related terms	37.2	25.7	2.4	2.4
Fatigue	37.0	66.8	1.6	25.0
Headache	33.6	43.3	0.5	3.6
Joint Pain	30.3	39.4	2.5	7.3
Abdominal Pain	29.9	25.0	2.5	3.9
Nasopharyngitis	26.9	8.4	0	0.2
Hemorrhage	24.1	20.8	1.1	1.5
- GI hemorrhages	1.3	1.1	0.5	0.2
- CNS hemorrhages	0.2	0.2	0	0.2
Myalgia	22.5	38.8	1.5	8.1
Vomiting	20.5	27.4	1.5	3.4
Dyspepsia	17.8	9.2	0	0.8
Cough	17.4	23.1	0.2	0.6
Pharyngolaryngeal Pain	16.9	11.3	0.2	0
Upper Respiratory Tract Infection	16.5	8.4	0.2	0.4
Dizziness	15.8	24.2	0.9	3.6
Pyrexia	15.4	42.4	0.9	3.0
Weight Increased	15.2	2.1	1.6	0.4
Insomnia	13.2	18.8	0	2.3
Depression	12.7	35.8	0.5	13.1
Influenza	11.1	6.0	0.2	0.2

[1] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

Table 5 **Adverse Experiences Reported in Other CML Clinical Trials (≥10% of all patients in any trial)[1]**

	Myeloid Blast Crisis (n= 260) %		Accelerated Phase (n=235) %		Chronic Phase, IFN Failure (n=532) %	
Preferred Term	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Fluid Retention	72	11	76	6	69	4
- Superficial Edema	66	6	74	3	67	2
- Other Fluid Retention Events[2]	22	6	15	4	7	2
Nausea	71	5	73	5	63	3
Muscle Cramps	28	1	47	0.4	62	2
Vomiting	54	4	58	3	36	2
Diarrhea	43	4	57	5	48	3
Hemorrhage	53	19	49	11	30	2
- CNS Hemorrhage	9	7	3	3	2	1
- Gastrointestinal Hemorrhage	8	4	6	5	2	0.4
Musculoskeletal Pain	42	9	49	9	38	2
Fatigue	30	4	46	4	48	1
Skin Rash	36	5	47	5	47	3
Pyrexia	41	7	41	8	21	2
Arthralgia	25	5	34	6	40	1
Headache	27	5	32	2	36	0.6
Abdominal Pain	30	6	33	4	32	1
Weight Increased	5	1	17	5	32	7
Cough	14	0.8	27	0.9	20	0
Dyspepsia	12	0	22	0	27	0
Myalgia	9	0	24	2	27	0.2
Nasopharyngitis	10	0	17	0	22	0.2
Asthenia	18	5	21	5	15	0.2
Dyspnea	15	4	21	7	12	0.9
Upper Respiratory Tract Infection	3	0	12	0.4	19	0
Anorexia	14	2	17	2	7	0
Night Sweats	13	0.8	17	1	14	0.2
Constipation	16	2	16	0.9	9	0.4
Dizziness	12	0.4	13	0	16	0.2
Pharyngitis	10	0	12	0	15	0
Insomnia	10	0	14	0	14	0.2
Pruritus	8	1	14	0.9	14	0.8
Hypokalemia	13	4	9	2	6	0.8
Pneumonia	13	7	10	7	4	1
Anxiety	8	0.8	12	0	8	0.4
Liver Toxicity	10	5	12	6	6	3
Rigors	10	0	12	0.4	10	0
Chest Pain	7	2	10	0.4	11	0.8
Influenza	0.8	0.4	6	0	11	0.2
Sinusitis	4	0.4	11	0.4	9	0.4

[1] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.

[2] Other fluid retention events include pleural effusion, ascites, pulmonary edema, pericardial effusion, anasarca, edema aggravated, and fluid retention not otherwise specified.

Hematologic Toxicity

Cytopenias, and particularly neutropenia and thrombocytopenia, were a consistent finding in all studies, with a higher frequency at doses ≥750 mg (Phase 1 study). However, the occurrence of cytopenias in CML patients was also dependent on the stage of the disease.

In patients with newly diagnosed CML, cytopenias were less frequent than in the other CML patients (see Tables 6 and 7). The frequency of grade 3 or 4 neutropenia and thrombocytopenia was between 2- and 3-fold higher in blast crisis and accelerated phase compared to chronic phase (see Tables 6 and 7). The median duration of the neutropenic and thrombocytopenic episodes varied from 2 to 3 weeks, and from 2 to 4 weeks, respectively.

These events can usually be managed with either a reduction of the dose or an interruption of treatment with Gleevec, but in rare cases require permanent discontinuation of treatment.

Hepatotoxicity

Severe elevation of transaminases or bilirubin occurred in 3%-6% (see Table 5) and were usually managed with dose reduction or interruption (the median duration of these episodes was approximately one week). Treatment was discontinued permanently because of liver laboratory abnormalities in less than 1% of patients. However, one patient, who was taking acetaminophen regularly for fever, died of acute liver failure.

Adverse Reactions in Pediatric Population

The overall safety profile of pediatric patients treated with Gleevec in 39 children studied was similar to that found in studies with adult patients, except that musculoskeletal pain was less frequent (20.5%) and peripheral edema was not reported.

Adverse Effects in Other Subpopulations

In older patients (≥65 years old), with the exception of edema, where it was more frequent, there was no evidence of an increase in the incidence or severity of adverse events. In women there was an increase in the frequency of neutropenia, as well as grade 1/2 superficial edema, headache, nausea, rigors, vomiting, rash, and fatigue. No differences were seen related to race but the subsets were too small for proper evaluation.

Table 6 Lab Abnormalities in Newly Diagnosed CML Trial

	Gleevec® N=551 %		IFN+Ara-C N=533 %	
CTC Grades	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology Parameters				
- Neutropenia*	12.3	3.1	20.8	4.3
- Thrombocytopenia*	8.3	0.2	15.9	0.6
- Anemia	3.1	0.9	4.1	0.2
Biochemistry Parameters				
- Elevated Creatinine	0	0	0.4	0
- Elevated Bilirubin	0.7	0.2	0.2	0
- Elevated Alkaline Phosphatase	0.2	0	0.8	0
- Elevated SGOT (AST)	2.9	0.2	3.8	0.4
- Elevated SGPT (ALT)	3.1	0.4	5.6	0

*p<0.001 (difference in grade 3 plus 4 abnormalities between the two treatment groups)

Table 7 Lab Abnormalities in Other CML Clinical Trials

	Myeloid Blast Crisis (n=260) 600 mg n=223 400 mg n=37 %		Accelerated Phase (n=235) 600 mg n=158 400 mg n=77 %		Chronic Phase, IFN Failure (n=532) 400 mg %	
CTC Grades	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology Parameters						
- Neutropenia	16	48	23	36	27	9
- Thrombocytopenia	30	33	31	13	21	<1
- Anemia	42	11	34	7	6	1
Biochemistry Parameters						
- Elevated Creatinine	1.5	0	1.3	0	0.2	0
- Elevated Bilirubin	3.8	0	2.1	0	0.6	0
- Elevated Alkaline Phosphatase	4.6	0	5.5	0.4	0.2	0
- Elevated SGOT (AST)	1.9	0	3.0	0	2.3	0
- Elevated SGPT (ALT)	2.3	0.4	4.3	0	2.1	0

CTC grades: neutropenia (grade 3 ≥0.5-1.0 x 10^9/L), grade 4 <0.5 x 10^9L), thrombocytopenia (grade 3 ≥10-50 x 10^9/L, grade 4 <10 x 10^9/L), anemia (hemoglobin ≥65-80 g/L, grade 4 <65 g/L), elevated creatinine (grade 3 >3-6 x upper limit normal range [ULN], grade 4 >6 x ULN), elevated bilirubin (grade 3 >3-10 x ULN, grade 4 >10 x ULN), elevated alkaline phosphatase (grade 3 >5-20 x ULN, grade 4 >20 x ULN), elevated SGOT or SGPT (grade 3 >5-20 x ULN, grade 4 >20 x ULN)

Gastrointestinal Stromal Tumors

The majority of Gleevec-treated patients experienced adverse events at some time. The most frequently reported adverse events were edema, nausea, diarrhea, abdominal pain, muscle

cramps, fatigue, and rash. Most events were of mild-to-moderate severity. Drug was discontinued for adverse events in 6 patients (8%) in both dose levels studied. Superficial edema, most frequently periorbital or lower extremity edema, was managed with diuretics, other supportive measures, or by reducing the dose of Gleevec® (imatinib mesylate). (See DOSAGE AND ADMINISTRATION.) Severe (CTC grade 3/4) superficial edema was observed in 3 patients (2%), including face edema in one patient. Grade 3/4 pleural effusion or ascites was observed in 3 patients (2%).

Adverse events, regardless of relationship to study drug, that were reported in at least 10% of the patients treated with Gleevec are shown in Table 8. No major differences were seen in the severity of adverse events between the 400-mg or 600-mg treatment groups, although overall incidence of diarrhea, muscle cramps, headache, dermatitis, and edema was somewhat higher in the 600-mg treatment group.

Table 8 **Adverse Experiences Reported in GIST Trial (≥10% of all patients at either dose)[1]**

	All CTC Grades Initial dose (mg/day)		CTC Grade 3/4 Initial dose (mg/day)	
Preferred Term	**400 mg (n=73) %**	**600 mg (n=74) %**	**400 mg (n=73) %**	**600 mg (n=74) %**
Fluid Retention	71	76	6	3
- Superficial Edema	71	76	4	0
- Pleural Effusion or Ascites	6	4	1	3
Diarrhea	56	60	1	4
Nausea	53	56	3	3
Fatigue	33	38	1	0
Muscle Cramps	30	41	0	0
Abdominal Pain	37	37	7	3
Skin Rash	26	38	3	3
Headache	25	35	0	0
Vomiting	22	23	1	3
Musculoskeletal Pain	19	11	3	0
Flatulence	16	23	0	0
Any Hemorrhage	18	19	5	8
- Tumor Hemorrhage	1	4	1	4
- Cerebral Hemorrhage	1	0	1	0
- GI Tract Hemorrhage	6	4	4	1
Nasopharyngitis	12	14	0	0
Pyrexia	12	5	0	0
Insomnia	11	11	0	0
Back Pain	11	10	1	0
Lacrimation Increased	6	11	0	0
Upper Respiratory Tract Infection	6	11	0	0
Taste Disturbance	1	14	0	0

[1] All adverse events occurring in ≥10% of patients are listed regardless of suspected relationship to treatment.Clinically relevant or severe abnormalities of routine hematologic or biochemistry laboratory values are presented in Table 9.

Table 9 **Laboratory Abnormalities in GIST Trial**

	400 mg (n=73) %		600 mg (n=74) %	
CTC Grades	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematology Parameters				
- Anemia	3	0	4	1
- Thrombocytopenia	0	0	1	0
- Neutropenia	3	3	5	4
Biochemistry Parameters				
- Elevated Creatinine	0	1	3	0
- Reduced Albumin	3	0	4	0
- Elevated Bilirubin	1	0	1	3
- Elevated Alkaline Phosphatase	0	0	1	0

- Elevated SGOT (AST)	3	0	1	1
- Elevated SGPT (ALT)	3	0	4	0

CTC grades: neutropenia (grade 3 ≥0.5-1.0 x 10^9/L, grade 4 <0.5 x 10^9/L), thrombocytopenia (grade 3 ≥10 - 50 x 10^9/L, grade 4 <10 x 10^9/L), anemia (grade 3 ≥65-80 g/L, grade 4 <65 g/L), elevated creatinine (grade 3 >3-6 x upper limit normal range [ULN], grade 4 >6 x ULN), elevated bilirubin (grade 3 >3-10 x ULN, grade 4 >10 x ULN), elevated alkaline phosphatase, SGOT or SGPT (grade 3 >5-20 x ULN, grade 4 >20 x ULN), albumin (grade 3 <20 g/L)

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 *Rare:* pericarditis

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, psoriasis *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, ileus/intestinal obstruction, pancreatitis

General Disorders and Administration Site Conditions: *Rare*: tumor necrosis

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), confusion, convulsions

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, glaucoma, vitreous hemorrhage

Vascular Disorders: *Rare*: thrombosis/embolism

OVERDOSAGE

Experience with doses greater than 800 mg is limited. Isolated cases of Gleevec® overdose have been reported. In the event of overdosage, the patient should be observed and appropriate supportive treatment given.

A patient with myeloid blast crisis experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin after inadvertently taking 1200 mg of Gleevec daily for 6 days. Therapy was temporarily interrupted and complete reversal of all abnormalities occurred within one week. Treatment was resumed at a dose of 400 mg daily without recurrence of adverse events [9]. Another patient developed severe muscle cramps after taking 1,600 mg of Gleevec daily for 6 days. Complete resolution of muscle cramps occurred following interruption of therapy and treatment was subsequently resumed [10]. Another patient that was prescribed 400 mg daily, took 800 mg of Gleevec on day 1 and 1,200 mg on day 2. Therapy was interrupted, no adverse events occurred and the patient resumed therapy.

DOSAGE AND ADMINISTRATION

Therapy should be initiated by a physician experienced in the treatment of patients with chronic myeloid leukemia or gastrointestinal stromal tumors.

The recommended dosage of Gleevec® (imatinib mesylate) is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. The recommended Gleevec dosage is 260 mg/m^2/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy. The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once-daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

In children, Gleevec treatment can be given as a once daily dose or alternatively the daily dose may be split into two - once in the morning and once in the evening. There is no experience with Gleevec treatment in children under 3 years of age.

For patients unable to swallow the film-coated tablets, the tablets may be dispersed in a glass of water or apple juice. The required number of tablets should be placed in the appropriate volume of beverage (approximately 50 mL for a 100-mg tablet, and 200 mL for a 400-mg tablet) and stirred with a spoon. The suspension should be administered immediately after complete disintegration of the tablet(s).

Treatment may be continued as long as there is no evidence of progressive disease or unacceptable toxicity.

In CML, a dose increase from 400 mg to 600 mg in adult patients with chronic phase disease, or from 600 mg to 800 mg (given as 400 mg twice daily) in adult patients in accelerated phase or blast crisis may be considered in the absence of severe adverse drug reaction and severe non-leukemia related neutropenia or thrombocytopenia in the following circumstances: disease progression (at any time); failure to achieve a satisfactory hematologic response after at least 3 months of treatment; failure to achieve a cytogenetic response after 6-12 months of treatment; or loss of a previously achieved hematologic or cytogenetic response. In children with chronic phase CML, daily doses can be increased under circumstances similar to those leading to an increase in adult chronic phase disease, from 260 mg/m^2/day to 340 mg/m^2/day, as clinically indicated.

Dosage of Gleevec should be increased by at least 50%, and clinical response should be carefully monitored, in patients receiving Gleevec with a potent CYP3A4 inducer such as rifampin or phenytoin.

Dose Adjustment for Hepatotoxicity and Other Non-Hematologic Adverse Reactions

If a severe non-hematologic adverse reaction develops (such as severe hepatotoxicity or severe fluid retention), Gleevec should be withheld until the event has resolved. Thereafter, treatment can be resumed as appropriate depending on the initial severity of the event.

If elevations in bilirubin >3 x institutional upper limit of normal (IULN) or in liver transaminases >5 x IULN occur, Gleevec should be withheld until bilirubin levels have returned to a <1.5 x IULN and transaminase levels to <2.5 x IULN. In adults, treatment with Gleevec may then be continued at a reduced daily dose (i.e., 400 mg to 300 mg or 600 mg to 400 mg). In children, daily doses can be reduced under the same circumstances from 260 mg/m^2/day to 200 mg/m^2/day or from 340 mg/m^2/day to 260 mg/m^2/day, respectively.

Dose Adjustment for Hematologic Adverse Reactions

Dose reduction or treatment interruptions for severe neutropenia and thrombocytopenia are recommended as indicated in Table 10.

Table 10 Dose Adjustments for Neutropenia and Thrombocytopenia

Chronic Phase CML (starting dose 400mg[1]) or GIST (starting dose either 400 mg or 600 mg)	ANC <1.0 x 10^9/L and/or Platelets <50 x 10^9/L	1. Stop Gleevec until ANC ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L 2. Resume treatment with Gleevec at the original starting dose of 400 mg[1] or 600 mg

		3. If recurrence of ANC <1.0 x 10^9/L and/or platelets <50 x 10^9/L, repeat step 1 and resume Gleevec at a reduced dose (300 mg[2] if starting dose was 400 mg[1], 400 mg if starting dose was 600 mg)
Accelerated Phase CML and Blast Crisis (starting dose 600 mg)	[3]ANC <0.5 x 10^9/L and/or Platelets <10 x 10^9/L	1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy) 2. If cytopenia is unrelated to leukemia, reduce dose of Gleevec to 400 mg 3. If cytopenia persist 2 weeks, reduce further to 300 mg 4. If cytopenia persist 4 weeks and is still unrelated to leukemia, stop Gleevec until ANC ≥1 x 10^9/L and platelets ≥20 x 10^9/L and then resume treatment at 300 mg.

[1] or 260 mg/m^2 in children

[2] or 200 mg/m^2 in children

[3]occurring after at least 1 month of treatment

HOW SUPPLIED

Each film-coated tablet contains 100 mg or 400 mg of imatinib free base.

100 mg Tablets

Very dark yellow to brownish orange film-coated tablets, round, biconvex with bevelled edges debossed with "NVR" on one side and "SA" with score on the other side.

Bottles of 100 tablets.....NDC 0078-0401-05

400 mg Tablets

Very dark yellow to brownish orange film-coated tablets, ovaloid, biconvex with bevelled edges, debossed with "NVR" on one side and "SL" on the other side.

Bottles of 30 tablets.....NDC 0078-0402-15

Storage

Store at 25 °C (77 °F); excursions permitted to 15 °C-30 °C (59 °F-86 °F) [see USP Controlled Room Temperature]. Protect from moisture.

Dispense in a tight container, USP.

REV: JANUARY 2004 Printed in U.S.A. T2004-10
89019002

NOVARTIS

Manufactured by:
Novartis Pharma Stein AG
Stein, Switzerland

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-588/S005

CLINICAL AND STATISTICAL REVIEW(S)

Application Type	NDA 21-588
Submission Number	SE8
Submission Code	005
Letter Date	9/7/04
Stamp Date	9/8/04
Reviewer Name	Martin H. Cohen, M.D. Yong-Cheng Wang, Ph.D.
Review Completion Date	10/27/04
Established Name	Imatinib mesylate (STI571)
Trade Name	Gleevec
Therapeutic Class	Molecularly targeted drug
Sponsor	Novartis
Priority Designation	P

Formulation

Gleevec® (imatinib mesylate) film-coated tablets contain imatinib mesylate equivalent to 100 mg or 400 mg of imatinib free base.

Dosing Regimen

The recommended dosage of Gleevec® (imatinib mesylate) is 400 mg/day for adult patients in chronic phase CML and 600 mg/day for adult patients in accelerated phase or blast crisis. The recommended Gleevec dosage is 260 mg/m^2/day for children with Ph+ chronic phase CML recurrent after stem cell transplant or who are resistant to interferon-alpha therapy. The recommended dosage of Gleevec is 400 mg/day or 600 mg/day for adult patients with unresectable and/or metastatic, malignant GIST.

The prescribed dose should be administered orally, with a meal and a large glass of water. Doses of 400 mg or 600 mg should be administered once-daily, whereas a dose of 800 mg should be administered as 400 mg twice a day.

Indication

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

Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled

trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). The effectiveness of Gleevec in GIST is based on objective response rate. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Intended Population

See indication

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1.0 EXECUTIVE SUMMARY

The purpose of the present submission is to update labeling of Gleevec tablet. The last labeling update was on December 8, 2003 (NDA 21-588/S-002).

The current submission also updates efficacy and safety results of the 4 pivotal chronic myeloid leukemia (CML) trials conducted by the sponsor (cut-off date 31-July 2003).

The current proposed labeling text includes changes recommended by the FDA in response to post-marketing commitments and miscellaneous information. (See below).

Dosage and Administration

b(4)

Clinical Pharmacology

Metabolism and Elimination b(4)

Precautions

Drug Interactions

Drugs that may have their plasma concentration altered by Gleevec

b(4)

Precautions

Fluid Retention and Edema:

b(4)

1.1 Recommendation On Regulatory Action

Review, modify and approve proposed labeling changes. Follow-up of patients study 0106 is still relatively short (median 31 months) so that the labeling indication should continue to read "Gleevec® (imatinib mesylate) is indicated for the treatment of newly diagnosed adult patients with Philadelphia chromosome

positive chronic myeloid leukemia (CML) in chronic phase. Follow-up is limited".

1.2 Recommendation On Post-marketing Actions

Continue post-marketing surveillance.

1.21 Risk Management Activity

Continue post-marketing surveillance of AE's .

1.22 Required Phase 4 Commitments

No new phase 4 commitments are required. Continued follow-up of patients on study 0106 is required.

1.23 Other Phase 4 Requests

None

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

The clinical program primarily consists of 4 pivotal trials

Controlled phase III study 0106

Study 0106 is an open-label, controlled, multicenter, international randomized phase III study comparing treatment with either Gleevec monotherapy or a standard combination of IFN-alpha + ara-C in patients with CML within 6 months of their initial diagnosis.

Phase II studies 0102, 0109, 0110

Studies 0102, 0109, 0110 are three large international multicenter phase II studies with blast crisis (study 0102), accelerated phase (study 0109) and late chronic phase CML failing prior IFN therapy (study 0110) that between 2-August 1999 and 3-July-2000, enrolled a total of 260, 235 and 532 patients, respectively.

1.3.2 Efficacy

The current data further confirms the benefits of STI571 therapy in patients with all stages of CML. Benefits of STI571 therapy can be summarized as follows:

- First-line therapy with STI571 significantly delays the onset of progression to accelerated phase and blast crisis in comparison with IFN + Ara-C.

- In newly diagnosed patients, molecular response appears as an important therapeutic endpoint being associated with an improved subsequent progression-free survival

- Longer follow-up has revealed the possibility for late onset cytogenetic responses. Consequently, the rates of major and complete cytogenetic responses have increased substantially in both chronic phase CML studies 0106 and 0110. These responses are durable with >92% and 83% of patients being in continuing response at 30 and 36 months in studies 0106 and 0110.

- Over historical series using a variety of chemotherapy or IFN-based regimens, treatment with Gleevec offers a better survival and quality of survival (with fewer adverse events) for patients with CML in accelerated phase or blast crisis.

1.3.3 Safety

In phase II trials in CML, the majority of patients experienced drug-related adverse events (AEs) at some time, but most were CTC grade 1 or 2 in severity. Discontinuation for drug related AEs occurred in 2%, 3% and 5% of patients in chronic, accelerated and blast phases, respectively. Skin rash and elevated transaminases were the most common reason for drug discontinuation (each in <1% of patients). The most frequently reported AEs were nausea, vomiting, diarrhea, superficial edema (primarily periorbital or lower limb), myalgia and muscle cramps. Grade 3/4 events occurring in <4% of patients included fluid retention (pleural or pericardial effusions, ascites, pulmonary edema), skin rash, liver toxicity and gastrointestinal (GI) hemorrhage. Myelosuppression was a consistent finding across studies. Grade 3/4 neutropenia and thrombocytopenia were more frequent in CML patients in accelerated phase or blast crisis patients than in chronic phase. In a randomized Phase III study the incidence of nausea was lower compared to the phase II trials possibly because the drug was administered with food. Myelosuppression was also less frequent in this study. Grade 3/4 neutropenia occurred in 33% and 12% of patients in studies 0110 and 0106, respectively, and grade 3/4 thrombocytopenia in 21% and 7% of patients. The long-term follow-up (>2 years of exposure) has not significantly modified the safety profile of Gleevec. The proportion of patients discontinuing treatment for adverse events has increased only modestly (in newly diagnosed patients, this percentage increased from 2% to 3.1% with an additional 18 months of follow-up). The frequency of grade 3 or 4 hematologic toxicity has also slightly increased in the two chronic phase trials 0110 and 0106. However, this has to be interpreted with caution as an increasing proportion of patients had their dose increased from 400 to 600 or 800 mg daily per protocol.

1.3.4 Dosing Regimen and Administration

As summarized in earlier applications, in the phase I trial 03-001, doses of 400 mg to 800 mg orally daily were considered as safe and effective and were recommended for the subsequent phase II and phase III trials. However, in this trial, no maximally tolerated dose was characterized up to 1000 mg/day. The recommended doses of 400 mg for patients in chronic phase CML has been based on results of the phase II trial 0110 and by the phase III trial 0106 in patients with newly-diagnosed CML. The recommended dose of 600 mg for patients in accelerated phase or blast crisis CML is based on the findings of the two phase II trials 0102 and 0109. In both the phase II and phase III study protocols, dose-escalation to 600 mg and 800 mg was allowed in the event of insufficient efficacy at pre-specified checkpoints.

1.3.5 Drug-Drug Interactions

CYP3A4 Inhibitors: There was a significant increase in exposure to imatinib (mean C_{max} and AUC increased by 26% and 40%, respectively) in healthy subjects when Gleevec was co-administered with a single dose of ketoconazole (a CYP3A4 inhibitor).

CYP3A4 Substrates: Gleevec increased the mean C_{max} and AUC of simvastatin (CYP3A4 substrate) by 2- and 3.5- fold, respectively, indicating an inhibition of CYP3A4 by Gleevec.

CYP3A4 Inducers: Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 8 days, followed by a single 400 mg dose of Gleevec, increased Gleevec oral-dose clearance by 3.8-fold (90% confidence interval = 3.5- to 4.3-fold), which represents mean decreases in C_{max}, $AUC_{(0-24)}$ and $AUC_{(0-\infty)}$ by 54%, 68% and 74%, of the respective values without rifampin treatment.

In Vitro Studies of CYP

Enzyme Inhibition: Human liver microsome studies demonstrated that Gleevec is a potent competitive inhibitor of CYP2C9, CYP2D6, and CYP3A4/5 with K_i values of 27, 7.5 and 8 μM, respectively. Gleevec is likely to increase the blood level of drugs that are substrates of CYP2C9, CYP2D6 and CYP3A4/5.

1.3.6 Special Populations

Pediatric patients

One open-label, single-arm study enrolled 14 pediatric patients with Ph+ chronic phase CML recurrent after stem cell transplant or resistant to alpha interferon therapy. Patients ranged in age from 3 to 20 years old; 3 were 3-11 years old, 9 were 12-18 years old, and 2 were >18 years old. Patients were treated at doses of 260 mg/m2/day (n=3), 340

mg/m2/day (n=4), 440 mg/m2/day 297 (n=5) and 570 mg/m2/day (n=2). In the 13 patients for whom cytogenetic data are available, 4 achieved a major cytogenetic response, 7 achieved a complete cytogenetic response, and 2 had minimal cytogenetic response. At the recommended dose of 260 mg/m2/day, 2 of 3 patients achieved a complete cytogenetic response. Cytogenetic response rate was similar at all dose levels.

In a second study, 2 of 3 patients with Ph+ chronic phase CML resistant to alpha interferon achieved a complete cytogenetic response at doses of 242 and 257 mg/m2/day.

Geriatric Use

In the CML clinical studies, approximately 40% of patients were older than 60 years and 10% were older than 70 years. In the study of patients with newly diagnosed CML, 22% of patients were 60 years of age or older. No difference was observed in the safety profile in patients older than 65 years as compared to younger patients, with the exception of a higher frequency of edema. The efficacy of Gleevec was similar in older and younger patients.

2.0 INTRODUCTION AND BACKGROUND

2.1 Product Information

Gleevec® (imatinib mesylate, STI571) is a small molecule protein-tyrosine kinase inhibitor, which potently inhibits the activity of the Bcr-Abl tyrosine kinase (TK), as well as two receptor TKs: Kit, the receptor for stem cell factor (SCF) coded for by the c-Kit proto-oncogene, and the platelet-derived growth factor receptors α and β (PDGFR-α and PDGFR-β). Gleevec® also inhibits the cellular events mediated by activation of the Kit and the PDGF receptors.

2.2 Currently Available Treatment For Indication(s)

Interferon alpha, ——————————b(4)

2.3 Availability Of Proposed Active Ingredient In The United States

Gleevec® is approved for use in the United States. See current indication.

2.4 Important Issues With Pharmacologically Related Products

None

2.5 Presubmission Regulatory Activity

None

2.6 Other Relevant Background Information

None

3.0 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (And Product Microbiology. If Applicable)

No new data are available and therefore no changes of the label are required.

3.2 Animal Pharmacology/Toxicology

No new data are available and therefore no changes of the label are required.

4.0 Data Sources, Review Strategy And Data Integrity

4.1 Sources of Clinical Data

Electronic Document Room document Cdsesub1\N21588\S_005\2004-09-07\

4.2 Table of Clinical Studies

Clinical studies are summarized in **Table 1.**

Table 1: Clinical studies

Study No.	Patient population	Purpose	n	Daily dose of Gleevec®
Newly diagnosed CML patients (Phase III)		safety, efficacy, PK, PD	553 (553)	400 mg (IFN + Ara-C)
0106	Newly diagnosed chronic phase CML patients within 6 months of initial diagnosis			
Pediatric patients with Ph+ leukemias (Phase I)				
0103	Children with CML or Ph+ acute leukemias	safety, PK, efficacy	31	260, 340, 440 and 570 mg/m2/day
03 001	Children with CML or Ph+ acute leukemias	safety, PK, efficacy	8	173 to 362 mg/m2/day
Late chronic phase and advanced phase CML (Phase II)				
0102	CML myeloid blast crisis	safety, efficacy, PK	260	400-600 mg
0109	CML accelerated phase	safety, efficacy, PK	235	400-600 mg
0110	CML chronic phase(failing 1st line IFN)	safety, efficacy, PK	532	400 mg
Total number of patients starting therapy with Gleevec®			**1619**	

4.3 Review Strategy

Efficacy data pertaining to hematologic and cytogenetic response rates and durations, as appropriate, were reviewed. All safety data was reviewed.

4.4 Data Quality And Integrity

Because this submission provided only updated data and because studies had previously been audited by DSI no new inspections were performed.

4.5 Compliance With Good Clinical Practices

All studies were conducted in full compliance with Good Clinical Practice. All studies were closely monitored by Novartis personnel or a contract organization for compliance to the protocol and the procedures described in it.

4.6 Financial Disclosures

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on Financial Disclosure by Clinical Investigators in previous NDA submissions. No new information is provided.

5.0 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new data are available and therefore no changes of the label are required.

5.2 Pharmacodynamics

No new data are available and therefore no changes of the label are required.

5.3 Exposure-Response Relationships

No new data are available and therefore no changes of the label are required.

6.0 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

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

Gleevec is also indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. Gleevec is also indicated for the treatment of pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy. There are no controlled trials in pediatric patients demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST). The effectiveness of Gleevec in GIST is based on objective response rate. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

6.1.1 Methods

Clinical information concerning trias 102, 106, 109 and 110 was updated based on the sponsor's EDR submission of 07 Sept 2004.

6.1.2 General Discussion of Endpoints

Efficacy endpoints have been discussed with, and approved by, the FDA

6.1.3 Study Design

Blast crisis (Study 102)

The study is titled "A phase II open-label study to determine the safety and anti-leukemic effects of 5T1571 in patients with Philadelphia chromosome-positive chronic myeloid leukemia in myeloid blast crisis". This study was carried out in the following countries (number of centers): France (3), Germany (5), Italy (5), UK (3), Switzerland (2) and the USA (14). The first patient enrolled on 26 Jul 1999. Data cut-off was 31 Jul 2002

A total of 260 patients were recruited, of whom 165 had not previously received antineoplastic treatment for advanced CML. The initial Gleevec dose was either 400 mg daily (qd) (pre-amendment 2), or 600 mg qd. (post-amendment 2). Dosage increase from 400 mg qd. to 600 mg qd. and from 600 mg qd. to 400 mg bid (800 mg qd) was permitted in all patients (post-amendment 2) for improved therapeutic effect.

Objectives:

Primary:

- Determination of the rate of hematologic response (confirmed after 4 weeks).

Secondary:

- Duration of hematologic response
- Overall survival
- Cytogenetic response
- Safety profile of ST1571
- Improvement in disease-related symptoms.
- Pharmacokinetic (PK) profile in a sub-group of patients.

Accelerated Phase CML (Study 109)

The study is titled "A phase II study to determine the safety and anti-leukemic effects of STI571 in adult patients with Philadelphia chromosome positive leukemia including acute lymphoblastic leukemia, acute myeloid leukemia, lymphoid blast crisis chronic myeloid leukemia and accelerated phase chronic myeloid leukemia. A total of 18 centers of which 2 were in France, 4 in Germany, 3 in Italy, 2 in the UK, 1 in Switzerland and 6 in the USA. The first patient enrolled on 9-Aug-1999. Data cut-off was 31-Jul-2002.

Objectives:

Primary

- To determine the rate of hematologic response (HR) lasting $\geq$4 weeks in adult patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the accelerated phase (AP).

Secondary

- Duration of HR
- Overall survival
- Cytogenetic response (CyR)
- Time to blast crisis
- Improvement of symptomatic parameters,
- Tolerability and safety of ST1571 treatment.

Patients enrolled and analyzed for safety and efficacy included 293 patients in total: 235 with CML AP, 48 with relapsed/refractory ALL, 2 with relapsed/refractory AML, and 8 with relapsed/refractory CML in Lymphoid BC. Patients received STI571 400 mg or 600 mg taken orally (po) once a day (qd.). Dose escalation was permitted, to a maximum of 800 mg daily, taken as 400 mg twice daily (bid.).

Chronic phase CML refractory to or intolerant of interferon-alpha (Study 110)
The title of the study is "A phase II study to determine the efficacy and safety of Gleevec in patients with chronic myeloid leukemia who are refractory to or intolerant of interferon-alpha". A total of 28 centers, 3 in France, 4 in Germany, 7 in Italy, 1 in Switzerland, 3 in the United Kingdom and 10 in the United States participated. The first patient enrolled on 6-Dec-1999. Data cut-off was 31-Jul-2002

Objectives

Primary

- To determine the rate of complete (CCyR) and major (MCyR) cytogenetic response to Gleevec.

Secondary

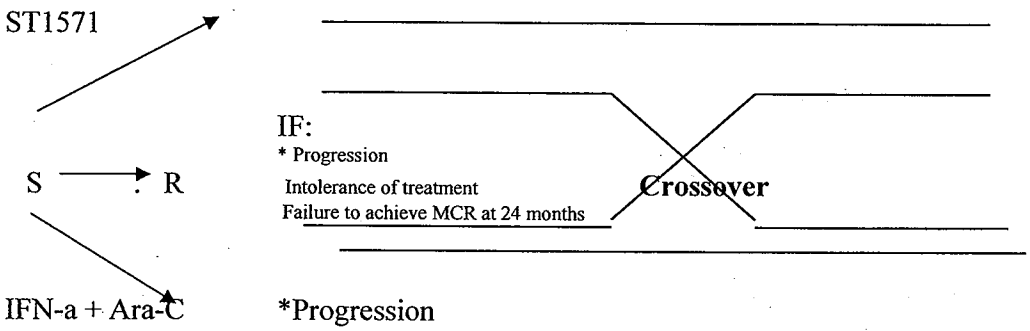
- To determine the rate and duration of complete hematologic response (CHR) and the duration of CCyR and MCyR;
- To evaluate the safety profile of Gleevec;
- To assess improvement in symptomatic parameters;
- To measure the time to accelerated phase (AP) disease (or blast crisis, BC) and overall survival;
- To evaluate the rate and the duration of hematologic and cytogenetic response in patients intolerant of IFN; and
- To evaluate the population pharmacokinetics (PK) of Gleevec.

Patients received 400 mg Gleevec orally (p.o.) once daily. Doses could be escalated to 600 mg daily or to 400 mg twice daily for individuals who had an unsatisfactory response to a lower Gleevec dose.

Newly diagnosed CML Chronic phase (Study 106)

The study is titled "A phase III study of ST1571 versus Interferon-a (IFN-a) combined with Cytarabine (Ara-C) in patients with newly diagnosed previously untreated Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia in chronic phase (CML-CP)" One thousand and thirty-two adult patients with newly diagnosed, previously untreated Ph+ CML-CP will be 1:1 randomized to receive either ST1571 or IFN-a + Ara-C, as initial therapy. The study design is shown in **Figure 1.**

Figure 1: Study 0106 design



*Progression
- •Death
- •Accelerated phase or blast crisis
- •Loss of MCR or CHR
- •Increasing WBC count

S - screening

R - randomization

The sample size estimates are based on a target hazard ratio of 0.75 (ST1571 relative to IFN + Ara-C). This is associated with an increase in the 5-year progression free survival rate from 50% in patients treated with IFN+Ara-C to approximately 60% in patients treated with ST1571. Assuming a median follow-up of 5.25 years the anticipated study duration is 5.5 years.

In addition, an analysis based on the 12-month MCR rate will be conducted 12 months after the last patient was enrolled.

Primary objective

- Demonstration of the superiority of ST1571 over IFN+Ara-C in terms of duration of progression free survival.

Secondary efficacy variables

- Complete hematological response (CHR)
- Major Cytogenetic Response (McyR)
- Duration of McyR
- Duration of CHR

Progression

The following events are considered progression:

- Death
- Accelerated or blastic phase, or
- Loss of CHR defined as the appearance of any of the following, confirmed by a second determination ≥ 1 month later:

  - WBC count that rises to > 20.0 x 109/L; the WBC rise must occur while under continuous treatment with maximum tolerated doses of STI571 or INF combined with Ara-C (or hydroxyurea administered within the first 6 months of start of therapy)
  - Platelet count that rises to ≥600 x 109/L- Progressing splenomegaly to a size ≥5 cm below the left costal margin to be confirmed on two occasions at least 4 weeks apart
  - Appearance of ≥ 5% myelocytes + metamyelocytes in the peripheral blood
  - Any appearance of blasts or promyelocytes in the peripheral blood

- Increasing WBC count: for patients not achieving a CHR, hematological progression will be defined as a doubling of WBC confirmed at least one month apart with at least the second value > 20.0 x 109/L. Patients must be on continuous treatment with maximum tolerated doses of ST1571 or INF combined with Ara-C (or hydroxyurea administered within the first 6 months of start of therapy).

- Loss of MCyR, defined as an increase in the Ph+ bone marrow cells by at least 30 percentage points (e.g., from 20% to 50%, or from 30% to 60%) confirmed by a second cytogenetic analysis at least • •1 month later.

Treatments

ST1571 will be administered orally at a dose of 400 mg/day on an outpatient basis. Patients randomized to the IFN-a +Ara-C arm will receive recombinant IFN-a and AraC subcutaneously. The concurrent administration of hydroxyurea, on either treatment arm will be permitted only during the first 6 months of study treatment to keep the WBC < 20.0 x 109/L.

For patients who fail to achieve either a complete hematologic response at 3 months or at least a minor cytogenetic response at 12 months, the STI571 dose will be escalated to 400 mg bid in the absence of dose limiting toxicities as described above.

IFN-a combined with Ara-C

Patients randomized to the IFN-a + Ara-C arm will receive recombinant IFN-a administered subcutaneously as induction regimen. It is recommended the dose of IFN-a be gradually escalated over four weeks of administration to the target dose of 5 MU/m2/day.

Once the maximum tolerated dose of IFN-a is achieved and tolerated for at least one month, Ara-C will be added at a dose of 20 mg/m2/day (maximum daily dose of 40 mg) for 10 days every month, administered once a day subcutaneously. Hydroxyurea may be used during the initial 6 months of therapy to keep the WBC < 20.0 x 109/L.

Study treatment, i.e. any of the two arms is of indefinite duration. Whenever progression occurs during the study according to the above definition, crossover to the alternative treatment arm may be considered or the patient may discontinue the study. The development or intolerance of treatment will lead to discontinuation of study when it occurs after crossover. Crossover to the alternative treatment arm does not constitute discontinuation of study. After crossover patients will continue to be monitored as per the standard visit schedule.

6.1.4 Efficacy Findings

Blast Crisis CML (Study 102) - efficacy results are displayed in **Table 2.**

Table 2: Study 102 Efficacy results

	400mg n=37	600 mg n=223	Untreated n=165	Pretreated n=95	All pts n=260
Hematologic response	16.2%	33.2%	35.8%	22.1%	30.8%
Complete hematologic response	0	9.4%	9.7%	5.3%	8:1%
No evidence of leukemia	10.8%	3.6%	4.8%	4.2%	4.6%
Return to ohronic phase	5.4%	20.2%	21.2%	12.6%	18.1%
Major cytogenetic response	8.1%	16.6%	15.2%	15.8%	15.4%
Complete cytogenetic response	5.4%	7.6%	7.9%	6.3%	7.3%
Partial cytogenetic response	2.7%	9.0%	7.3%	9.5%	8.1%
Overall survival					
Median (months)	4.7	7,1	7.7	4.7	6.9
Estimated 12-month rate	31.7%	32.1%	35.2%	26.6%	32.1%
Estimated 24-month rate	23.0%	17.6%	20.7%	14.5%	18.4%
Estimated 36-month rate	17.3%	14.3%	17.7%	9.7%	14.8%

Conclusion

These results confirm those of the interim analysis and suggest that ST1571 represents an effective therapeutic agent for the treatment of patients with CML in blast crisis.

Accelerated Phase CML (Study 109) - Efficacy results are displayed in **Table 3.**

Table 3: Study 0109 Efficacy results

CML AP	400 mg n=77	600 mg n=158	All pts N=235
Hematologic response	64.9%	74.7%	71.5%
Complete hematologic response	33.8%	46.2%	42.1%
No evidence of leukemia	10.4%	13.3%	12.3%
Return to chronic phase	20.8%	15.2%	17.0%
Major cytogenetic response	19.5%	31.6%	27.7%
Complete cytogenetic response	15.6%	22.8%	20.4%
Partial cytogenetic response	3.9%	8.9%	7.2%
Duration of hematologic response			
Median (months)	16.7	30.7	p=0. 0027
Estimated 24-month rate still in HR	40.0%	61.4%	
Time to progression			
Median (months)	10.0	22.9	p=0.0009
Estimated 24-month rate without PD	33.5%	49.7%	
Estimated 36-month rate without PD	18.7%	39.2%	
Overall survival			
Median (months)	20.9	Not reached	P=0.0081
Estimated 24-month rate alive	46.2%	65.9%	
Estimated 36-month rate alive	37.4%	55.2%	

The median survival in the advanced leukemia population (ALL, AML, LBC) was only 5 months; and only 2 patients are still on treatment.

Conclusion

These results confirm those of the interim analysis and suggest that ST1571 represents an effective therapeutic agent for the treatment of patients with CML in accelerated phase.

Study 0110-CML Late Chronic phase, Interferon refractory or intolerant Primary-efficacy results

Table 4 shows the numbers (%) of cytogenetic responders.

Table 4 Study 0110 Cytogenetic response rates

Response	Hematologic failure N=152 (%)	Cytogenetic failure N=188 (%)	IFN intolerant N=192 (%)	All patients N=532 (%)
Unconfirmed response				
MCyR = CCyR + PCyR	84 (55.3)	128 (68.1)	136 (70.8)	348 (65.4)
95% CI	[47.0, 63.3]	[60.9, 74.7]	[63.9, 77.2]	[61.2, 69.5]
CCyR	65 (42.8)	104 (55.3)	113 (58.9)	282 (53.0)
95% CI	[34.8, 51.0]	[47.9, 62.6]	[51.5, 65.9]	[48.7, 57.3]
PCyR	19 (12.5)	24 (12.8)	23 (12.0)	66 (12.4)
Minor	6 (3.9)	11 (5.9)	4 (2.1)	21 (4.0)
Minimal	21 (13.8)	18 (9.6)	16 (8.3)	55 (10.3)
Confirmed response				
MCyR = CCyR + PCyR	71 (46.7)	122 (64.9)	129 (67.2)	322 (60.5)
95% CI	[38.6, 55.0]	[57.6, 71.7]	[60.1, 73.8]	[56.2, 64.7]
CCyR	50 (32.9)	80 (42.6)	98 (51.0)	228 (42.9)
95% CI	[25.5, 41.0]	[35.4, 50.0]	[43.7, 58.3]	[38.6, 47.2]
PCyR	21 (13.8)	42 (22.3)	31 (16.1)	94 (17.7)

Secondary efficacy results

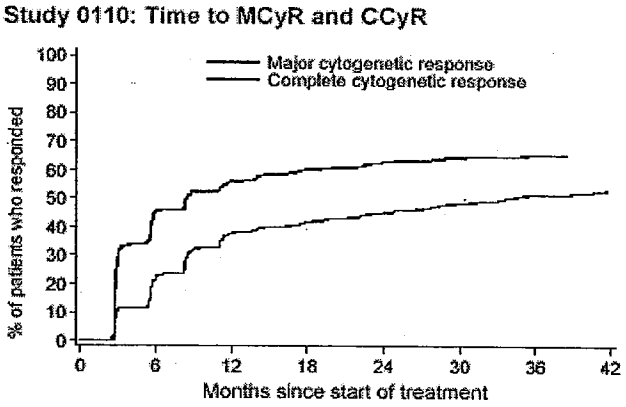
Time to and duration of MCyR and CCyR

Of the 348 MCyRs, 13 (4% of MCyRs, 2% of all patients) were achieved only after 2 years of treatment. Of these late 13 MCyRs, 6 were seen after a dose increase to 800 mg.

Of the 282 CCyRs, 42 (15% of CCyRs, 9% of all patients) were achieved only after 2 years of treatment. Of these late 42 CCyRs, 17 were achieved after a dose increase to 800 mg.

Time to cytogenetic response is depicted in **Figure 2.**

Figure 2: Study 0110: Time to cytogenetic response

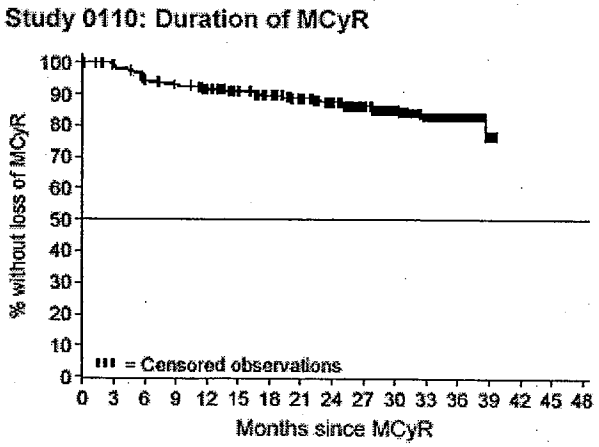


About 15% of the 348 patients who had achieved MCyR had confirmed loss of response or discontinued for progression. Of these 53 cases, 30 had achieved a CCyR (of which 19 were confirmed). Only 23 (7%) of the patients with MCyR later progressed to AP or BC. Overall, the estimated proportions of patients still in MCyR are:

- 91.4% [88.5, 94.4] at 12 months after achievement of response
- 87.5% [83.9, 91,1] at 24 months after achievement of response
- 82.8% [78.3, 87.2] at 36 months after achievement of response

Duration of MCyR, study 0110 is indicated in **Figure 3**.

Figure 3: Study 0110: Duration of MCyR



Time to Progression

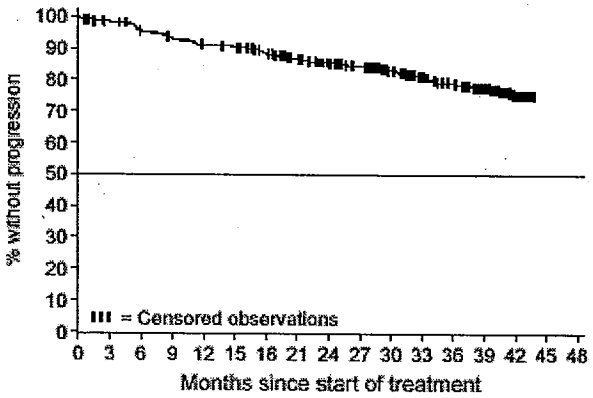
Of the 532 patients, 117 (22%) patients had values indicating progression to accelerated phase (AP) or blast crisis (BC) or died during treatment (due to any

cause).The estimated probabilities of being free of progression to accelerated or blast crisis are:

- 91.0% [88.5, 93.4] at 12 months
- 85.4% [82.4, 88.5] at 24 months
- 79.1% [75.5, 82.7] at 36 months.

Time to Accelerated phase or blast crisis, study 0110, is shown in Figure 4.

Figure 4: Study 0110: Time to Accelerated phase or blast crisis,



Complete Hematologic Response

About 95% of the patients achieved a confirmed complete hematologic response (CHR, 95% CI [92.3, 96.3]). Responses were usually achieved within 1 month after start of treatment. Of the 503 patients with confirmed CHR, 138 (27.0%) lost response during treatment. But only 98 (19.0%) of these patients progressed to accelerated phase or blast crisis and only 64 discontinued treatment. Overall, an estimated 72.3% [68.3,76.3] of patients are still in CHR at 36 months after achieving CHR.

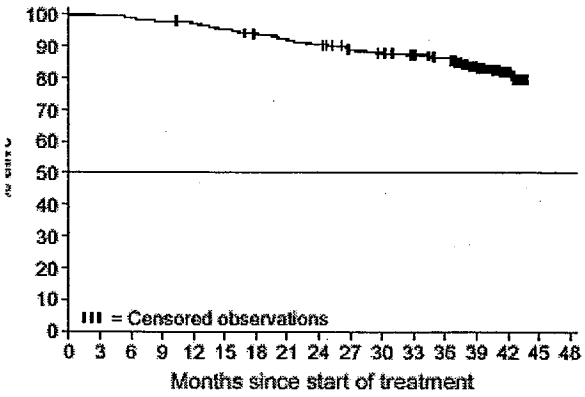
Overall survival

At time of analysis, 94 (18%) of the 532 patients had died. The survival analysis included 93 deaths (1 death was reported after BMT): 17 patients died on study treatment and the remaining 76 patients died during follow-up after discontinuation of treatment (mostly due to progression, n=61).
The estimated survival rates are:

- 97.2% [95.8, 98.6] at 12 months
- 90.8% [88.3, 93.2] at 24 months
- 86.7% [83.8, 89.6] at 36 months.

Overall survival is shown in Figure 5.

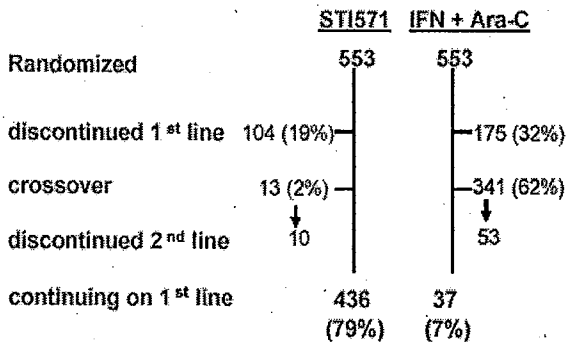
Figure 5: Study 0110 Overall survival



Study 106 Newly diagnosed CP CML

Patient disposition is illustrated in **Figure 6.**

Figure 6: Study 0106: Patient Disposition



Reasons for crossover are summarized in **Table 5.**

Table 5: Study 0106: Reasons for crossover

	STI571 N=553 (%)	IFN+Ara-C N=553 (%)
Number of patients who did not cross over	540 (97.6)	212 (38.3)
Number of patients who crossed over	13 (2.4)	341 (61.7)
Reason other than progression :		
Intolerance of treatment (needed approval by SMC)	4 (0.7)	139 (25.1)
No CHR at 6 months (prior to amendment 2)	0	41 (7.4)
No MCyR at 24 months (prior to amendment 3)	0	3 (0.5)
No CHR at 12 months (after amendment 3)	0	3 (0.5)
No MCyR at 12 months (after amendment 3)	1 (0.2)	48 (8.7)
Reluctance to continue on IFN (after amendment 3)	0	35 (6.3)
Progression :		
Increase in WBC count (needed approval by SMC)	2 (0.4)	25 (4.5)
Loss of CHR	5 (0.9)	29 (5.2)
Loss of MCyR	1 (0.2)	18 (3.3)

The median duration of STI571 treatment is 31.1 months, whereas IFN patients were only treated for a median of 8.2 months with IFN (+Ara-C). In the meantime, the median duration on second-line STI571 (341 patients) is now 18.8 months (maximum 33.6 months). Whereas 83% of patients have now been treated with STI571 for more than 24 months, only 10% of patients randomized to IFN+Ara-C have data available for more than 24 months.

Confirmed Cytogenetic response rate and duration for study 0106 is summarized in **Table 6.**

Table 6: Study 0106: Confirmed Cytogenetic response rate and duration

	STI571 N=553	IFN+Ara-C N=553
No. of patients with confirmed MCyR	461 (83.4%)	90 (16.3%)
No. of patients who lost MCyR	27 (5.9%)	14 (15.6%)
Log-rank test / Wilcoxon test		p<0.001
Estimated % [95% CI] still in MCyR at 24 months	94.7% [92.6,96.8]	71.6% [58.1,85.1]
Estimated % [95% CI] still in MCyR at 30 months	92.8% [90.0,95.6]	71.6% [58.1,85.1]
No. of patients with confirmed CCyR	378 (68.4%)	30 (5.4%)
No. of patients who lost CCyR	24 (6.3%)	1 (3.3%)
Log-rank test / Wilcoxon test	p=0.81 / p=0.88	
Estimated % [95% CI] still in CCyR at 24 months	92.6% [89.7,95.5]	95.7% [87.3,100]
Estimated % [95% CI] still in CCyR at 30 months	92.6% [89.7,95.5]	95.7% [87.3,100]

The time to achievement of MCyR and CCyR is shown in **Figures 7 and 8**, respectively. Although the majority of MCyRs were achieved within the first 3-9 months, some patients achieved a MCyR and even more so a CCyR after greater than one year of treatment.

Figure 7: Study 0106: Time to achievement of a MCyR

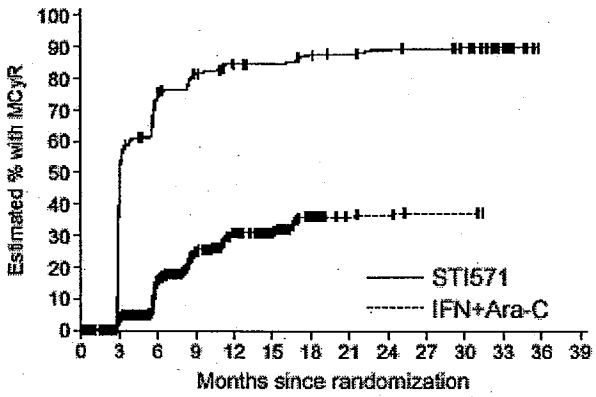
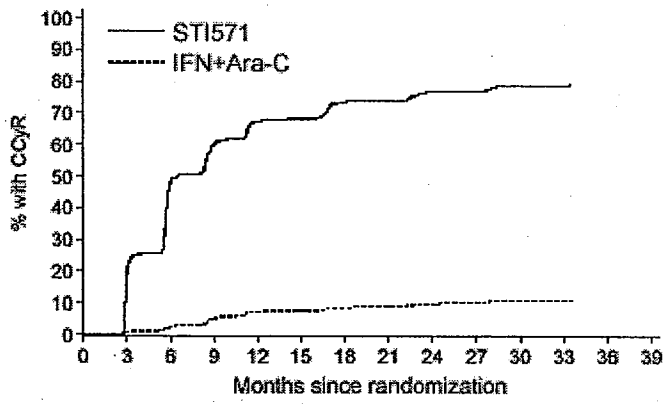


Figure 8: Study 0106: Time to achievement of a CCyR



Time to progression (Study 0106) is summarized in **Table 7**.

Table 7: Study 0106: Time to progression (ITT)

	STI571 N=553	IFN+Ara-C N=553
No. of events	66 (11.9%)	139 (25.1%)
Log-rank test / Wilcoxon test	p<0.001	
Estimated % [95% CI] without progression at 24 months	89.4% [86.8, 92.1]	70.7% [66.4,75.0]
Estimated % [95% CI] without progression at 30 months	87.8% [84.9, 90.6]	68.3% [63.8,72.7]

3.2.2.4 Survival

A total of 33 patients (6%) randomized to STI571 have died; 2 after cross-over to IFN. Of the patients randomized to IFN+Ara-C, 46 (8%) died, 18 of whom had received second-line treatment with STI571 before they died. Bone marrow transplant was reported for 31 patients randomized to STI571 and 45 patients randomized to IFN+Ara-C, and 8 and 14 of these patients died during follow-up respectively.

Considering the 33 and 46 deaths, the estimated survival at 24 months is 96.0% for STI571 vs. 93.6% for patients randomized to IFN+Ara-C. At 30 months the estimated survival is 94.6% vs. 91.6% respectively.

Patients population for PCR analysis

From 370 out of the 495 patients (74.7%) reaching CCyR within 30 months after start of 1st line study medication, at least one PCR sample yielded an evaluable BCR-ABL value within 14 days before and any time after CCyR. This rate of patients with evaluable

blood samples at or after CCyR was higher in the STI571 group (333 of 436 patients, 76.4%) than in the IFN + Ara-C group (37 of 59 patients, 62.7%).

Among all responders who had PCR data available at 6 months, 50% of those in the STI571 group had a BCR-ABL log reduction ≥ 3 log for STI571, as compared with 0% in the IFN + Ara-C group (p=0.03). At 12 months, 59% of the patients in the STI571 group had a BCR-ABL log reduction ≥ 3 log for STI571, as compared with 24% in the IFN + Ara-C group (p=0.001). At 24 months, 72% of those in the STI571 group had a BCR-ABL log reduction ≥ 3 log for STI571, as compared with only 50% in the IFN + Ara-C group (p=0.5, only 2 patients with PCR data available in the IFN+AraC group).

6.1.5 Clinical Microbiology

Not applicable

6.1.6 Efficacy Conclusions

The current data confirms the benefits of STI571 therapy in patients with all stages of CML. Benefits of STI571 therapy can be summarized as follows:

- First-line therapy with STI571 significantly delays the onset of progression to accelerated phase and blast crisis in comparison with IFN + Ara-C.

- Longer follow-up has revealed the possibility for late onset cytogenetic responses. Consequently, the rates of major and complete cytogenetic responses have increased substantially in both chronic phase CML studies 0106 and 0110. These responses are durable with >92% and 83% of patients being in continuing response at 30 and 36 months in studies 0106 and 0110.

- Over historical series using a variety of chemotherapy or IFN-based regimens, treatment with STI571 offers a better survival and quality of survival (with fewer adverse events) for patients with CML in accelerated phase or blast crisis.

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Methods And Findings

Table 8 summarizes clinical studies in Philadelphia chromosome-positive leukemias.

Table 8: Clinical studies in Philadelphia chromosome-positive leukemias

Study	Phase	Patient population(s)	No. of pts enrolled (as of 31-Dec-2003)
03 001	I	Chronic phase CML resistant or intolerant to interferon, advanced Ph+ leukemias (excluding CML in accelerated phase)	152
03 001	I	In combination with ara-C in CML patients in blast crisis	62
0103	I	Patients < 18 years with Ph+ leukemias	31
0102	II	CML in myeloid blast crisis	260
0109	II	CML in acceleration or lymphoid blast crisis, Ph+ ALL and AML	293
0110	II	Chronic phase CML resistant or intolerant to interferon	532
01131	II	Chronic phase CML resistant or intolerant to interferon	3634
01141	II	CML in accelerated phase or lymphoid blast crisis, Ph+ ALL	2650
01151	II	CML in myeloid or lymphoid blast crisis, Ph+ AML	1086
22131	II	Chronic phase CML resistant or intolerant to interferon	412
22141	II	CML in accelerated phase	243
0106	III	Newly diagnosed CML patients in chronic phase (randomized to imatinib vs IFN and ara-C)	5533

1=expanded access

7.1.1 Deaths

There were 190 deaths on study or within 28 days of discontinuation (111 in 0102, 51 in 0109 (only CML), and 28 in 0110). There were 27 newly reported deaths on study or within 28 days of discontinuation (five (102), seven (109) and 15 (110) versus nine, three and seven in the respective studies when compared to the previous Safety Update (dated 29-Apr-02, using cut-off date: 31-Jul-01). In blast crisis (study 0102), 111 (42.7%) of the patients have died during treatment or within 28 days after the last study drug (106 (40.8%) in the previous ISS). A total of 215 (82.7%) of patients have died (104 of them (40%) > 28 days after stopping drug) compared to the reported in the previous ISS 190 (73%) patients (84 of them > 28 days after stopping drug). In accelerated phase CML (study 0109), 51 (21.7%) of the patients have died during treatment or within 28 days after the last study drug (44 in the previous ISS). A total of 130 (55.3%) of patients have died (79 of them (33.6%) > 28 days after stopping drug) compared to the reported in the previous ISS, 88 (37%) patients (44 of them > 28 days after stopping drug). In chronic phase CML (study 0110), 28 (5.2%) of the patients have died during treatment or within 28 days after the last study drug (13 (2.4%) in the previous ISS). A total of 94 (17.7%) of patients have died (66 of them (12.4%) > 28 days after stopping drug) compared to the reported in the previous ISS, 33 (6%) patients (20 of them > 28 days after stopping drug).

7.1.2 Other Serious Adverse Events

In blast crisis (**study 0102**), SAE's were noted in 25 (68%) of the patients on 400mg (vs 24 (65%) in previous ISS); in 168 (75%) of the patients on 600mg (vs 164 (74%) in previous ISS); in total of 260 patients, 193 (74%) experienced SAE (versus 188 (72%) in the previous ISS). From those SAE 169 (65%) were reported to be Grade 3/4. Forty-eight (18.5%) were rated as study drug related from investigators compared to 47(18%) in the previous ISS (which used a cut-off date of 31-Jul-01). The most frequently reported SAEs were neoplasms or disorders affecting the blood and lymphatic system, followed by infections & infestations, and general disorders, reflecting the fact that disease progression or loss of response was often reported as an SAE.

In accelerated phase (**study 0109**), SAE's were noted in 49 (64%) of the patients on 400mg (vs 44 (57%) in previous ISS); in 91 (58%) of the patients on 600mg (vs 81 (51%) in previous ISS); in total of 235 patients, 140 (60%) experienced SAE (versus 125 (53%) in the previous ISS). From those SAE 109 (46%) were reported to be Grade 3/4. Forty (17%) were rated as study drug related from investigators compared to 34 (15%) in the previous ISS (which used a cut-off date of 31-Jul-01). Most of the SAEs reported were attributable to general disorders, infections and infestations, neoplasms and disorders affecting the blood and lymphatic system.

In chronic phase (**study 0110** in total of 532 patients, 161 (30%) experienced SAE (versus 121 (23%) in the previous ISS). From those SAE 124 (23%) were rated as Grade 3/4. Fortyone (7.7%) were rated as study drug related from investigators compared to 29 (5.5%) in the previous ISS (which used a cut-off date of 31-Jul-01). Most of the SAEs reported were attributable to infections and infestations, gastrointestinal disorders, general disorders, neoplasms and disorders affecting the blood and lymphatic system.

In study 0106, the most frequently reported SAEs in the Gleevec-treated patients were infections & infestations (6.8%), general disorders (5.3%), neoplsms (3.8%), SAEs affecting the gastrointestinal (6.5%), respiratory and nervous systems (both 3.6%). The most frequently reported SAEs in the first-line IFN+Ara-C treatment arm were: general disorders (7.3%), musculoskeletal disorders (6.2%), nervous system (5.6%), infections & infestations (4.3%), gastrointestinal (3.9%) and febrile disorders (3.8%). The most frequently reported grade 3/4 SAEs in the Gleevec-treated patients were infections and infestations (4.9%) and gastrointestinal disorders (4.7%), while in the IFN+Ara-C arm were musculoskeletal disorders (5.8%) and nervous system (4.7%) disorders. SAE were noted in 132 (24%) of the patients treated with first-line Gleevec (vs 79 (15%) in previous ISS); in 154 (29%) of the patients treated with first-line IFN + Ara-C. From the SAEs noted in the Gleevec arm, 111 (20%) were reported to be Grade 3/4; while from the SAEs in the IFN + Ara-C group, 137 (26%) were Gared 3/4. SAEs which occurred more frequently and with a greater severity in the IFN + Ara-C group than in Gleevec-treated

patients included pyrexia, depression, myalgia and arthralgia. In the second-line Gleevec--IFN arm 2 (15%) had SAE (vs 1 (14%) in previous ISS), all rated as Grade 3/4. In the 2ndline IFN Gleevec 71 (21%) of the patients had SAE, 60 (18%) of which rated Grade 3/4 (versus 32 (15%), with 28 /13%) having severity grade 3/4.

Study 106 SAE's during Gleevec treatment are listed in **Table 9**.

Table 9: Study 106 SAE's during Gleevec treatment

Serious adverse event (preferred term)	**Gleevec All N=551 (%)**	**Gleevec < 1 year N=551 (%)**	**Gleevec 1-<2 years N=509 (%)**	**Gleevec 2 years N=456 (%)**
Any SAE	**132 (24.0)**	**77 (14.0)**	**58 (11.4)**	**26 (5.7)**
Abdominal pain	2.2	1.5	0.6	0.4
Hemorrhages	1.8	1.3	0.4	0.2
- GI hemorrhages	0.7	0.2	0.4	0.2
- Other hemorrhages	0.9	0.9	.	.
Pyrexia	1.8	1.3	0.4	0.2
Chest pain	1.6	0.7	0.8	0.4
Pneumonia	1.6	0.7	0.8	0.7
Dyspnea	1.5	1.3	0.2	.
Vomiting	1.1	0.7	0.4	.
Diarrhea	0.9	0.7	0.2	.
Nausea	0.9	0.4	0.6	.
Syncope	0.9	0.5	0.4	.
Fluid retention	0.7	.	0.2	0.7
- Other fluid retention events	0.7	.	0.2	0.7
Blast crisis in myelogenous leukemia	0.7	0.2	0.6	.
Cardiac arrest	0.7	0.4	0.2	0.2
Cellulitis	0.7	0.2	0.6	.
Cholecystitis	0.7	0.7	.	.
Dizziness	0.7	0.4	0.4	.
Musculoskeletal pain	0.7	.	0.2	0.7
Rash and related terms	0.7	0.7	.	.
Atrial fibrillation	0.5	0.4	0.2	.
Blood creatine phosphokinase increased	0.5	.	0.2	0.4
Cough	0.5	0.4	.	0.2
Gastroenteritis	0.5	0.4	0.2	.
Multiple myeloma	0.5	0.4	0.2	.
Pain	0.5	0.4	.	0.2
Prostate cancer	0.5	.	0.4	0.2
Sepsis	0.5	.	0.2	0.4
Alanine aminotransferase increased	0.4	0.2	0.2	.
Arrhythmia	0.4	0.2	0.2	.
Aspartate aminotransferase increased	0.4	.	0.4	.
Cholelithiasis	0.4	0.4	.	.
Constipation	0.4	0.4	.	.
Coronary artery disease	0.4	.	0.4	.

Dehydration	0.4	0.2	0.2	.
Disease progression	0.4	.	0.2	0.2
Febrile neutropenia	0.4	0.2	0.2	.
Hepatic enzyme increased	0.4	0.2	0.2	.
Hepatitis	0.4	0.2	0.2	.
Hiatus hernia	0.4	0.2	.	0.2
Influenza like illness	0.4	0.2	.	0.2
Joint pain	0.4	0.2	0.2	.
Lung adenocarcinoma	0.4	0.4	.	.
Myocardial infarction	0.4	.	0.2	0.2
Neoplasm malignant	0.4	0.4	.	.
Pharyngitis	0.4	0.4	.	.
Respiratory failure	0.4	0.2	0.2	.
Rigors	0.4	0.4	.	.

7.1.3 Dropouts and Other Significant Adverse Events

Discontinuation for drug-related AEs occurred in 2%, 3% and 5% of patients in chronic, accelerated and blast phases, respectively. Skin rash and elevated transaminases were the most common reason for drug discontinuation (each in <1% of patients). The most frequently reported AEs were nausea, vomiting, diarrhea, superficial edema (primarily periorbital or lower limb), myalgia and muscle cramps. Grade 3/4 events occurring in <4% of patients included fluid retention (pleural or pericardial effusions, ascites, pulmonary edema), skin rash, liver toxicity and gastrointestinal (GI) hemorrhage. Myelosuppression was a consistent finding across studies. Grade 3/4 neutropenia and thrombocytopenia were more frequent in CML patients in accelerated phase or blast crisis patients than in chronic phase. In a randomized Phase III study (Gleevec 400 mg daily compared to the combination of IFN + Ara-C; study 0106) in 1,106 newly diagnosed CML patients,) the incidence of nausea was lower compared to the phase II trials possibly because the drug was administered with food. Myelosuppression was also less frequent in this study. Grade 3/4 neutropenia occurred in 33% and 12% of patients in studies 0110 and 0106, respectively, and grade 3/4 thrombocytopenia in 21% and 7% of patients.

The long-term follow-up (>2 years of exposure) has not significantly modified the safety profile of Gleevec. The proportion of patients discontinuing treatment for adverse events has increased only modestly (in newly diagnosed patients, this percentage increased from 2% to only 3.1% with an additional 18 months of follow-up). The frequency of grade 3 or 4 hematologic toxicity has also slightly increased in the two chronic phase trials 0110 and 0106. However, this has to be interpreted with caution as an increasing proportion of patients had their dose increased from 400 to 600 or 800 mg daily per protocol.

7.1.4 Other Search Strategies

None

7.1.5 Common Adverse Events

Adverse Events - (0102, 0109, 0110):
Non-hematologic AEs regardless of presumed relationship to Gleevec and occurring in ≥10% of patients in the phase II leukemia studies as of 7/31/02 are listed in **Table 10.**

Table 10: AE's in ≥ 10% of patients during phase II studies

	Myeloid Blast Crisis (n = 260) %		Accelerated Phase (n = 235) %		Chronic Phase, IFN Failure (n = 532) %	
Toxicity	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Fluid Retention	72	11	76	6	69	4
Superficial Edema	66	6	74	3	67	2
Other Fluid Retention Events**	22	6	15	4	7	2
Nausea	71	5	73	5	63	3
Muscle Cramps	28	1	47	0.4	62	2
Vomiting	54	4	58	3	36	2
Diarrhea	43	4	57	5	48	3
Hemorrhage	53	19	49	11	30	2
CNS hemorrhage	9	7	3	3	2	1
Gastrointestinal Hemorrhage	8	4	6	5	2	0.4
Musculoskeletal Pain	42	9	49	9	38	2
Fatigue	30	4	46	4	48	1
Skin Rash	36	5	47	5	47	3
Pyrexia	41	7	41	8	21	2
Arthralgia	25	5	34	6	40	1
Headache	27	5	32	2	36	0.6
Abdominal Pain	30	6	33	4	32	1
Weight Increased	5	1	17	5	32	7
Cough	14	0.8	27	0.9	20	0
Dyspepsia	12	0	22	0	27	0
Myalgia	9	0	24	2	27	0.2
Nasopharyngitis	10	0	17	0	22	0.2
Asthenia	18	5	21	5	15	0.2
Dyspnea	15	4	21	7	12	0.9
Upper Respiratory Tract Infection	3	0	12	0.4	19	0
Anorexia	14	2	17	2	7	0
Night Sweats	13	0.8	17	1	14	0.2
Constipation	16	2	16	0.9	9	0.4
Dizziness	12	0.4	13	0	16	0.2
Pharyngitis	10	0	12	0	15	0
Insomnia	10	0	14	0	14	0.2
Pruritus	8	1	14	0.9	14	0.8
Hypokalemia	13	4	9	2	6	0.8

Pneumonia	13	7	10	7	4	1
Anxiety	8	0.8	12	0	8	0.4
Liver Toxicity	10	5	12	6	6	3
Rigors	10	0	12	0.4	10	0
Chest Pain	7	2	10	0.4	11	0.8
Influenza	0.8	04	6	0	11	0.2
Sinusitis	4	0.4	11	0.4	9	0.4

The adverse events in study 106 (**Table 11**) are based on a median duration of follow-up of 31.1 months (Cut-off date 31-Jul-03).

Table 11: AE's in ≥ 10% of patients in Study 0106.

Adverse event (preferred term)	All grades		CTC grades 3/4	
	Gleevec N=551 (%)	IFN+Ara-C N=533 (%)	Gleevec N=551 (%)	IFN+Ara-C N=533 (%)
Fluid retention	59.2	10.7	1.8	0.9
- Superficial edemas	57.5	9.2	1.1	0.4
- Other fluid retention events	6.9	1.9	0.7	0.6
Nausea	47.0	61.5	0.9	5.1
Muscle cramps	43.2	11.4	1.6	0.2
Musculoskeletal pain	39.9	44.1	3.4	8.1
Diarrhea	38.5	42.0	2.0	3.2
Rash and related terms	37.2	25.7	2.4	2.4
Fatigue	37.0	66.8	1.6	25.0
Headache	33.6	43.3	0.5	3.6
Joint pain	30.3	39.4	2.5	7.3
Abdominal pain	29.9	25.0	2.5	3.9
Nasopharyngitis	26.9	8.4	0	0.2
Hemorrhages	24.1	20.8	1.1	1.5
- GI hemorrhages	1.3	1.1	0.5	0.2
- CNS hemorrhages	0.2	0.2	0	0.2
- Other hemorrhages	23.4	19.9	0.5	1.1
Myalgia	22.5	38.8	1.5	8.1
Vomiting	20.5	27.4	1.5	3.4
Dyspepsia	17.8	9.2	0	0.8
Cough	17.4	23.1	0.2	0.6
Pharyngolaryngeal pain	16.9	11.3	0.2	0
Upper respiratory tract infection	16.5	8.4	0.2	0.4
Dizziness	15.8	24.2	0.9	3.6
Pyrexia	15.4	42.4	0.9	3.0
Weight increased	15.2	2.1	1.6	0.4
Insomnia	13.2	18.8	0	2.3
Depression	12.7	35.8	0.5	13.1
Influenza	11.1	6.0	0.2	0.2

* All adverse events occurring in □10% of patients regardless of suspected relationship to treatment
Source: Investigators' Brochure, edition 6 (dated: 05-Apr-04)

7.1.7 Laboratory Findings

Patients with newly occurring or worsening Grade 3/4 laboratory abnormalities in phase II leukemia studies (cut-off date 31-Jul-02) are summarized in **Table 12.**

Table 12: Grade 3/4 laboratory abnormalities in phase II studies

	Study 0102 Myeloid blast crisis n= 260 (%)		Study 0109 Accelerated phase n=235 (%)		Study 0110 Chronic phase n=532 (%)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Hematology parameters						
Anemia	42	11	34	7	6	1
Neutropenia	16	48	23	36	27	9
Thrombocytopenia	30	33	31	13	21	<1
Biochemistry parameters						
Creatinine Increase	1.5	0	1.3	0	0.2	0
Bilirubin Increase	3.8	0	2.1	0	0.6	0
Alkaline phosphatase Increase	4.6	0	5.5	0.4	0.2	0
SGOT (AST) Increase	1.9	0	3.0	0	2.3	0
SGPT (ALT) Increase	2.3	0.4	4.3	0	2.1	0

7.1.8 Vital Signs

No special analysis of vital signs were conducted in the trials presented in this report.

7.1.9 Electrocardiograms (ECGs)

No ECGs were performed for study 0102, 110 and 0106. The protocol for study 0109 specified that the results of vital signs examinations, ECG recordings etc would only be recorded on the CRF if they constituted AEs.

7.1.10 Immunogenicity

There is no new relevant information.

7.1.11 Human Carcinogenicity

There is no new relevant information.

7.1.12 Special Safety Studies

There is no new relevant information.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Gleevec has no known potential for abuse..

7.1.14 Human Reproduction and Pregnancy Data

Because of the potential risks to the human fetus, women of child-bearing potential were advised to avoid becoming pregnant and to use effective contraception during treatment. As of 31-Dec-2003, a total of 21 pregnancies had been reported among women participating in clinical trials who had received imatinib for 5- 65 weeks. The pregnancies were detected at 5- 22 weeks of gestation. The patients included 20 women with chronic phase CML (16 of whom had received imatinib 400 mg and one who had received 600 mg), and one patient in blast crisis who received imatinib 600 mg. Outcomes were available for all 21 pregnancies; 10 underwent therapeutic abortions, four had spontaneous abortions (including one at 18 weeks gestation) and seven proceeded to term following discontinuation of imatinib. There was one delivery at 35 weeks. Among the infants, 6 were normal (including the offspring of the patient in blast crisis who had received imatinib for 30 weeks), and one had hypospadias. Imatinib is not genotoxic though reduced spermatogenesis was noted in animal studies, possibly due to inhibition of c-kit in testicular tissues. Therefore, the sperm of male patients taking imatinib should be genotypically normal, though low sperm counts are a possibility. Fifteen pregnancies have been reported in partners of male CML patients taking imatinib. Therefore, the issue of low sperm counts may not be clinically relevant though it requires further study. Among these 15 male patients, 11 were in chronic phase CML (all received imatinib 400 mg), 4 had accelerated CML (all received imatinib 600 mg). Outcomes were available for 14 of the pregnancies; 10 pregnancies proceeded to term with delivery of normal infants (1 of which had respiratory distress syndrome), one pregnancy is ongoing as of 31- Dec-2003, there were 2 therapeutic abortions on social grounds, and 1 death *in utero* at 14 weeks followed by an induced abortion.

7.1.15 Assessment of Effect on Growth

No data was reported.

7.1.16 Overdose Experience

Experience with doses greater than 800 mg is limited. Isolated cases of Gleevec overdose have been reported. In these instances the highest dose ingested was 1600 mg/day for several days. A patient with myeloid blast crisis inadvertently took Gleevec 1200 mg for 6 days and experienced Grade 1 elevations of serum creatinine, Grade 2 ascites and elevated liver transaminase levels, and Grade 3 elevations of bilirubin. Therapy was temporarily interrupted and there was complete reversal of all abnormalities within one

week. Treatment was resumed at a dose of 400 mg without recurrence of problems. Another patient developed severe muscle cramps after taking 1,600 mg of Gleevec daily for six days. Complete resolution of muscle cramps occurred following interruption of therapy and treatment was subsequently resumed. Another patient took 400 mg three times a day (1,200 mg) for two days. Therapy was interrupted, no adverse events occurred and the patient resumed therapy.

7.1.17 Postmarketing Experience

The Post marketing experience with Gleevec has been reviewed on an ongoing basis in the following PSUR and the US Periodic Reports respectively:

- PSUR 1 covering the period 10 May 2001-30 November 2001
- PSUR 2 covering the period 01 Dec 2001-31 May 2002
- PSUR 3 covering the period 01 June 2002- 30 Nov 2002
- PSUR 4 covering the period 01 Dec 2002 - 10 May 2004
- PSUR 5 covering the period 11 May 2003 – 10 may 2004
- USPR Capsule formulation covering the period 10 Nov 2002 – 9 Feb. 2004
- USPR Tablet formulation covering the period 18 July 200314 May 2004

The Core Data Sheet (CDS) in effect at the beginning of the launch period is the Basic Prescribing Information (BPI) dated 27 February 2001 amended on 23 October 2001, 26 June 2002 and 19 February 2003 (Hard Gelatin Capsule) and dated 19 November 2002 amended 19 February 2003 (Film Coated Tablets), which is used as reference for the prescribing information in all countries where the product is marketed.

The Basic Prescribing Information (BPI/CDS) and the US Package Insert (USPI) have been updated to reflect the results discussed in these PSURs and USPRs. The most recent version of the BPI dated February 2003 reflects the safety aspects of the drug except that in the last PSUR, number 5, issued on 6 July 2004, the event of [redacted] b(4) was proposed for inclusion to the BPI.

In the previous PSUR version 4 the following events were identified as requiring close monitoring: myocardial infarction, angina pectoris, cardiomegaly/cardiomyopathy thrombo- cythemia disseminated intravascular coagulation hemolytic anemia glucose metabolism disorders), deafness/ hypoacusia Raynaud's phenomenon/intermittent claudication /ischemic episodes Parkinson's disease Sweet's syndrome and rhabdomyolysis. Furthermore, the following events were monitored at the request of the CPMP: Thrombosis /embolism), splenic rupture) and myopathy / myositis). Monitoring of cases of inflammatory bowel disease, worsening of ulcerative colitis and Crohn's disease), intestinal ulcer, splenic necrosis), suicide attempt), nephrolithiasis/renal colic, scleroderma, hepatic necrosis/cirrhosis, arthritis and pulmonary hypertension.

Based upon cumulative reviews in the most recent PSUR version 5 it was recommended to continue to monitor the following events: Myocardial infarction, angina pectoris, cardiomegaly/cardiomyopathy, thrombocythemia, disseminated intravascular coagulation, Raynaud's phenomenon/intermittent claudication /ischemic episodes, Parkinson's disease, rhabdomyolysis, hemolytic anemia, glucose metabolism disorders, deafness/hypoacusia, nephrolithiasis, myopathy/myositis, arthritis, inflammatory bowel disease, worsening of ulcerative colitis and Crohn's disease, intestinal ulcer, splenic necrosis, suicide attempt, splenic rupture, renal colic, scleroderma, hepatic necrosis/cirrhosis and pulmonary hypertension will continue to be monitored. Sweet's syndrome was considered for inclusion in the Core Data Sheet.

7.2 Adequacy of Patient Exposure And Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Phase II studies 0102, 0109 and 0110 using data with a cut-off of 31-Jul-02. This represents an additional 12 months of data when compared to the prior ISS Update. Phase III trial 0106 using data with a cut-off of 31-Jul-03. This represents an additional 18 months compared to the prior ISS for first-line treatment of newly diagnosed Ph+CML (study 0106). **Table 13** summarizes this data.

Table 13: Cut-off dates and patient numbers in safety updates

	Key safety population			
	Study 0102 n=260	Study 0109 n=293	Study 0110 n=532	Study 0106 n= 551
First patient recruited	02-Aug-1999	12-Aug-1999	06-Dec-1999	16-Jun-2000
Last patient recruited	30-Jun-2000	13-Mar-2000	30-May-2000	31-Jan-2002
ISS (dated 14-Feb-01)				
Cut-off (AEs, LAB)	02-Oct-2000	09-Oct-2000	30-Oct-2000	NA
Cut-off (SAEs)	02-Oct-2000	09-Oct-2000	30-Oct-2000	NA
ISSs (dated 31-Jul-01) & (14-Jun-02)				
Cut-off	31-Jul-2001	31-Jul-2001	31-Jul-2001	31-Jan-2002
Current Safety Update				
Cut-off	31-Jul-2002	31-Jul-2002	31-Jul-2002	31-Jul-2003

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

See literature review, Section 8.6

7.2.3 Adequacy of Overall Clinical Experience

An adequate number of subjects were exposed to the drug, including adequate numbers of various demographic subsets and people with pertinent risk factors
Doses and durations of exposure were adequate to assess safety for the intended use.
Design of studies (open, active-control, placebo-control) was adequate to answer critical questions.
Potential class effects were adequately evaluated.
There were no study exclusions that limit the relevance of safety assessments..

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new information was provided. Animal and/or In-Vitro Testing was adequate based on previous submissions.

7.2.5 Adequacy of Routine Clinical Testing

Adequate

7.2.6 Adequacy of Metabolic. Clearance. and Interaction Workup

Adequate

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Evaluation for potential adverse events was adequate. No new recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

Data was of high quality and was complete.

7.2.9 Additional Submissions. Including Safety Update

All relevant information was submitted.

7.3 Summary Of Selected Drug- Related Adverse Events. Important Limitations Of Data. And Conclusions

In phase II trials in CML, the majority of patients experienced drug-related adverse events (AEs) at some time, but most were mild to moderate in severity. Discontinuation for drugrelated AEs occurred in 2%, 3% and 5% of patients in chronic, accelerated and blast phases, respectively. Skin rash and elevated transaminases were the most common reason for drug discontinuation (each in <1% of patients). The most frequently reported AEs were mild nausea, vomiting, diarrhea, superficial edema (primarily periorbital or

lower limb), myalgia and muscle cramps. Grade 3/4 events occurring in <4% of patients included fluid retention (pleural or pericardial effusions, ascites, pulmonary edema), skin rash, liver toxicity and gastrointestinal (GI) hemorrhage. Myelosuppression was a consistent finding across studies. Grade 3/4 neutropenia and thrombocytopenia were more frequent in CML patients in accelerated phase or blast crisis patients than in chronic phase. In a randomized Phase III study in 1106 newly diagnosed CML patients, Gleevec 400 mg daily has been compared to the combination of IFN + Ara-C (study 0106). The incidence of nausea was lower in this study compared to the phase II trials possibly because the drug was administered with food. Myelosuppression was also less frequent in this study. Grade 3/4 neutropenia occurred in 33% and 12% of patients in studies 0110 and 0106, respectively, and grade 3/4 thrombocytopenia in 21% and 7% of patients. The long-term follow-up (>2 years of exposure) has not significantly modified the safety profile of Gleevec. The proportion of patients discontinuing treatment for adverse events has increased only modestly (in newly diagnosed patients, this percentage increased from 2% to only 3.1% with an additional 18 months of follow-up). The frequency of grade 3 or 4 hematologic toxicity has also slightly increased in the two chronic phase trials 0110 and 0106. However, this has to be interpreted with caution as an increasing proportion of patients had their dose increased from 400 to 600 or 800 mg daily per protocol. The data indicate that the drug is well tolerated in the target population.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Separate safety data was provided for each study and the data was then pooled. This was appropriate.

7.4.2 Explorations for Predictive Factors

Predictive factors for each stage of CML are known and were analyzed in this submission. These included explorations for dose dependency, time dependency, drug-demographic interactions, and drug-disease interactions.

7.4.3 Causality Determination

AE's occurring with Gleevec treatment likely represent the effect of the drug in the population of patients with CML.

8.0 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

In the phase I trial 03 001, doses of 400 mg to 800 mg were considered as safe and effective and were recommended for the subsequent phase II and phase III trials. However, in this trial, no maximally tolerated dose was characterized up to 1000 mg/day.

The recommended doses of 400 mg for patients in chronic phase CML has been based on the findings of the initial phase I trial 03 001, subsequently confirmed by the phase II trial 0110 in patients failing prior IFN therapy and by the phase III trial 0106 in patients with newly-diagnosed CML. The recommended dose of 600 mg for patients in accelerated phase or blast crisis CML is based on the findings of the initial phase I trial 03 001 and on the two phase II trials 0102 and 0109. In both the phase II and phase III study protocols, dose-escalation to 600 mg and 800 mg was allowed in the event of insufficient efficacy as pre-specified checkpoints.

8.2 Drug-Drug Interactions

Gleevec is a substrate for CYP3A4 indicating a potential for decreased plasma levels when administered concomitantly with inducers of this enzyme class. A loss of therapeutic efficacy can be anticipated when Gleevec is administered together with inducers of this enzyme class.

8.3 Special Populations

No new information is available.

8.4 Pediatrics

No new information is available.

8.5 Advisory Committee Meeting

No ODAC meeting to discuss this application is planned.

8.6 Literature Review

[Champagne MA, Capdeville R, Krailo M, Qu W, Peng B, Rosamilia M, Therrien M, Zoellner U, Blaney S, Bernstein M (2004).] Imatinib mesylate (STI571) for treatment of children with Philadelphia chromosome-positive leukemia: results from a Children's Oncology Group phase I study. Blood. 2004 Jul 1 [Epub ahead of print]

[Sawyers C, Hochhaus A, Druker BJ. (2001).] Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood, May 2002, 99(10):3530-3539.

[Talpaz M, Silver RT, Druker BJ. (2002)]. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. Blood, March 2002; 99 (6):1928-1937

[Ottman OG, Druker BJ, O'Brien SG. (2002)]. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood, Sep 2002; 100(6):1965-1971

[Kantarjian H, Sawyers C, Hochhaus A, et al.(2002)]. Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. Engl J Med 2002, Vol.346, No.9, 645– 652.

[Milojkovic D, Short K, Salisbury JR, et al (2003)]. Dose-limiting dermatological toxicity secondary to imatinib mesylate (STI571) in chronic myeloid leukemia. Leukemia;17:1414-16.

[O'Brien SG, Guilhot F, Larson RA, et al (2003)]. Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. N Eng J Med; 348: 994-1004.

8.7 Postmarketing Risk Management Plan

Based upon cumulative reviews in the most recent PSUR version 5 it was recommended to continue to monitor the following events: Myocardial infarction, angina pectoris, cardiomegaly/cardiomyopathy, thrombocythemia, disseminated intravascular coagulation, Raynaud's phenomenon/intermittent claudication /ischemic episodes, Parkinson's disease, rhabdomyolysis, hemolytic anemia, glucose metabolism disorders, deafness/hypoacusia, nephrolithiasis, myopathy/myositis, arthritis, inflammatory bowel disease, worsening of ulcerative colitis and Crohn's disease, intestinal ulcer, splenic necrosis, suicide attempt, splenic rupture, renal colic, scleroderma, hepatic necrosis/cirrhosis and pulmonary hypertension will continue to be monitored. Sweet's syndrome was considered for inclusion in the Core Data Sheet.

8.8 Other Relevant Materials

No new information is available.

9.0 0VERALL ASSESSMENT

9.1 Conclusions

The reviewer concurs with the sponsor's assessment of efficacy and safety of Gleevec in the treatment of CML.

9.2 Recommendation on Regulatory Action

The Gleevec team will review the proposed labeling update.

9.3 Recommendation On Postmarketing Actions

9.3.1 Risk Management Activity

Continue post-marketing surveillance

9.3.2 Required Phase 4 Commitments

No new commitments.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

Label reviewed by DODP Gleevec team.

9.5 Comments To Applicant

None.

10.0 APPENDICES

10.1. Review Of Individual Study Reports

See clinical section

10.2 Line-By-Line Labeling Review

Done.

REFERENCES

[Branford S, Rudzki Z, Harper A, et al (2003) Imatinib produces significantly superior molecular reponses compared to interferon alfa plus cytarabine in patients with newly diagnosed chronic myeloid leukemia in chronic phase. Leukemia 17 : 2401-9]

[Hughes T.P, Kaeda J, Brandford S, et al (2003) Frequency of Major Molecular Responses to Imatinib or Interferon Alfa plus Cytarabine in Newly Diagnosed Chronic Myeloid Leukemia. N.E.J.M 349:1421-30]

[O'Brien SG, Guilhot F, Larson R et al. (2003). Imatinib compared with interferon and low dose cytarabine for newly diagnosed chronic phase chronic myeloid leukemia. N Engl. J. Med. 348: 994-1004]

[Sawyers C., Hochhaus A, Feldman E et al. Imatinib Induces Hematologic and Cytogenetic Responses in Patients with Chronic Myeloid Leukemia in Myeloid Blast Crisis: Results of a Phase II Study. (2002). Blood 99:3530-3539.]

[Talpaz M., Silver RT, Druker B et al. STI571™ (imatinib mesylate) Induces Durable Hematologic and Cytogenetic Responses in Patients with Accelerated Phase Chronic Myeloid Leukemia: Results of a Phase 2 Study (2002). Blood **99**: 1928-1937.]

[Ottman OC, Druker BJ, O'Brien SC. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood 2002; 100:1965-1971.]

[Kantarjian H., Sawyers C, Hochhaus A et al. (2002) Hematologic and cytogenetic responses to imatinib mesylate in chronic myelogenous leukemia. N. Engl. J. Med. 346, 645-652.]

[Mueller M.C Gattermann N, Lahaye T, et al (2003) Dynamics of BCR-ABL mRNA expression in first-line therapy of chronic myelogenous leukemia patients with imatinib or interferon-a/ara-C. Leukemia 17:2392-400]

[Sawyers C., Hochhaus A, Feldman E et al. Imatinib Induces Hematologic and Cytogenetic Responses in Patients with Chronic Myeloid Leukemia in Myeloid Blast Crisis: Results of a Phase II Study. (2002). Blood 99:3530-3539.]

[Talpaz M., Silver RT, Druker B et al. STI571™ (imatinib mesylate) Induces Durable Hematologic and Cytogenetic Responses in Patients with Accelerated Phase Chronic Myeloid Leukemia: Results of a Phase 2 Study (2002). Blood **99**: 1928-1937.]

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/s/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-588/S005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PROJECT MANAGER REVIEW OF LABELING

NDA 21-588/S-005

Drug:	**Gleevec (imatinib mesylate) Tablets, 100 and 400 mg**
Applicant:	**Novartis Pharmaceutical Corporation**
Submission Date:	**September 7, 2004 (SE8)**
Receipt Date:	**September 8, 2004**

BACKGROUND:

On September 7, 2004, Novartis submitted FPL for S-003.

On September 7, 2004, Novartis submitted this new sNDA which provides for changes to the package insert to reflect additional data accumulated from the ongoing pivotal study (106) in newly diagnosed Ph+ CML.

DOCUMENTS REVIEWED:

I compared the approved S-003 FPL dated September 7, 2004 to the proposed S-005 labeling in this new sNDA dated September 7, 2004.

REVIEW:

The comparison revealed that some of the approved changes in the FPL for S-003 were erronously omitted in the proposed labeling submitted September 7, 2004.

I have added the approved changes from the FPL for S-003 to the proposed PI for S-005.

CONCLUSION - RECOMMENDED REGULATORY ACTION:

In this new sNDA, the sponsor has correctly identified all of the proposed changes to the package insert using the track changes feature with the exception to the changes from the approved S-003 FPL. The proposed PI has been modified to include the missing information and this sNDA should be approved pending Statistical and Clinical reviewers concurrence.

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

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

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/s/

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EXCLUSIVITY SUMMARY

NDA # 21-588 SUPPL # 005 HFD # 150

Trade Name Gleevec

Generic Name imatinib mesylate

Applicant Name Novartis

Approval Date, If Known 3-14-05

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement? YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

This supplemental new drug application provides for changes to the package insert to reflect additional data accumulated from the ongoing pivotal study (106) in newly diagnosed Ph+ CML.

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-588 Gleevec

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is

"yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☒	NO ☐
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

study 106 was reviewed previously - this application provided updated data (numbers) for existing tables in the package insert.

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

study 106 was reviewed previously - this application provided updated data (numbers) for existing tables in the package insert.

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

study 106 was reviewed previously - this application provided updated data (numbers) for existing tables in the package insert.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 55,666	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Ann Staten
Title: Project Manager
Date: 6-7-05

Name of Office/Division Director signing form: Richard Pazdur, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Richard Pazdur
6/7/05 03:35:37 PM

Staten, Ann M

From: robert.miranda@pharma.novartis.com
Sent: Tuesday, February 15, 2005 11:42 AM
To: Staten, Ann M
Subject: Re: NDA 21-588/S-005 Gleevec proposed labeling

Dear Ann,

We agree with the proposed labeling, an look forward to your approval letter.

Thank you very much,
Bob

****
Robert A. Miranda, R.A.C.
Director
Drug Regulatory Affairs
Oncology Business Unit
Building 105/ Room 2W200
East Hanover, New Jersey 07936
Phone: 862-778-2282
Fax: 973-781-5217
E-mail: Bob Miranda

b(6)

"Staten, Ann M" <STATENA@cder.fda.gov>

02/14/2005 03:08 PM

To: Robert Miranda/PH/Novartis@PH
cc:
Subject: NDA 21-588/S-005 Gleevec proposed labeling

Dear Bob,

Please refer to my voicemail message I left today regarding your supplement 005 for NDA 21-588 Gleevec which provides for changes to the package insert to reflect additional data accumulated from the ongoing pivotal study (106) in newly diagnosed Ph+ CML.

b(4)

These proposed labeling changes are OK except for the ——— of "Follow up is limited" from the INDICATIONS section. This would convert the accelerated approval to : ——— b(4) ——— As a corollary, you need to keep all previous Phase 4 commitments regarding Study 106.

If you agree with the attached package insert, we will be able to take an approval action now.

Sincerely,
Ann

Ann M. Staten, R.D., CDR, USPHS

Senior Regulatory Project Manager

Division of Oncology Drug Products

Center for Drug Evaluation and Research, FDA

301.594.0490 (phone)

301.827.4590 (fax)

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

/s/

Ann Staten
2/15/05 02:46:15 PM
CSO